

Hypofractionated Radiotherapy for 35 Patients with Adrenal Metastases: A Single-Institution Experience

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Ruizhi Zhao¹ 
Yuchao Ma¹
Siran Yang¹
Qingfeng Liu¹
Yuan Tang¹
Kai Wang¹
Ye Zhang¹
Nan Bi¹
Hongmei Zhang²
Junlin Yi¹
Yexiong Li¹
Jingwei Luo¹
Jianping Xiao¹

¹Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, People's Republic of China; ²Department of Radiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, People's Republic of China

Correspondence: Jianping Xiao; Jingwei Luo
National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, People's Republic of China
Tel +86-10-87788281;
+86-10-87788288
Fax +86-10-67706153
Email jpxiao8@163.com; jingwei-luo@outlook.com

Objective: To investigate the clinical outcomes of hypofractionated radiotherapy for adrenal metastases.

Materials and Methods: We retrospectively reviewed patients diagnosed with adrenal metastases and treated with hypofractionated radiotherapy, who did not receive adrenalectomy or have disease progression after chemotherapy, from 2007 to 2019. The Kaplan–Meier method was used to estimate local control rate (LCR), progression-free survival (PFS), and overall survival (OS). Univariate analysis was performed using Log rank test.

Results: Thirty-five patients with 42 lesions were enrolled, and the lung was the most common primary site (80.0%). The median follow-up time was 46.4 months. The median volume of GTV and PTV was 23.2 cm³ (range: 3.5–97.8 cm³) and 38.3 cm³ (range: 10.2–135.6 cm³), respectively. The main dose regimens were 60 Gy delivered in 4–15 fractions, with the median dose of PTV being 60 Gy (range: 40–66.3 Gy) and the biologically effective dose (BED) being 84 Gy (range: 56–110 Gy). The 1-year and 2-year LCR, OS, and PFS were 92.7% and 88.1%, 76.9% and 45.4%, and 25.1% and 14.4%, respectively. Univariate analysis showed that chemotherapy, disease-free interval from primary disease diagnosis to adrenal metastases diagnosis, and age were significant factors for LCR, OS, and PFS, respectively ($p=0.017$, 0.049 , and 0.004 , respectively). No more than grade III toxicities were observed.

Conclusion: As a non-invasive approach, hypofractionated radiotherapy is safe and effective for metastatic adrenal lesions, without serious complications.

Keywords: adrenal metastases, hypofractionated radiotherapy, prognosis, toxicities

Introduction

Adrenal gland is a common metastatic site of primary cancers owing to rich blood sinus. The most common primary sites are lung, stomach, esophagus, and melanoma.¹ Typically, most patients are asymptomatic. With advancements in diagnostic imaging, percutaneous biopsy, and fine-needle aspiration, the detection rate of adrenal metastases has increased.^{1,2} Adrenalectomy is considered the standard curative treatment in case of solitary metastasis. However, adrenalectomy is reserved for patients who met strict criteria, including well-controlled primary disease, solitary adrenal metastasis, without co-metastatic lesions in other organs, and good performance status.² Therefore, more alternative approaches are required.

Radiotherapy is a non-invasive treatment and has been widely used to treat malignant tumors. However, traditional radiotherapy has been of limited use in

metastatic adrenal disease because of the tolerance dose of organs at risk. Hypofractionated radiotherapy can deliver a higher biological equivalent dose to tumor targets than traditional radiotherapy, and has hence been used in many metastatic sites such as lung and liver^{3,4} with satisfying clinical outcomes. Thus far, except a Phase II, prospective stereotactic ablative body radiotherapy (SABR)-COMET study, most studies regarding adrenal metastases are retrospective analyses; the SABR-COMET trial demonstrated a survival benefit with SABR for all metastatic lesions, including adrenal gland, in various primary cancers.⁵

In our single-institution study, we aimed to analyze the clinical effects, failure patterns, and toxicities of hypofractionated radiotherapy for adrenal metastases.

Materials and Methods

Inclusion Criteria

Patients aged ≥ 18 years with pathologically confirmed primary tumor and adrenal metastatic disease were included. All patients had inoperable tumors and/or refused surgery and had experienced failed therapy or were intolerant to systemic therapy. All patients had no history of irradiation to the treated sites. The Karnofsky Performance Scale (KPS) was ≥ 80 for all patients. All included patients signed an informed consent form before undergoing hypofractionated radiotherapy.

Radiation Procedures

Patients were positioned supinely with arms crossed over their foreheads and immobilized with a body mask. Four-dimensional enhanced computed tomography (CT) was performed from the carina to the fifth lumbar vertebra with a 3-mm slice thickness. The localization images were transferred to the Pinnacle planning system, version 9.10. Gross tumor volume (GTV) was delineated on 4-dimensional CT simulation images and expanded 3-dimensionally by 3 mm to generate planning target volume (PTV). Meanwhile, organs at risk (OAR) including liver, kidney, intestine, colon, stomach, and spinal cord were delineated. The spinal cord was expanded by 5 mm to obtain the planning organ-at-risk volume (PRV). The main prescribed dose was 60 Gy delivered in 4–15 fractions, and prescribed to the 95% isodose line. For lesions adjacent to vital normal tissues such as gastrointestinal tract, great vessels, and kidney, the GTV was contracted by 3 mm to create a simultaneously integrated boost region (Boost), and the prescribed doses were adjusted

according to the actual dose distribution. Biological equivalent dose (BED) was calculated using the following formula: $BED_{10} = nd[1 + d/(\alpha/\beta)]$, assuming that α/β was 10. The radiation technology included intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and tomotherapy (TOMO). Image-guided radiotherapy (IGRT) was applied during every treatment.

Efficacy Evaluation

An enhanced CT or MRI scan was performed after 2–3 months of radiotherapy and evaluated by clinicians and radiologists together. Tumor lesions were measured in the maximum diameter. Efficacy evaluation was defined as follows: complete response (CR): complete disappearance of the treated lesion; partial response (PR): reduction of the treated lesion by $\geq 30\%$; progressive disease (PD): enlargement of the treated lesion by $\geq 20\%$; and stable disease (SD): not met the definitions of CR, PR, or PD. Thereafter, a follow-up was planned every 3 months, including enhanced CT or MRI scan, complete blood count, biochemical and tumor marker tests. Local control was defined as the time from the beginning of radiotherapy to the progression of treated lesion; progression-free survival (PFS) was defined as time from the beginning of radiotherapy to progression of the treated lesion, new metastases to the adrenal gland, or other organs; and overall survival (OS) was defined as time from the beginning of radiotherapy to death or the end of follow-up. Failure patterns were recorded including the progression of treated lesion or primary disease and new metastases to the adrenal or other organs. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTC AE, Version 4.0).

Statistical Analysis

Data analyses were performed using SPSS, version 20.0. The Kaplan–Meier method was used to estimate median LCR, PFS, and OS. Univariate analysis was performed using Log rank test. For variables with more than two categories, Log rank test was used for the overall test, followed by pairwise comparison with Bonferroni correction to adjust for multiple testing if the overall test is significant. $P < 0.05$ was considered statistically significant.

Results

Clinical Characteristics

From September 2007 to May 2019, 35 patients with adrenal metastases were enrolled. All patients were diagnosed by CT

or MRI. The median KPS was 80, and the median age was 59 years. Median disease-free interval from primary disease diagnosis to adrenal metastases diagnosis (DFI) was 12.6 months. Overall, 22 patients (62.9%) had distant metastases

to other organs, and seven patients received prior target therapy. The clinical characteristics are summarized in [Table 1](#). One patient diagnosed with adrenal metastasis and follow-up results were displayed in [Figure 1](#).

Table 1 Clinical Characteristics and Univariate Analysis of 35 Adrenal Metastatic Patients

	Number (%)	LCR	PFS		OS	
		p value	Median (Month)	p value	Median (Month)	p value
Sex						
Male	26 (74.3)	0.305	3.4	0.955	22.7	0.752
Female	9 (25.7)		3.3		22.4	
Age						
>59 years	19 (54.3)	0.716	11.3	0.004	30.2	0.078
≤59 years	16 (45.7)		2.8		18.7	
Primary tumor						
NSCLC	14 (40)	0.904	5.8	0.242	24.5	0.817
SCLC	14 (40)		2.4		22.7	
Others	7 (20)		3.4		29.3	
Prior chemotherapy						
Yes	22 (62.9)	0.017	2.8	0.244	21.7	0.092
No	13 (37.1)		5.9		–	
Extra-adrenal metastasis						
Yes	22 (62.9)	0.333	3.4	0.776	28.0	0.822
No	13 (37.1)		2.8		22.4	
Sites of the adrenal						
Left	17 (48.6)	0.173	3.3	0.865	29.3	0.081
Right	11 (31.4)		3.5		28.0	
Bilateral	7 (20.0)		2.4		18.7	
Oligometastasis						
Yes	21 (60)	0.922	3.3	0.526	24.5	0.294
No	14 (40)		3.4		10.0	
Type of metastasis						
Synchronous	14 (40.0)	0.846	2.4	0.554	22.4	0.326
Metachronous	21 (60.0)		4.2		29.3	
DFI						
>12.6 months	17 (48.6)	0.575	4.3	0.321	34.0	0.049
≤12.6 months	18 (51.4)		2.4		21.7	
Radiation technology						
IMRT	20 (57.1)	0.120	3.5	0.797	22.4	0.474
VMAT	13 (37.1)		2.7		–	
TOMO	2 (5.7)		2.4		18.7	
4D-CT scan						
Yes	27 (77.1)	0.795	3.3	0.920	22.4	0.389
No	8 (22.9)		3.5		22.7	

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; Other tumors, including two breast cancer, two colorectal cancer, one bladder cancer and two sarcoma; DFI, disease-free interval from primary disease diagnosis to adrenal metastases diagnosis; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; TOMO, tomotherapy; LCR, local control rate; OS, overall survival; PFS, progression-free survival.

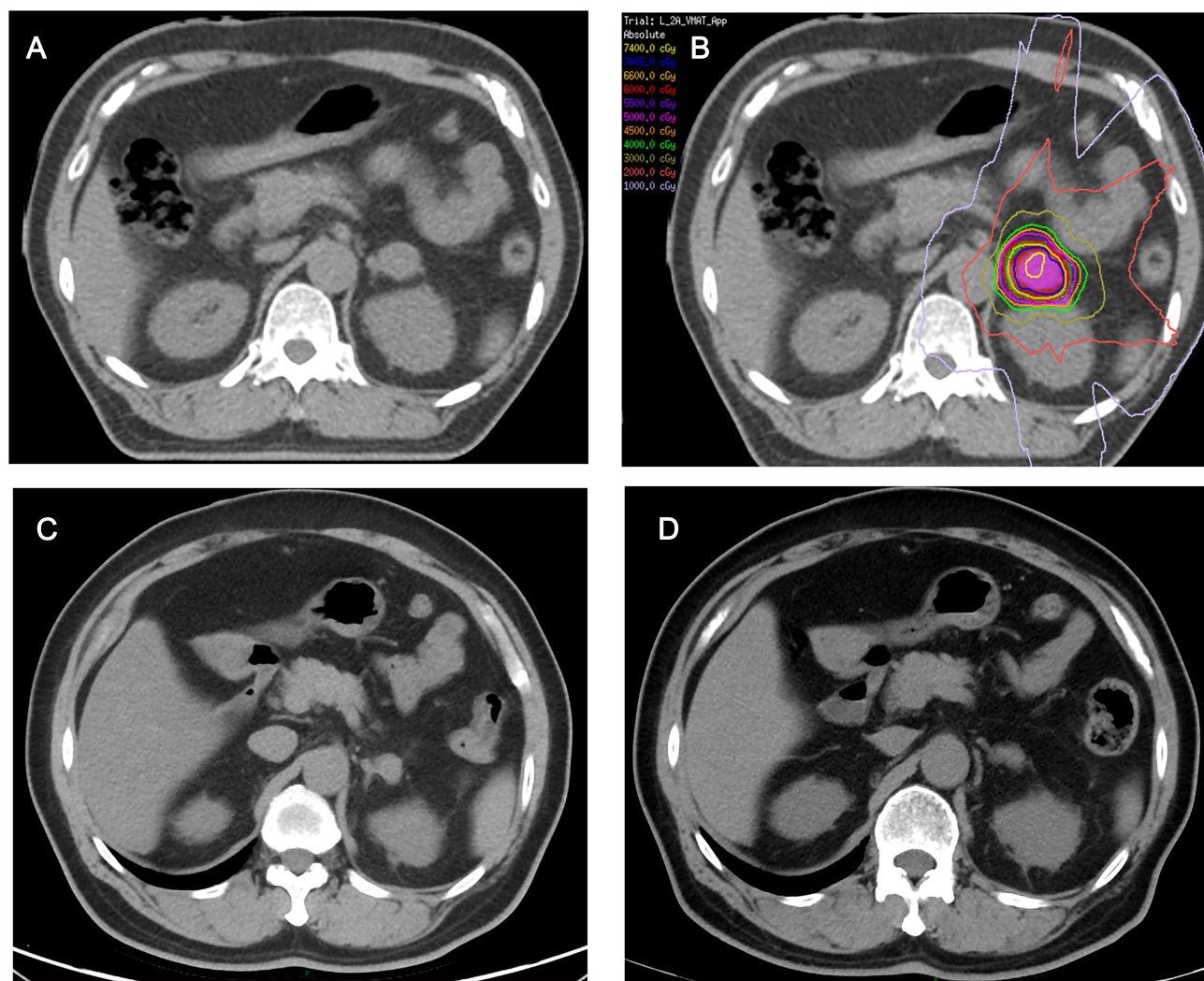


Figure 1 One patient diagnosed with adrenal metastasis (A) originating from synoviosarcoma in the lung received local hypofractionated radiotherapy from March 2018 to April 2018. A total dose of 60 Gy in 15 fractions was delivered to PTV, 66 Gy to GTV, and 70 Gy to the simultaneously integrated Boost region. The dose distribution is shown in (B). The patient has been regularly followed-up. The one-year CT scan in March 2019 and 2-year CT scan in June 2020 are displayed in (C and D), respectively. No disease progression or severe toxicities were recorded.

Clinical Results

In all, 42 lesions were treated. The largest diameter was 2.9 cm (range: 1.3–4.6 cm). The median volume of GTV and PTV were 23.2 cm³ (range: 3.5–97.8 cm³) and 38.3 cm³ (range: 10.2–135.6 cm³), respectively. Dose regimens included 60 Gy in 15 fractions (40.0%), 60 Gy in 12 fractions (14.3%), and 60 Gy in 20 fractions (28.6%). The median dose of PTV and BED₁₀ was 60 Gy (range: 40–66.3 Gy) and 84 Gy (range: 56–110 Gy). Twenty-three lesions had Boost regions. The median volume of Boost was 10.5 cm³ (range: 1.5–33.2 cm³), and the median dose was 69 Gy (range: 52.5–75 Gy). The dosimetric characteristics are shown in Table 2.

At the end of follow-up, three cases showed progression from treated lesions, and the local control duration was 17.0

months, 14.9 months, and 1.1 months, respectively. The first patient received another round of radiotherapy at a local hospital with unclear treatment information, the second patient received atezolizumab and ipilimumab for 8 weeks, and the last patient who was diagnosed with lung sarcomatoid carcinoma with synchronous metastasis, died with a short time. The proportions of CR, PR, SD, and PD were 42.9%, 25.7%, 28.6%, and 2.9%, respectively. The 1- and 2-year LCR were 92.7% and 88.1%, respectively. The median local control time could not be calculated because of limited progression events of treated lesions. The results of the univariate analysis are listed in Tables 1 and 2. Prior chemotherapy was a significant factor for LCR ($p=0.017$). The 1- and 2-year OS and PFS were 76.9% and 45.4%, and 25.1% and 14.4%, respectively. The median survival time

Table 2 The Dosimetric Characteristics of 42 Lesions and Univariate Analysis of LCR

	Lesions (%)	LCR
		p value
Volume of GTV ≥23.2 cm ³ <23.2 cm ³	21 (50) 21 (50)	0.706
Volume of PTV ≥38.3 cm ³ <38.3 cm ³	21 (50) 21 (50)	0.706
Prescribed dose ≥60 Gy <60 Gy	32 (71.2) 10 (23.8)	0.884
BED ₁₀ ≥84 Gy <84 Gy	23 (54.8) 19 (45.2)	0.894
Boost Yes No	23 (54.8) 19 (45.2)	0.797

Abbreviations: LCR, local control rate; GTV, gross tumor volume; PTV, planning target volume; BED₁₀, biological equivalent dose (α/β was 10); Boost, simultaneously integrated boost region.

(MST) was 22.7 months, and the median PFS was 3.4 months. Univariate analysis showed that DFI was a significant factor for OS ($p=0.049$), and age for PFS ($p=0.004$). The originally planned multivariate analysis was not performed because of the limited sample size. The survival curves are shown in [Figure 2](#).

Failure Patterns

Thirty-three of 35 patients had progressed finally; three cases had progressed from only primary disease, 22 had progressed from metastasis to other organs, three cases had progressed from both treated lesions and other organs, and five cases had progressed from new metastasis to the contralateral adrenal gland and other organs. Of these progressed patients, eight received systemic therapy, and one received another round of radiotherapy; the remaining patients did not undergo any treatment.

Toxicities

The median V20 of the left and right kidneys were 8.3% (range: 0–63.2%) and 7.3 (range: 0–27.8%), respectively. The median V20 and mean dose of the liver were 2.3% (range: 0–37.8%) and 5.0 Gy (range: 0–17.4 Gy), respectively. The maximum dose of the stomach, intestine, and

colon was 29.2 Gy (range: 5.1–65.9 Gy), 49.4 Gy (range: 0–70.2 Gy), and 29.1 Gy (range: 1.3–65.5 Gy), respectively. The maximum dose of the spinal cord PRV was 26.0 Gy (range: 12.4–49.3 Gy). All patients tolerated the treatment well, as no greater than grade 3 toxicities were observed during follow-up. Overall, 23 of 35 patients died. The reasons for death included systemic failure ($n=17$), progression of primary disease ($n=3$), brain metastasis ($n=2$), and other reasons ($n=1$). No death due to treatment-related toxicities was recorded.

Discussion

Adrenal metastasis is usually associated with poor prognosis.¹ Surgery has been considered a curative treatment for cancers with metastasis to the lung and liver.^{3,4} A meta-analysis regarding adrenalectomy for adrenal metastasis originating from non-small cell lung cancer (NSCLC) showed that the median survival time was 31 months for metachronous metastasis, and 12 months for synchronous metastasis, with a 5-year OS of 25–26%.⁶ Lam¹ summarized that patients with adrenal metastasis undergoing surgical resection had better survival when than those without surgical resection over a 30-year period ($p=0.03$). However, many patients had metastases to other organs concurrently with poor medical conditions, which likely made them unsuitable for adrenalectomy. In our study, 20% patients were diagnosed with bilateral adrenal metastasis, and 62.9% had metastasis to other organs. These patients were not suitable for curative adrenalectomy.

As another effective local treatment, hypofractionated radiotherapy has been increasingly used in adrenal metastasis. Our study showed the 1- and 2-year LCR and OS were 92.7% and 88.1%, and 76.9% and 45.4%, respectively, comparable with previous literature. Several published studies were summarized in [Table 3](#). In the literature,^{5,7–21} studies were mostly retrospective with a small number of patients. The primary disease was multiple including lung, breast, and colorectal cancer. The dose regimens varied with different BED₁₀. The one-year LCR ranged from 55% to 100%, and the 1-year OS, from 44% to 90%. The MST ranged from 7.2 to 41 months, and the median PFS ranged from 3.5 to 12.0 months. SABR-COMET⁵ was a prospective Phase 2 study, aimed to compare SABR with standard therapy for patients with oligometastatic cancers. A dosage of 60 Gy in eight fractions was delivered for adrenal metastases. The MST and PFS in the SABR group were 41 months

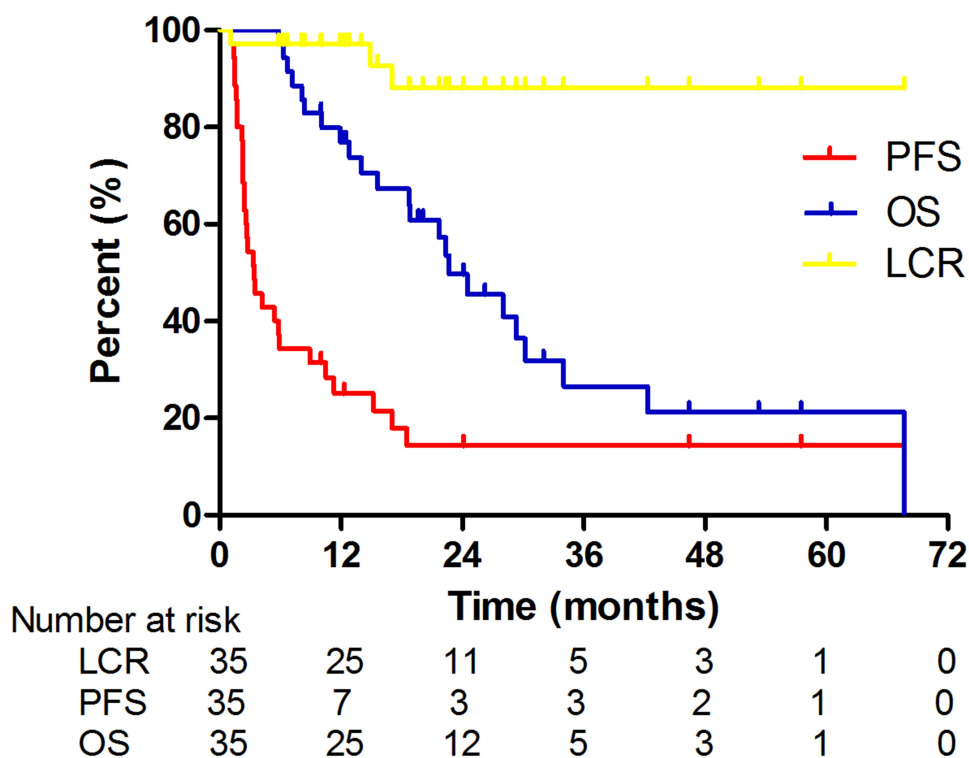


Figure 2 The survival curve of LCR, OS, and PFS in the 35 patients with adrenal metastases by Kaplan–Meier method.

and 12 months, respectively, significantly longer than the standard therapy group.

Our study did not find significant differences between LCR and volume or dose of PTV or between LCR and BED₁₀. The significant factors for LCR differed in published studies. Zhao¹³ reported that BED₁₀ ≥ 85.5 Gy and a volume of GTV < 30 cm³ were correlated with LCR in univariate analysis. König et al²² found a superior local control if BED₁₀ was ≥ 75 Gy or the volume of PTV was < 100 mL, but these findings were not significant. Buergy et al¹² reported that neither lesion size nor radiation dose were significant factors for local control. While the increased dose of adrenal metastases might improve LCR, considering the unique location of the adrenal gland, it would be hard to deliver a higher radiation dose with respect to the surrounding normal organs. Although the SABR-COMET study⁵ reported improved PFS and OS rates, toxicities of > grade 2 had increased from 9% to 29% (p=0.026), and three patients died due to treatment-related causes. Therefore, BED₁₀ of adrenal metastases was often lower than lung or liver metastases.^{3,23} The range of BED varied from 30 Gy⁹ to 151 Gy²² in published studies about adrenal metastasis, and the median BED ranged from 60 Gy²⁴ to 112.5 Gy.¹⁴ In our study, a portion of the lesions was given lower BED to protect

the adjacent vital organs; the median BED was 84 Gy, and hence consistent with other studies.

In the current study, DFI was the unique significant factor for OS (p=0.049). OS was longer if DFI was ≥ 12.6 months, consistent with the study from Howell,²⁵ which reported that DFI < 12 months was associated with worse survival (p=0.038) in surgically resected patients. DFI represents the disease-free interval from primary disease to diagnosis of adrenal metastases, and was different from oligometastatic (OM) or oligoprogressive (OP) disease, which required consideration of more complicated metastatic burden and progression of malignancy. In our study, the MST was 24.5 months in the OM patients and 10.5 months in the OP patients, but without significant statistical differences. Similar survival results were shown in the metachronous or synchronous metastases. Figura et al¹⁵ also showed that there were no significant differences between OS and OM or OP and between metachronous and synchronous metastases. However, Buergy¹² reported that patients with OM had a longer OS (33 months) than those with OP disease (6.5 months). We should note that accurate clinical definitions of OM or OP are still unclear and differ across research studies. Besides, most reports, including the prospective SABR-COMET study, enrolled various primary diseases, which represented different

Table 3 Published Studies About Radiotherapy in the Treatment of Adrenal Metastases

Author	Number	Dose	Primary	LCR	OS	PFS	Toxicities
Chawla, ⁷ 2009	30	16Gy in 4f to 40Gy in 10 f	multiple	1y 55%	1y 44%	–	No ≥grade 2
Holy, ⁸ 2011	18	5 × 4Gy to 5 × 8Gy	NSCLC	21m: 77%	median 4.2m	median 23m	No ≥grade 3
Scorsetti, ⁹ 2012	34	median 32Gy in 4f	multiple	1y 66%	–	median 22m	No ≥grade 3
Casamassima, ²⁶ 2012	48	36 Gy in 3f, SRS	multiple	1y 90%	1y 39.7%	–	One grade 2 adrenal insufficiency
Ahmed, ¹⁰ 2013	13	33.75–60Gy in 5f	multiple	1y 100%	1y 62.9%	–	No ≥grade 3
Rudra S, ²⁴ 2013	10	8–12Gy in 3f, 4–5Gy in 10f	multiple	1y 73%	1y 90%	–	One grade 2 adrenal insufficiency
Li, ¹⁶ 2013	18	median 45Gy in 5f	multiple	1y 77%	median 17m	median 14m	No ≥grade 3
Gamsiz, ¹⁷ 2015	15	30Gy in 3f	NSCLC	16m 86.7%	16m 33.3%	–	No ≥grade 3
Haidenberger, ¹⁸ 2017	23	median 22Gy in 1f, median 40.5Gy in 3f	multiple	1y 95%	1y 77%	–	No report
Celik, ¹⁹ 2017	15	42Gy in 6f	NSCLC	1y 60%	1y 93.3%	1y 60%	No ≥grade 3
Chance, ²⁰ 2017	43	median 60Gy in 10f	multiple	1y 74%	1y 65%	median 6m	No ≥grade 3
Franzese, ¹¹ 2017	46	40Gy in 4f	multiple	1y 65.5%	–	median 28.5m	No ≥grade 3
				2y 40.7%		1y 87.6%	
Toesca, ²¹ 2018	35	median 40Gy in 1–6f	multiple	1y 92.4%	median 19m	–	No ≥grade 3
Buergy, ¹² 2018	18	20–60 Gy in 4–25f	multiple	–	median 11.9m	median 3.1m	No ≥grade 3
Zhao, ¹³ 2018	30	32–50Gy in 3–8f	Lung cancer	1y 96.9%	1y 58.1%	1y 39.5%	one grade 3 diarrhea
Scourneac, ¹⁴ 2019	31	30–55Gy in 3–9 f	multiple	1y 96.5%	median 33.5m	median 7.4m	No ≥grade 3
				2y 92.6%			
Figura, ¹⁵ 2020	41	median 50Gy in 5f	multiple	1y 96%	–	1y 71%	one hypertensive crisis
						2y 51%	
Palma, ⁵ 2019	66	adrenal 60Gy in 8f	multiple	75%	median 12m	median 6m	≥grade 2: 29%, 3 treatment-related deaths

Abbreviations: NSCLC, non-small cell lung cancer; LCR, local control rate; OS, overall survival; PFS, progression-free survival.

prognosis and treatment options. Therefore, the true relationship between survival with metastatic status may require further detailed prospective studies.

Our study showed that age was a significant factor for PFS ($p=0.004$) in the univariate analysis. In the database, there were more cases diagnosed with SCLC (9/16 vs 5/19), more patients with extra-adrenal metastases (13/16 vs 9/19), and fewer cases of oligometastases (7/16 vs 14/19) in the age ≤ 59 years group. These factors might have led to positive results in univariate analysis.

The failure patterns revealed that failure was mainly due to new metastases or progression to other organs. Therefore, subsequent regular imaging examinations for early detection and diagnosis of progression, and timely systemic therapy may be beneficial for metastatic patients.

We did not observe severe toxicities or deaths due to radiotherapy in our study. The previously reported toxicities included nausea, fatigue, diarrhea, and digestive ulcers. Except for the SABR-COMET⁵ study discussed in the previous section, Casamassima²⁶ reported one patient with grade 2 adrenal insufficiency, and Zhao¹³ reported one patient with grade 3 diarrhea. In our study, other approaches to reduce radiation dose to OAR included a 4-dimensional CT scan, a smaller expansion

margin from GTV to PTV, Boost regions, and IGRT to ensure accuracy during every treatment.

Our study has some limitations. First, it was a retrospective study in a single institution, with only 35 patients, similar to other studies with limited sample size. Second, we were unable to carry out multivariate statistical analyses to identify risk factors of local control and survival. Furthermore, adrenal metastases from various primary cancers were included, similar to previous literature. These limitations might influence the results of different therapeutic options. A large-sized randomized control trial should be designed in future to validate these findings.

Conclusions

It is usually difficult to deliver higher radiation doses to adrenal metastases considering surrounding organs at risk. This retrospective study indicates that hypofractionated radiotherapy for adrenal metastases is effective and safe without severe toxicities or treatment-related deaths. More strategies are needed to deliver higher BED with minimal toxicities. Further prospective randomized controlled trials are required to investigate the role of hypofractionated radiotherapy for adrenal metastases.

Abbreviations

GTV, gross tumor volume; PTV, planning target volume; OAR, organs at risk; PRV, planning organ-at-risk volume; BED, biological equivalent dose; Boost, simultaneously integrated boost region; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; TOMO, tomotherapy; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; LCR, local control rate; OS, overall survival; PFS, progression-free survival; MST, median survival time. DFI: disease-free interval from primary disease diagnosis to adrenal metastases diagnosis; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; OM, oligometastatic disease; OP, oligoprogressive disease; IGRT, image-guided radiotherapy.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author (Jianping Xiao) upon request.

Ethics Approval and Consent to Participate

This retrospective research has been reviewed, and approved to publish by the ethics committee of National Cancer Center/National Cancer Clinical Medical Research Center/Chinese Academy of Medical Sciences, Peking Union Medical College, Cancer Hospital, Beijing, China. The consents of all the patients was waived due to the retrospective nature of the review, and all the data were anonymized to maintain confidentiality and in compliance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work.

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