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

Ruizhi Zhao, Yuchao Ma, Siran Yang, Qingfeng Liu, Yuan Tang, Kai Wang, Ye Zhang, Nan Bi, Hongmei Zhang, Junlin Yi, Yexiong Li, Jingwei Luo, Jianping Xiao

Department 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; Department 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

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. Typically, most patients are asymptomatic. With advancements in diagnostic imaging, percutaneous biopsy, and fine-needle aspiration, the detection rate of adrenal metastases has increased. Adrenalectomy is considered the standard curative treatment in case of solitary metastasis. However, adrenalectomy is reserved for patients who meet strict criteria, including well-controlled primary disease, solitary adrenal metastasis, without co-metastatic lesions in other organs, and good performance status. 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\textsuperscript{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.\textsuperscript{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 \(\geq 18\) 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 \(\geq 80\) 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: \(\text{BED}_{10} = nd[1+d/(\alpha/\beta)]\), assuming that \(\alpha/\beta \) 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 p value | Median (Month) | PFS p value | Median (Month) | OS 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.
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 cm$^3$ (range: 3.5–97.8 cm$^3$) and 38.3 cm$^3$ (range: 10.2–135.6 cm$^3$), 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 BED$_{10}$ 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 cm$^3$ (range: 1.5–33.2 cm$^3$), 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

Figure 1 One patient diagnosed with adrenal metastasis (A) originating from synoviosarcoma in the lung received 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.
(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. Surgery has been considered a curative treatment for cancers with metastasis to the lung and liver. 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%. Lam 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, 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-COMET 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.
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 BED$_{10}$. The significant factors for LCR differed in published studies. Zhao$^{13}$ reported that BED$\geq 85.5$ Gy and a volume of GTV$<30$ cm$^3$ were correlated with LCR in univariate analysis. Konig et al$^{22}$ found a superior local control if BED$_{10}$ was $\geq 75$ Gy or the volume of PTV was $< 100$ mL, but these findings were not significant. Buergy et al$^{12}$ also found 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 study$^5$ 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, BED$_{10}$ of adrenal metastases was often lower than lung or liver metastases.$^3,23$ The range of BED varied from 30 Gy$^9$ to 151 Gy$^{-22}$ in published studies about adrenal metastasis, and the median BED ranged from 60 Gy$^{24}$ 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 $\geq 12.6$ 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 oligoproggressive (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 al$^{15}$ also showed that there were no significant differences between OS and OM or OP and between metachronous and synchronous metastases. However, Buergy$^{12}$ 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

**Figure 2** The survival curve of LCR, OS, and PFS in the 35 patients with adrenal metastases by Kaplan–Meier method.
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-COMET study discussed in the previous section, Casamassima reported one patient with grade 2 adrenal insufficiency, and Zhao reported one patient with grade 3 diabetes. 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; TOME, 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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