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Factors influencing local control after MR-guided stereotactic body radiotherapy (MRgSBRT) for adrenal metastases

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ABSTRACT

Purpose: Stereotactic body radiotherapy (SBRT) is an effective treatment for adrenal gland metastases, but it is technically challenging and there are concerns about toxicity. We performed a multi-institutional pooled retrospective analysis to study clinical outcomes and toxicities after MR-guided SBRT (MRgSBRT) using for adrenal gland metastases.

Methods and Materials: Clinical and dosimetric data of patients treated with MRgSBRT on a 0.35 T MR-Linac at 11 institutions between 2016 and 2022 were analyzed. Local control (LC), local progression-free survival (LPFS), distant progression-free survival (DPFS) and overall survival (OS) were estimated using Kaplan-Meier method and log-rank test.

Results: A total of 255 patients (269 adrenal metastases) were included. Metastatic pattern was solitary in 25.9 % and oligometastatic in 58.0 % of patients. Median total dose was 45 Gy (range, 16–60 Gy) in a median of 5 fractions, and the median BED10 was 100 Gy (range, 37.5–132.0 Gy). Adaptation was done in 87.4 % of delivered fractions based on the individual clinicians' judgement. The 1- and 2- year LPFS rates were 94.0 % (95 % CI: 90.7–97.3 %) and 88.3 % (95 % CI: 82.4–94.2 %), respectively and only 2 patients (0.8 %) experienced grade 3 + toxicity. No local recurrences were observed after treatment to a total dose of BED10 > 100 Gy, with single fraction or fractional dose of > 10 Gy.

Conclusions: This is a large retrospective multi-institutional study to evaluate the treatment outcomes and toxicities with MRgSBRT in over 250 patients, demonstrating the need for frequent adaptation in 87.4 % of delivered fractions to achieve a 1- year LPFS rate of 94 % and less than 1 % rate of grade 3 + toxicity. Outcomes

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analysis in 269 adrenal lesions revealed improved outcomes with delivery of a $BED_{10} > 100$ Gy, use of single fraction SBRT and with fraction doses > 10 Gy, providing benchmarks for future clinical trials.

Introduction

The adrenal glands represent a common site of metastatic dissemination, with a prevalence of around 0.5–3.8 % and originate most commonly from lung, genitourinary, and gastrointestinal malignancies [1,2]. Adrenal metastases are increasing being identified because of comprehensive disease-specific staging and follow-up guidelines. The proximity of the adrenal glands to stomach, liver, kidneys, bowel and large vessels poses a challenge for local radiation therapy (RT) [3]. Although adrenalectomy has long been the gold standard in the management of adrenal gland metastases [4]; local control (LC) and overall survival (OS) at 2-year were a modest 84 % and 46 %, respectively. In addition, 6 % of patients can develop intraoperative complications, 13.4 % postoperative complications, and 2.6 % with severe postoperative complications [5,6].

In patients who are medically unfit for metastasectomy, stereotactic body radiation therapy (SBRT, also known as stereotactic ablative radiation therapy [SABR]), and percutaneous catheter ablation techniques have been explored [5]. For SBRT, continuous and unpredictable motion of abdominal structures results in inherent positional uncertainties, causing both intra- and inter-fraction changes, particularly challenging when employing hypofractionated schedules [7,8]. However, the integration of an magnetic resonance imaging (MRI) system and a megavoltage RT system into a single treatment delivery unit has provided the possibility to acquire an MRI in the treatment position and continuously during RT delivery [9]. MR-guided SBRT (MRgSBRT), with its ability to better visualize soft tissue and track tumors during treatment, has been shown to be a novel but reproducible and accurate treatment modality that may reduce treatment volumes and may consequently minimize toxicity [10]. Early single-institution clinical outomes of adrenal SBRT with MRgRT have also been published [10–19]. The main aim of this multi-institutional pooled analysis was to report the clinical outcomes and toxicities after adrenal MRgSBRT on a 0.35 T MR-linac. A secondary objective was to study the prognostic factors that may be related to the long-term control rates.

Materials and methods

We analyzed clinical and dosimetric data of patients treated with MRgSBRT for adrenal metastases at 11 institutions across Europe (7) and USA (4) between 2016 and 2022 retrospectively. Ethics approval had been obtained in the coordinating study center (Acibadem MAA University, 2022-13/20) and in participating institutions in accordance with local standards through individual data transfer agreements. Institutional databases for medical records were reviewed for demographic, pathologic, radiologic, treatment and outcome related information. Part of this data has been reported recently by Amsterdam University Medical Centers (AUMC) [19]. Baseline patient characteristics including age, gender, performance status, histopathology, the timing of metastasis (synchronous, metachronous, oligoprogressive, or oligopersistent based on the ESTRO-ASTRO consensus definition [20]), metastatic pattern, laterality, and whether chemotherapy or immunotherapy was administered concurrently (within 3 months before and/or after MRgSBRT) were recorded. For dosimetric analysis, prescription dose (cGy), number of fractions, fractional dose, respiratory motion management techniques, tracking boundary (mm), number of adapted fractions, gross tumor volume (GTV) (cc), planning target volume (PTV) (cc), margin expansion (mm), GTV Dmean (Gy), GTV D95%, PTV D95%, PTV conformity index (CI), and PTV homogeneity index (HI) were recorded. Patients treated up to 8 fractions with a minimum dose of 5 Gy per fraction were included. All patients were treated with MRgSBRT on 0.35 T MR Linac units. Simulation protocols, and total dose and fractionation schedules were at the discretion of the treating institution. The dose was prescribed to PTV to ensure the required coverage of the PTV with the 95 % isodose line. The response evaluation included clinical and radiological (CT scan, MRI, or PET/CT) evaluations as well as toxicity scoring at each visit according to each institutional practice. Details of adaptive MRgSBRT procedures have been reported previously [9,17]. Organ-at-risk (OAR) dose constraints were set according to the institutional protocols or international guidelines. The BED was calculated due to heterogeneous dose prescription patterns and fractionation schedules; an α/β ratio of 10 Gy was assumed for the adrenal metastases.

Tumor responses were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [21]. Acute toxicity was defined as toxicity occurring up to 90 days post-MRgSBRT and late toxicity as occurring after more than 90 days after treatment. Radiation-related toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Descriptive statistics were used to describe demographic, clinical, and treatment-related characteristics. The start date for the time-to-event analysis was defined as the first day of MRgSBRT treatment. Treatment response to adrenal MRgSBRT was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). LC was defined as no progressive disease (CR, PR, or SD) of the treated adrenal metastasis. OS was calculated from the first date of MRgSBRT to the day of last follow-up or death. Time from the MRgSBRT to the in-field progression was defined as local progression-free survival (LPFS) and out of field progression was defined as distant progression-free survival (DPFS). LPFS, DPFS, and OS were estimated using Kaplan-Meier method and log-rank test. OS and DPFS were calculated on a per-patient basis, while LC and LPFS were calculated on a per-lesion basis. Univariate analysis was performed with the log-rank test, and Cox proportional hazards regression was used to estimate hazard ratios (HR). Multivariate Cox regression analysis was performed to evaluate the association between clinical factors and survival for the variables. Variables which were determined to have a potential effect on results with a p value < 0.15 were entered into multivariable models. A p-value below 0.05 was accepted as statistically significant. Data analysis was performed using SPSS version 23.0 (IBM, Armonk, USA).

Results

A total of 255 patients treated to 269 adrenal tumors between 2016 and 2022 with MRgSBRT were included in this retrospective multi-institutional study. Forty patients were excluded due to lack of follow-up or response evaluation data. Baseline patient characteristics are summarized in Table 1. The median patient age at the start of treatment was 65 years (range, 28–91 years) and 66.3 % were male. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0–1 in 83.9 % of patients. The most common primary tumor was lung cancer (68.6 %), followed by genitourinary system tumors (9.9 %). Adrenal metastases were synchronous, metachronous, oligoprogressive or oligopersistent in 19.2 %, 41.6 %, 35.3 %, and 3.9 % of patients, respectively. Metastatic pattern was solitary in 25.9 % and oligometastatic in 58.0 % of patients. Metastases were right sided in 41.6 %, left sided in 52.9 %, and bilateral in 5.5 % of patients. Patients with bilateral adrenal metastases were treated synchronously except one patient who had a treatment interval of 8 months. The primary tumor was definitively treated in 84.3 % of patients, and chemotherapy and immunotherapy were administered in 66.7 % and 61.1 % of patients, respectively. Of nine patients (3.5 %) tumor-induced symptoms were reported before MRgSBRT initiation, of which palliation of symptoms were described in

Table 1
Baseline patient characteristics.

Characteristics (255 patients)	Number (%)
Median age (at the start of MRgSBRT)	65 (range, 28–91 years)
Gender	
Male	169 (66.3 %)
Female	86 (33.7 %)
Performance score (ECOG)	
0	93 (36.5 %)
1	121 (47.5 %)
2	37 (14.5 %)
3	4 (1.5 %)
Primary tumor	
Lung	175 (68.6 %)
Genitourinary	25 (9.8 %)
Gastrointestinal	14 (5.5 %)
Hepatobiliary	13 (5.1 %)
Melanoma	11 (4.3 %)
Gynecological	5 (2.0 %)
Other	12 (4.7 %)
Tumor laterality	
Right	107 (42.0 %)
Left	136 (53.3 %)
Bilateral	12 (4.7 %)
Timing of metastases	
Synchronous	49 (19.2 %)
Metachronous	106 (41.6 %)
Oligoprogressive	90 (35.3 %)
Oligopersistent	10 (3.9 %)
Metastatic pattern	
Solitary	66 (25.9 %)
Oligometastatic	148 (58.0 %)
Multiple	41 (16.1 %)
Primary tumor definitively treated	
Yes	215 (84.3 %)
No	37 (14.5 %)
Unknown	3 (1.2 %)
Systemic chemotherapy	
3 months before MRgSBRT	102 (40.0 %)
3 months after MRgSBRT	19 (7.5 %)
Concurrent	24 (9.4 %)
None	85 (33.3 %)
Others	25 (9.8 %)
Immunotherapy	
3 months before MRgSBRT	59 (23.1 %)
3 months after MRgSBRT	36 (14.1 %)
Concurrent	39 (15.3 %)
None	92 (36.1 %)
Others	29 (11.4 %)

Table 2
MRgSBRT tumor and treatment planning characteristics.

Characteristics (269 lesions)	Number (%)
Median gross tumor (GTV) volume	22.0 cc (range, 1.1–383.2 cc)
Median planning target (PTV) volume	37.1 cc (range, 2.9–516.9 cc)
Median PTV margin	3 mm (range, 3–6 mm)
3 mm	240 (89.2 %)
4 mm	2 (0.7 %)
5 mm	25 (9.3 %)
6 mm	2 (0.7 %)
Median total dose	45 Gy (range, 16–60 Gy)
<45 Gy	118 (43.8 %)
≥45 Gy	151 (56.2 %)
Median fraction number	5 fractions (range, 1–8)
Single fraction	12 (4.5 %)
<5	51 (18.9 %)
≥5	206 (76.6 %)
Median fraction dose	10 Gy (range, 5–24 Gy)
<10 Gy	87 (32.3 %)
≥10 Gy	182 (67.7 %)
Median BED_{10} (Biologically Effective Dose 10)	100 Gy (range, 37.5–132 Gy)
<100 Gy	124 (46.1 %)
≥100 Gy	145 (53.9 %)
Median PTV conformity index (CI)	1.02 (IQR, 0.95–1.11)
Median PTV homogeneity index (HI)	1.23 (IQR, 1.17–1.30)
Adapted fractions	1052/1203 fractions (87.4 %)
Respiratory motion management	
Breath hold	266 (98.9 %)
Free breathing	3 (1.1 %)
Median tracking boundary	3 mm (range, 2–5 mm)
2	1 (0.4 %)
3	264 (98.1 %)
4	1 (0.4 %)
5	3 (1.1 %)

eight patients (89 %).

Median GTV was 22.0 cc (range, 1.1–383.2 cc) and median PTV was 37.1 cc (range, 2.9–516.9 cc). Median PTV margin was 3 mm (range, 3–6 mm), 29 lesions (10.8 %) were treated with a margin greater than 3 mm. Median total dose was 45 Gy (range, 16–60 Gy), median fraction number was 5 (range, 1–8) and median fractional dose used was 10 Gy (range, 5–24 Gy). Twelve patients (4.7 %) were treated with single fraction MRgSBRT (fraction dose range, 16–24 Gy). Median BED_{10} was 100 Gy (range, 37.5–132.0 Gy). Twenty-five patients (9.3 %) were treated with a $BED_{10} > 100$ Gy. The median PTV CI and HI were 1.02 (IQR, 0.95–1.11) and 1.23 (IQR, 1.17–1.30), respectively. A total of 1203 fractions of MRgSBRT were delivered, with 87.4 % of fractions (n = 1052) using on-table adapted plans **based on the individual clinicians' judgement.** Breath hold was used for respiratory motion management in majority of patients (98.9 %). Median tracking boundary was 3 mm (range, 2–5 mm) and 98.1 % of lesions were treated with a 3 mm boundary. Patients were treated on consecutive days (26.7 %), every other day (68.6 %) or with single fraction (4.7 %). MRgSBRT tumor and treatment planning details are summarized in Table 2.

At a median follow-up of 17.7 months (range, 0.4–72.6 months), local responses were scored as CR, PR, SD, or PD in 35.5 %, 30.2 %, 25.0 %, and 9.3 %, respectively.

Median OS was 30.4 months (95 % CI 22.7–38.0 months), with 1- and 2- year OS rates of 74.1 % (95 % CI 67.8–80.4 %) and 56.3 % (95 % CI 48.3–64.3 %), respectively (Fig. 1**a**). On univariate analysis, ECOG of 0–1 ($p < 0.0001$, HR 0.39, 95 % CI 0.25–0.61) and achieving a CR ($p < 0.0001$, HR 0.42, 95 % CI 0.26–0.67) were significant prognostic factors for increased OS. This correlation remained statistically significant for ECOG score ($p < 0.0001$, HR 0.43, 95 % CI 0.27–0.68) and patients achieving a CR ($p < 0.0001$, HR 0.42, 95 % CI 0.26–0.68) on multivariate analysis. On multivariate analysis gender was a significant prognostic factor and female gender had a worse OS ($p = 0.04$, HR 1.57, 95 % CI 1.02–2.41).

Median LPFS was not reached and the 1- and 2- year LPFS rates were 94.0 % (95 % CI 90.7–97.3 %) and 88.3 % (95 % CI 82.4–94.2 %), respectively (Fig. 1**b**). Patients whose primary tumor were definitively treated had better LPFS in multivariate analysis ($p = 0.004$, HR 1.96, 95 % CI 1.33–3.09). For LPFS, comparison between immunotherapy groups (none, concurrent, 3 months before MRgSBRT, 3 months after MRgSBRT or others) the difference was statistically significant ($p = 0.004$, HR 1.73, 95 % CI 1.19–2.51). Patients in whom lesions were treated with a PTV CI of ≥ 0.90 ($p = 0.016$, HR 2.70, 95 % CI 1.21–6.08) was associated with improved LPFS on univariate analysis. On multivariate analysis, significant findings were (i) patients whose primary tumors were definitively treated ($p = 0.017$, HR 3.44, 95 % CI 1.25–9.43) and (ii) a PTV CI of < 0.90 ($p = 0.024$, HR 2.58, 95 % CI 1.13–5.87). Although not statistically significant, no local recurrences were observed after treatment to a total dose of $BED_{10} > 100$ (24 lesions), with single fraction (range, 16–24 Gy, 12 lesions) or fractional dose of > 10 Gy (50 lesions).

Median DPFS was 7.9 months (95 % CI 5.7–10.0 months) with a 1- and 2-year DPFS rates of 41.0 % (95 % CI 34.3–47.7 %) and 28.4 % (95 % CI 21.5–35.3 %), respectively (Fig. 1**c**). For DPFS, the comparison between chemotherapy groups (none, concurrent, 3 months before MRgSBRT, 3 months after MRgSBRT or others) was statistically significant ($p = 0.003$, HR 1.19, 95 % CI 1.06–1.33) on univariate analysis. Patients receiving chemotherapy concurrently had the worst DPFS rates. Achieving a CR improved DPFS significantly on univariate analysis ($p < 0.0001$, HR 0.46, 95 % CI 0.32–0.65). Chemotherapy groups and

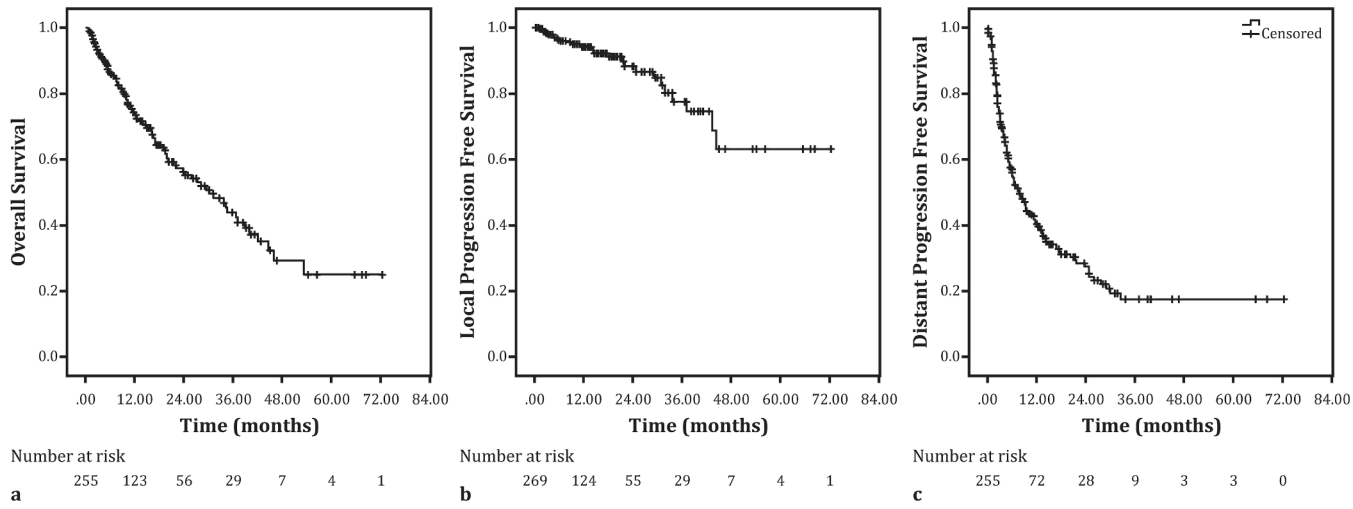

Fig. 1. Kaplan-Meier curves for **a)** overall survival, **b)** local progression free survival, **c)** distant progression free survival.

achieving a CR remained significant on multivariate analysis with p values of 0.003 (HR 1.49, 95 % CI 1.14–1.93) and < 0.0001 (HR 0.45, 95 % CI 0.32–0.65), respectively. Univariate and multivariate analysis detailed results are shown in Table 4.

Only 2 patients (0.8 %) had ≥ grade 3 late toxicity, one was adrenal insufficiency in a patient with prior contralateral SBRT who was treated with a dose of 40 Gy in 5 fractions and the other was a vertebral insufficiency fracture 5 months after MRgSBRT of 50 Gy in 5 fractions. The detailed toxicities are summarized in Table 3.

Discussion

This multi-institutional pooled retrospective analysis of adrenal MRgSBRT with daily online adaptation in the majority of patients revealed 1-year and 2-year LPFS rates of 94 % and 88.3 %, respectively. A median dose delivered was a BED_{10} of 100 Gy, and progressive disease was noted in just 9.3 % of lesions. To our knowledge, this study is the largest series evaluating outcomes of MRgSBRT for adrenal metastases.

A strength of the present analysis was inclusion of patients from 11 institutions, using a range of delivered doses. A previous systematic review and pooled *meta*-analysis of SBRT for adrenal metastases in 1036 patients had demonstrated a significant and positive correlation between the dose of SBRT and the LC rates at 1- and 2-years ($p < 0.0001$, $p = 0.0002$), as well as a correlation with the 2-year OS ($p = 0.03$)[22]. Prescribed doses exceeding 60, 80, and 100 Gy (BED_{10}) resulted in an improved local control in the higher-dose groups and the overall rate of grade 3 or higher toxicity was 1.8 % [22]. In the present study, 65.4 % of patients received a $BED_{10} \geq 80$ Gy and 53.9 % received $BED_{10} \geq 100$ Gy. Although we did not find a correlation between higher BED_{10} doses and improved LC, local recurrences were not observed after treatment to a total dose of BED10 > 100, as was SBRT delivered in a single fraction or using a fraction dose of > 10 Gy.

Frequent changes in OAR position can occur during MRgSBRT, and dosimetric advantages have been shown for online plan of adaptation to take such changes into account [17]. In the present study, 87 % of all SBRT fractions were treated using on-table adapted plans. This approach could lead to decreases in PTV coverage. Our analysis revealed that a PTV CI of ≥ 0.90 was associated with an improved LPFS on both univariate and multivariate analysis. Previous studies found that compromises in delivered PTV doses are common in adrenal SABR due to the proximity of critical normal organs. For example, it was reported that the coverage compromise index (CCI, defined as D99/prescription dose) was lower for adrenal metastases as compared to bone, liver, and lung metastases, in patients treated in both the SABR-COMET and SABR 5 trials [23,24]. A single institutional experience with adrenal MRgRT revealed that the CCI exceeding 0.90 in just 48 % of all cases, no differences in dose-related LC rates were seen using a BED_{10} 80 or 100 Gy[19].

Results of selected studies of SBRT for adrenal gland metastases have been summarized in Table 5. Previous studies have suggested that MRgSBRT is effective for adrenal metastases, delivering a higher median BED_{10} doses, and with better 1-year LC rates and comparable late toxicity rates. The low incidence of grade 3 or worse late toxicity of 0.8 % after MRgRT contrasts with the reported outcomes after adrenalectomy for adrenal metastasis [5,6,25]. Similarly, microwave and radiofrequency ablation have been used for the treatment of adrenal metastases, the pooled rates of treatment-related failure or toxicity ranging from 44 to 48 % and 6.6–8 %, respectively. A single center evaluation of treatment patterns for adrenal metastases during a 10-year period using either surgery (43 patients) or SBRT (54 patients) concluded that both treatments resulted in low rates of acute toxicity and similar survivals, but 1-year LC rates were higher for MRgSBRT (96 %) compared to 74 % for surgery ($p = 0.003$) [14].

Some limitations of our study include its retrospective nature and the heterogeneity of the cohort in terms of primary tumors and SBRT doses.. Additionally, longer follow-up is necessary to further analyze the prognosis of MRgSBRT.

Table 3
Acute and chronic toxicity scores (CTCAE v5.0).

Acute toxicity	Patient number (%)
Fatigue	5 (1.9) Grade I; 6 (2.2) Grade II
Gastrointestinal	7 (2.6) Grade I; 4 (1.5) Grade II
Abdominal pain	1 (0.4) Grade I
Anorexia	2 (0.7) Grade I; 1 (0.4) Grade 1
Chronic toxicity	
Fatigue	3 (1.1) Grade I
Adrenal insufficiency	3 (1.1) Grade II; 1 (0.4) Grade III
Other (vertebral fracture)	1 (0.4) Grade III

Conclusion

This pooled retrospective analysis of MRgSBRT in 269 lesions revealed a 2- year LPFS rate of 88 %, and that tumors treated with PTV CI of ≥ 0.90 had an improved LPFS. Although not statistically significant, outcomes analysis in 269 adrenal lesions revealed improved

Table 4
Univariate and multivariate analysis.

	Overall survival (OS)					
	Univariate analysis			Multivariate analysis		
	HR	95 % CI	P value	HR	95 % CI	P value
Age (≤65 years vs > 65 years)	1.17	0.78–1.75	0.452	–	–	–
Gender	1.40	0.92–2.14	0.117	1.57	1.02–2.41	0.04
ECOG PS (0–1 vs 2–3)	0.39	0.25–0.61	p < 0.0001	0.43	0.27–0.68	p < 0.0001
Primary (lung vs others)	0.81	0.51–1.29	0.376	–	–	–
Laterality	0.88	0.62–1.24	0.460	–	–	–
Timing of metastases	0.99	0.77–1.27	0.941	–	–	–
Metastatic pattern	1.19	0.84–1.68	0.322	–	–	–
Primary treated	1.22	0.17–8.78	0.845	–	–	–
Systemic chemotherapy	1.25	0.87–1.81	0.225	–	–	–
Systemic immunotherapy	0.83	0.62–1.11	0.204	–	–	–
	Local Progession Free survival (LPFS)					
	Univariate analysis			**Multivariate analysis**		
	HR	**95 % CI**	**P value**	**HR**	**95 % CI**	**P value**
Age (≤65 years vs > 65 years)	0.93	0.42–2.06	0.864	–	–	–
Gender	0.66	0.25–1.78	0.413	–	–	–
ECOG PS (0–1 vs 2–3)	0.99	0.55–1.79	0.969	–	–	–
Primary (lung vs others)	0.97	0.40–2.31	0.936	–	–	–
Laterality	0.89	0.46–1.75	0.752	–	–	–
Timing of metastases	0.81	0.50–1.33	0.409	–	–	–
Metastatic pattern	1.65	0.83–3.28	0.157	1.17	0.57–2.40	0.676
Primary treated	1.96	1.33–3.09	0.004	3.44	1.25–9.43	0.017
Systemic chemotherapy	1.09	0.83–1.44	0.542	–	–	–
Systemic immunotherapy	1.73	1.19–2.51	0.004	1.20	0.91–4.57	0.196
PTV volume (<37.1 cc vs ≥ 37.1 cc)	1.58	0.71–3.51	0.262	–	–	–
GTV volume (<22 cc vs ≥ 22 cc)	1.38	0.62–3.07	0.425	–	–	–
Median dose (<45 Gy vs ≥ 45 Gy)	0.95	0.40–2.24	0.910	–	–	–
Fraction dose (<10 Gy vs ≥ 10 Gy)	0.04	0.00–13.40	0276	–	–	–
BED_{10} (<100 Gy vs ≥ 100 Gy)	1.01	0.43–2.39	0.974	–	–	–
PTV CI (<0.90 vs ≥ 0.90)	2.70	1.21–6.08	0.016	2.58	1.13–5.87	0.024
	Distant Progession Free survival (DPFS)					
	Univariate analysis			**Multivariate analysis**		
	HR	**95 % CI**	**P value**	**HR**	**95 % CI**	**P value**
Age (≤65 years vs > 65 years)	0.76	0.55–1.04	0.086	–	–	–
Gender	1.18	0.85–1.64	0.324	–	–	–
ECOG PS (0–1 vs 2–3)	0.89	0.58–1.36	0.591	–	–	–
Primary (lung vs others)	0.75	0.53–1.06	0.103	0.85	0.59–1.21	0.360
Laterality	0.84	0.64–1.10	0.208	–	–	–
Timing of metastases	1.02	0.84–1.24	0.819	–	–	–
Metastatic pattern	1.23	0.96–1.58	0.104	1.21	0.97–1.58	0.910
Primary treated	0.92	0.58–1.44	0.703	–	–	–
Local control (CR vs others)	0.46	0.32–0.65	p < 0.0001	0.45	0.32–0.65	p < 0.0001
Systemic chemotherapy	1.19	1.06–1.33	0.003	1.49	1.19–1.07	0.002
Systemic immunotherapy	1.04	0.93–1.16	0.521	–	–	–

ECOG Eastern Cooperative Oncology Group, BED biological effective dose.

Table 5
Summary of selected cited studies of SBRT in adrenal gland metastases.

Study	Lesion number	IGRT method	BED10	Median Follow-up	Local control	Overall survival	Grade 3 + toxicity
Buergy D, 2021 [26]	260	CBCT	60.3 (38.3–102.7)	11.7 months	1-year 80.8 %	1-year 67.1 %	0.4 %
Franzese C, 2021 [27]	149	CBCT	78.75 (20–120.0)	14.4 months	1-year 85.4 %	1-year 72.3 %	0.7 %
Zhao X, 2020 [28]	84	Cyberknife	79.6 (44.8–112.5)	12.7 months	1-year 83.8 %	1-year 62.5 %	2.6 %
Michalet M, 2022 [13]	13	MR-guided	75.6 (59.5–100.0)	15.5 months	1-year 100 %	1-year 91.7 %	0 %
Schneiders FL, 2023 [19]	114	MR-guided	≥100 Gy 67.5 %	13.8 months	1-year 98.5 %	1-year 67.8 %	1.8 %
Current study	269	MR-guided	100 (37.5–132.0)	17.7 months	1-year 94 %	1-year 74.1 %	0.8 %

outcomes with delivery of a BED10 > 100, use of single fraction SBRT (range between 16 and 24 Gy) and with fraction doses > 10 Gy, providing benchmarks for future clinical trials with more patients and longer follow-up, suggesting that techniques such as adaptive MRgSBRT may be beneficial as they facilitate delivery of such doses.

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CRediT authorship contribution statement

Gamze Ugurluer: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Famke L. Schneiders:** Data curation, Investigation, Methodology, Project administration. **Stefanie Corradini:** Data curation, Investigation, Methodology, Project

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Data availability:

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

References

[1] Lam KY, Lo CY. Metastatic tumours of the adrenal glands: a 30-year experience in a teaching hospital. Clin Endocrinol (oxf) 2002;56(1):95–101.
[2] Mao JJ, Dages KN, Suresh M, Bancos I. Presentation, disease progression and outcomes of adrenal gland metastases. Clin Endocrinol (oxf) 2020;93(5):546–54.
[3] Barresi RV, Prinz RA. Laparoscopic adrenalectomy. Arch Surg 1999;134(2):212–7.
[4] Shiue K, Song A, Teh BS, Ellis RJ, Yao M, Mayr NA, et al. Stereotactic body radiation therapy for metastasis to the adrenal glands. Expert Rev Anticancer Ther 2012;12(12):1613–20.
[5] Gunjur A, Duong C, Ball D, Siva S. Surgical and ablative therapies for the management of adrenal 'oligometastases' - a systematic review. Cancer Treat Rev 2014;40(7):838–46.
[6] Fouche D, Chenais G, Haissaguerre M, Bouriez D, Gronnier C, Collet D, et al. Risk factors for intraoperative complications, postoperative complications, and prolonged length of stay after laparoscopic adrenalectomy by transperitoneal lateral approach: a retrospective cohort study of 547 procedures. Surg Endosc 2023;37(10):7573–81.
[7] Singh AK, Tierney RM, Low DA, Parikh PJ, Myerson RJ, Deasy JO, et al. A prospective study of differences in duodenum compared to remaining small bowel motion between radiation treatments: implications for radiation dose escalation in carcinoma of the pancreas. Radiat Oncol 2006;1:33.
[8] Liu F, Erickson B, Peng C, Li XA. Characterization and management of interfractional anatomic changes for pancreatic cancer radiotherapy. Int J Radiat Oncol Biol Phys 2012;83(3):e423–9.
[9] Sahin B, Zoto Mustafayev T, Gungor G, Aydin G, Yapici B, Atalar B, et al. First 500 fractions delivered with a magnetic resonance-guided radiotherapy system: initial experience. Cureus 2019;11(12):e6457.
[10] Rodriguez LL, Kotecha R, Tom MC, Chuong MD, Contreras JA, Romaguera T, et al. CT-guided versus MR-guided radiotherapy: impact on gastrointestinal sparing in adrenal stereotactic body radiotherapy. Radiother Oncol 2022;166:101–9.
[11] Giraud N, Schneiders FL, van Sornsen de Koste JR, Palacios MA, Senan S. Tumor volume changes during stereotactic ablative radiotherapy for adrenal gland metastases under MRI guidance. Radiother Oncol 2023;186:109749.
[12] Hoegen P, Katsigiannopulos E, Buchele C, Regnery S, Weykamp F, Sandrini E, et al. Stereotactic magnetic resonance-guided online adaptive radiotherapy of adrenal metastases combines high ablative doses with optimized sparing of organs at risk. Clin Transl Radiat Oncol 2023;39:100567.
[13] Michalet M, Bettaieb O, Khalfi S, Ghorbel A, Valdenaire S, Debuire P, et al. Stereotactic MR-guided radiotherapy for adrenal gland metastases: first clinical results. J Clin Med 2022;12(1).
[14] van Vliet C, Dickhoff C, Bahce I, Engelsman AF, Hashemi SMS, Haasbeek CJA, et al. Treatment patterns for adrenal metastases using surgery and SABR during a 10-year period. Radiother Oncol 2022;170:165–8.
[15] van Sornsen de Koste JR, van Vliet CC, Schneiders FL, Bruynzeel AME, Slotman BJ, Palacios MA, et al. Renal atrophy following gated delivery of stereotactic ablative radiotherapy to adrenal metastases. phys imaging. Radiat Oncol 2021;20:1–4.
[16] van Sornsen de Koste JR, Palacios MA, Chen H, Schneiders FL, Bruynzeel AME, Slotman BJ, et al. Changes in gastric anatomy after delivery of breath-hold MR-guided SABR for adrenal metastases. Radiother Oncol 2020;152:26–9.
[17] Palacios MA, Bohoudi O, Bruynzeel AME, van Sorsen de Koste JR, Cobussen P/, Slotman BJ, et al. Role of daily plan adaptation in MR-guided stereotactic ablative radiation therapy for adrenal metastases. Int J Radiat Oncol Biol Phys 2018;102(2):426–33.
[18] Chen H, Schneiders FL, Bruynzeel AME, Lagerwaard FJ, van Sornsen de Koste JR, Cobussen P, et al. Impact of daily plan adaptation on organ-at-risk normal tissue complication probability for adrenal lesions undergoing stereotactic ablative radiation therapy. Radiother Oncol 2021;163:14–20.
[19] Schneiders FL, van Vliet C, Giraud N, Bruynzeel AME, Slotman BJ, Palacios MA, et al. Clinical outcomes of MR-guided adrenal stereotactic ablative radiotherapy with preferential sparing of organs at risk. Clin Transl Radiat Oncol 2023;43:100680.
[20] Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. Radiother Oncol 2020;148:157–66.
[21] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47.
[22] Chen WC, Baal JD, Baal U, Pai J, Gottschalk A, Boreta L, et al. Stereotactic body radiation therapy of adrenal metastases: a pooled meta-analysis and systematic review of 39 studies with 1006 patients. Int J Radiat Oncol Biol Phys 2020;107(1):48–61.
[23] Van Oirschot M, Bergman A, Verbakel W, Ward L, Gagne I, Huang V, et al. Determining planning priorities for SABR for oligometastatic disease: a secondary analysis of the SABR-COMET phase II randomized trial. Int J Radiat Oncol Biol Phys 2022;114(5):1016–21.
[24] Eufemon Cereno R, Mou B, Baker S, Chng N, Arbour G, Bergman A, et al. Should organs at risk (OARs) be prioritized over target volume coverage in stereotactic ablative radiotherapy (SABR) for oligometastases? a secondary analysis of the population-based phase II SABR-5 trial. Radiother Oncol 2023;182:109576.
[25] Goujon A, Schoentgen N, Betari R, Thoulouzan M, Vanalderwerelt V, Oumakhlouf S, et al. Prognostic factors after adrenalectomy for adrenal metastasis. Int Urol Nephrol 2020;52(10):1869–76.
[26] Buergy D, Wurschmidt F, Gkika E, Horner-Rieber J, Knippen S, Gerum S, et al. Stereotactic or conformal radiotherapy for adrenal metastases: patient characteristics and outcomes in a multicenter analysis. Int J Cancer 2021;149(2):358–70.
[27] Franzese C, Nicosia L, Facondo G, Lo Faro L, Cuccia F, Vullo G, et al. Stereotactic body radiation therapy for adrenal gland metastases: outcome and predictive factors from a multicenter analysis. Clin Exp Metastasis 2021;38(6):511–8.
[28] Zhao X, Zhu X, Zhuang H, Guo X, Song Y, Ju X, et al. Clinical efficacy of stereotactic body radiation therapy (SBRT) for adrenal gland metastases: a multi-center retrospective study from China. Sci Rep 2020;10(1):7836.