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ORIGINAL ARTICLE

Stereotactic Body Radiotherapy for Adrenal Gland Metastases: Single-Center Experience

Gökhan YAPRAK, Naciye IŞIK, Cengiz GEMİCİ, Harun DEMİR, Melike PEKYÜREK

Departmet of Radiation Oncology, University of Health Sciences Dr. Lütfi Kırdar Kartal Training and Research Hospital, Istanbul-*Turkey*

OBJECTIVE

In this study, we aimed to analyze the results of stereotactic body radiotherapy (SBRT) in patients with adrenal gland metastasis due to different primary tumors.

METHODS

26 patients with 29 adrenal gland metastases who were treated between 2011-2018 with Cyberknife Robotic System were evaluated retrospectively.

RESULTS

The origin of adrenal gland metastasis was lung in 22 patients, breast in 1 patient, parotid gland in 1 patient, and sarcoma in 2 patients. Fifteen patients (58 %) had other organ metastasis in addition to the adrenal metastases. Six patients were treated for synchronous metastasis and 20 patients for metachronous metastasis. SBRT was performed in median 3 fractions (3–5 fractions), and the median prescription dose to PTV was 30 Gy (18- 45 Gy), with a BED10 (Biological Equivalent Dose) value of 60 Gy (28.8-112,5 Gy). The median follow-up time was 11 months (1-34 months), and median overall survival was 12 months after SBRT, 1,2-years survival rates were 49,7%, 21% respectively. Median time to local failure was not reached, and the 6-months, 1 and 2-years local failure free survival rates were 78,6%, 66,5% and 66,5% respectively. The presence of metastatic disease outside the adrenal gland was found to be a significant prognostic factor on survival after SBRT in both univariate and multivariate analyzes, (HR:3; 95% CI 1,06-8,55 p:0,04). In general treatment was well tolerated and no major acute toxicities were observed.

CONCLUSION

SBRT provides high local control rates and a well tolerated treatment in patients with adrenal gland metastases. Survival is particularly encouraging for patients with solitary adrenal metastasis.

Keywords: Adrenal metastasis; cyberknife; stereotactic body radiotherapy.

Introduction

Metastatic involvement of adrenal glands is very common. Many different tumors can metastasize to the adrenal gland. Lung, breast, kidney and colon cancers are the most common tumors with a high potential of spread to the adrenal glands.[1] Adrenal metastasis does not have specific symptoms. Patients usually present with pain when the metastatic mass in the adrenal gland is large. Adrenal insufficiency with the presentation of fatigue, nausea, hyperpigmentation, hypotension and electrolyte disturbances are rarely observed and usu-

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Dr. Gökhan YAPRAK
Sağlık Bilimleri Üniversitesi,
Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi,
Radyasyon Onkolojisi,
İstanbul-Turkey
E-mail: gokhanyaprak@gmail.com

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ally occur when both glands are involved.[2] The classical treatment of adrenal metastasis is systemic chemotherapy. However, in solitary adrenal metastases with the primary tumor under control, surgical resection (adrenalectomy) is the primary treatment modality providing the cure.[3,4] Local therapies other than surgery, namely radiotherapy or radiofrequency ablation, are offered mostly in the palliative setting. Recently, with the technological improvements in radiation oncology, it has become possible to deliver high radiation doses to localized tumors. Stereotactic body radiotherapy (SBRT) has gained popularity and emerged as a noninvasive technique. The advantage of SBRT is the delivery of ablative radiation doses in a shorter time, resulting in a potent radiobiological effect. While classical fractionated radiotherapy provides only palliative benefit, SBRT can be an alternative to surgery in localized tumors.[2,5-7]

Recently, the oligometastatic disease has been defined by Hellman and Weichselbaum as an intermediate state between locoregional and metastatic disease.[8] SBRT is now a prominent treatment modality in oligometastatic cancer patients with isolated metastatic masses.

Long term survival has been reported after adrenalectomy in patients with solitary adrenal metastases.[9] For patients with medically inoperable or technically unresectable masses, SBRT has emerged as an encouraging method instead of surgery, and recently, data have accumulated in the treatment of adrenal metastasis with SBRT.[2,3,10-12]

In the present study, we aimed to analyze the results of stereotactic body radiotherapy (SBRT) in patients with adrenal metastasis associated with different primary tumors.

Materials and Methods

Twenty-six patients with 29 adrenal gland metastases who were treated between 2011-2018 were evaluated retrospectively in this study. All of the patients had biopsy-proven primary disease and either positron emission tomography (PET/CT) or biopsy-confirmed adrenal metastases. Patients having a life expectancy of >3 months, with Karnofsky performance score ≥70, and who were not operable were considered for SBRT. This study was approved by the local ethics committee of the hospital, and informed consent was obtained from all the patients.

Treatments

All patients presented with oligometastatic disease or solitary adrenal metastasis. Among 29 tumors treated with SBRT, nine patients had bulky tumors. SBRT was delivered by CyberKnife Robotic System (Accuray Corporation, Sunnyvale, CA, USA). The CyberKnife system consists of a six megavolt linear accelerator (LINAC) mounted on to a precisely controlled industrial robotic arm and image guidance system. Before the treatment, one to three gold fiducials were placed by a radiologist under computed tomography (CT) guidance around the tumor within the adrenal gland at least seven days before the treatment to account for seed migration.

Immobilization was achieved with a vacuum bed, and patients lied in the supine position. Simulation CT (GE Healthcare, Waukesha, WI, USA) was obtained by 1.25-mm slice thickness while administering intravenous contrast material. Synchrony™ Respiratory Tracking System was utilized in all patients, which is a realization of real-time tracking of tumors that move with respiration. The gross tumor volume (GTV) was defined as the visible tumor in the CT. While the clinical target volume (CTV) was equal to the GTV, planning target volume (PTV) was obtained by adding a 5-mm margin to the CTV. Treatment planning was performed in MultiPlanTM software. Figure 1 demonstrates the treatment plan for one of our patients.

SBRT was performed in median 3 fractions (range, 3–5 fractions), and the median prescription dose to PTV was 30 Gy (range, 18-45 Gy), which was biologically equivalent (BED 10) to the dose of 60 Gy (range, 28.8-112,5 Gy). The median tumor volume was 66,6 ml (range: 25.6–78.4 ml). The treatment parameters were summarized in Table 1.

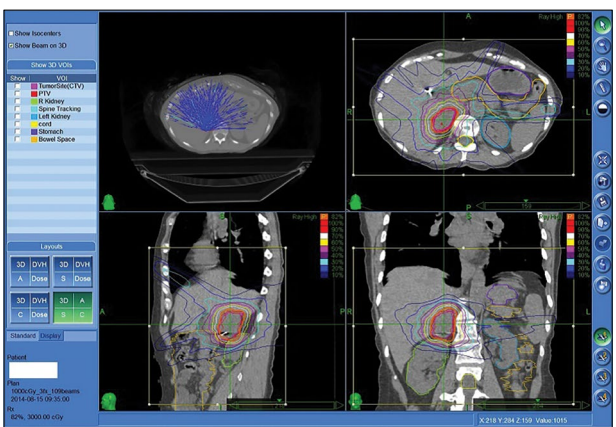

Fig. 1. The treatment plan for one of our patients.

An illustrative case of the fifty-years-old man with metastatic non-small cell lung cancer. SBRT was performed for left adrenal metastasis. Fiducials were placed around the lesion one week before treatment as a tracking marker for respiratory movements. 45 Gy in 3 fractions prescribed to the 87% isodose line.

Table 1 SBRT treatment parameters

	Median value (Range)
PTV (ml)	66.6 (25.6–78.4)
Total prescribed dose (Gy)	30 (18–45)
Number of fractions	3 (3-5)
Dose per fraction (Gy)	10 (5-15)
BED10 (Gy)	60 (28.8–112.5)
Dmax (Gy)	35.1(23.3-53.3)
Dmean (Gy)	32 (19.7-49.3)
HI	1.2 (1.11-1.45)
CI	1.19 (1.03-2.79)
nCI	1.27 (1.15-2.95)
Prescription isodose line (%)	84 (69-95)
Number of fiducials	2 (1-3)

PTV: Planning target volume; BED: Biologically equivalent dose; Dmax: Maximum dose; Dmean: Mean dose; HI: Homogeneity index; CI: Conformity index; nCI: New conformity index

End-Points and Follow-Up

Patients were followed regularly with CT scans or PET-CT scans after SBRT at every three months. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0.[13] Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[14] and considered as either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The local control (LC) rate was defined as the ratio of the number of lesions with a response after SBRT to a total number of lesions at the beginning of this study. Overall survival after SBRT (OS) and time to local failure (tLF) were calculated from the date of completion of SBRT to death from any cause or the last follow-up. Adrenal function was evaluated during follow up for patients with bilateral adrenal gland metastases.

Statistical Analysis

The local control (LC) and OS rates were computed using the Kaplan-Meier analysis. Prognostic factors associated with LC and OS were evaluated using univariate log-rank test and multivariate Cox regression analysis. P values of less than 0.05 were regarded as statistically significant. All statistical analyses were performed using the SPSS 17.0 software (The Statistical Package for Social Sciences 17).

Results

Patient Characteristics

A total of 26 patients with a median age of 57 (34-78), including 22 male and four female patients, were treated with SBRT. While 12 lesions treated were right-sided, 11 lesions were left-sided, and three lesions were located on both sides. The origin of adrenal gland metastasis was lung in 22 patients, breast in one patient, the parotid gland in one patient, and sarcoma in two patients. The pathologic diagnosis of the patients with lung cancer was adenocarcinoma in 14 patients (53%), squamous cell carcinoma in six patients (23%), and small cell cancer in two patients (8%). Fifteen patients (58%) had other organ metastasis in addition to the adrenal metastases. While six patients presented with synchronous metastasis, the other 20 patients presented with metachronous metastasis. While 20 out of 26 patients (77%) had received chemotherapy before SBRT, 18 patients (69%) received chemotherapy after SBRT. Adrenal metastases were asymptomatic in the majority of the patients (21 out of 26 patients, 81%), while five patients (19%) suffered from abdominal pain. Patient and tumor characteristics are summarized in Table 2.

Efficacy Outcomes

At the time of analysis, only seven of the 26 patients (16.6 %) were alive. The median follow-up time from the

Table 2 Patient and tumor characteristics

Characteristics	Values
Median age (years)	57 (34-78)
Gender (male/female)	22/4 (85% /15%)
Primary tumor sites	
Lung	22 (%84)
Breast	1 (4%)
Sarcoma	2 (%8)
Parotid gland	1 (4%)
Laterality of adrenal gland metastasis	
Left	11 (42%)
Right	12 (46%)
Bilateral	3 (12%)
Symptoms at the time of metastasis	
Yes	5 (19%)
No	21 (81%)
Systemic therapy after SBRT	
Yes	18 (69%)
No	8 (31%)
Extent of disease	
Oligometastatic	15 (58%)
Isolated adrenal metastasis	11 (42%)
Time of adrenal metastasis	
Synchronous with primary	6 (23%)
Metachronous	20 (77%)

SBRT: Stereotactic body radiation therapy

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initial diagnosis was 26 months (12–149 months). The median follow-up time from SBRT was 11 months (1-34 months). Median overall survival from initial diagnosis was 33 months, and 1, 3, 5-years overall survival rates were 96%, 43%, and 33%, respectively. Median overall survival after SBRT was 12 months, and 1,2-years survival rates were 49.7%, 21%, respectively. Median time to local failure was not reached, and the 6-month, 1-year and 2-year local failure-free survival rates were 78,6%, 66,5% and 66,5%, respectively (Fig. 2a-c).

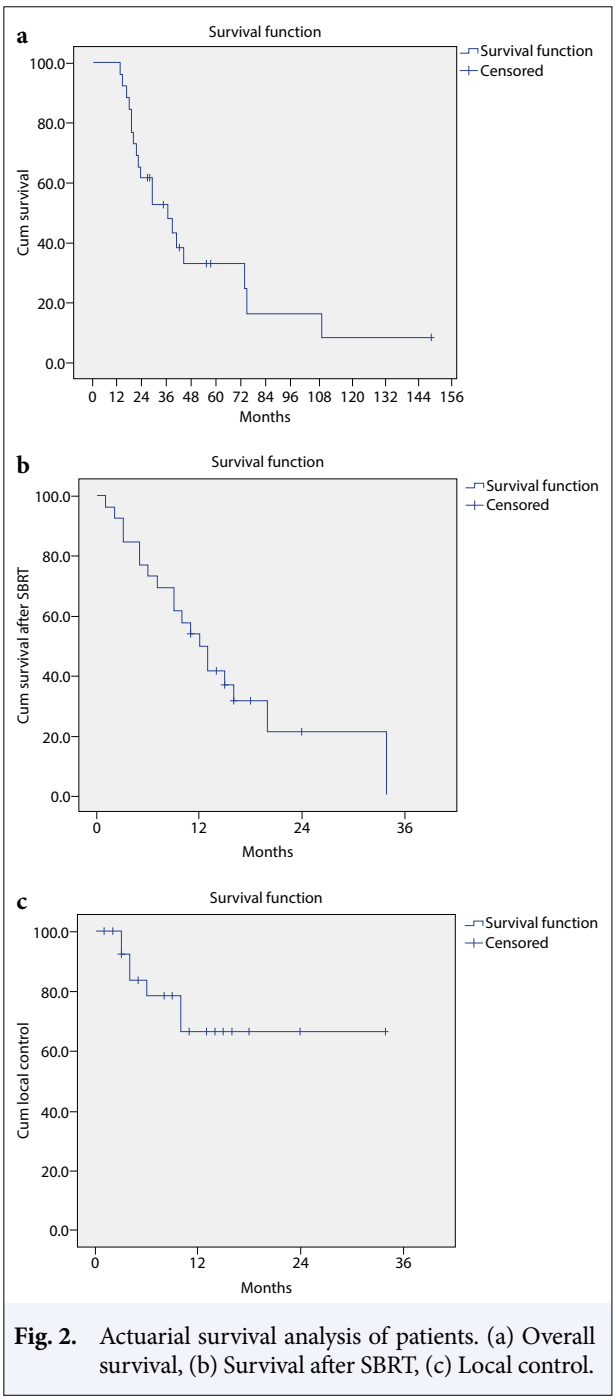

Fig. 2. Actuarial survival analysis of patients. (a) Overall survival, (b) Survival after SBRT, (c) Local control.

Table 3 Univariate analysis for LC and OS rates

	L.C after SBRT	O.S after SBRT
Gender (male/female)	0.14	0.37
Age (years) (57≥ and 57<)	0.16	0.08
BED10 (100 Gy>and 100 Gy≤)	0.44	0.15
PTV(cc) (66.5≥ and 66.5<)	0.14	0.98
Dmean (Gy)	0.14	0.07
Dmax (Gy)	0.18	0.13
Systemic therapy after SRBT (Yes/No)	0.52	0.8
Extent of disease (Oligometastatic-Isolated adrenal metastasis)	0.71	0.03
Time of adrenal metastasis (Synchronous with primary-Metachronous)	0.16	0.04
Laterality of adrenal gland metastasis (Left-Right-Bilateral)	0.58	0.02

L.C: Local control; O.S: Overall survival; PTV: Planning target volume; BED: Biologically equivalent dose; Dmax: Maximum dose; Dmean: Mean dose; SBRT: Stereotactic body radiation therapy

According to RECIST criteria, CR, PR, SD, and rates were 14% (n=4), 17% (n=5), and 45% (n=13), respectively, while seven patients (24%) had progressed (PD) after SBRT. The local control rate after SBRT was found to be 76%. Disease progression outside the adrenal gland was observed in 19 patients (73%) after SBRT.

While presence of metastatic disease besides adrenal gland (oligometastatic vs. solitary metastasis), synchronous or metachronous disease presentation, laterality versus bilateral disease presentation was found to be significant for overall survival after SBRT according to the univariate analysis, the presence of metastatic disease outside the adrenal gland was found to be a significant prognostic factor on survival after SBRT in both univariate and multivariate analyses. None of the risk factors were found to be significant for local control in the univariate analysis. Univariate analysis findings were summarized in Table 3.

Overall survival was found to be nine months in oligometastatic patients, whereas it was 34 months in patients treated for solitary adrenal metastasis (HR 3; 95% CI 1.06-8.55 p=0.04).

SBRT provided pain relief in all patients presenting with pain. The treatment was well-tolerated. Seven patients developed acute grade I-II toxicity, including nausea (n=6), and fatigue (n=5) and abdominal pain (n=1). No patients presented with grade III-IV late toxicity.

Discussion

Metastatic disease presentation in the adrenal gland is very common. Diagnosis and treatment of tumors in the adrenal gland is very problematic, especially in patients with a controlled primary tumor. The optimal management of patients with adrenal metastases is unclear, and there is heterogeneity in oncologist's approach to these patients. Surgical resection is the primary treatment for patients with isolated adrenal metastases. There are several studies reporting long survival after adrenalectomy.[15]

The role of surgical and ablative therapies in adrenal metastases has been reviewed in a recent publication.[3] Image-guided RFA is another effective local-regional treatment. A retrospective study evaluated 35 patients who were treated with RFA for 41 adrenal metastases with a mean size of 3.3 cm from various primary tumors and demonstrated a 77% local control rate. The 1-, 3-, and 5-year OS rates were 75%, 34%, and 30%, respectively, with a median survival time of 26.0 months.[16]

Classically fractionated external radiotherapy has been used with palliative intent and provides good response rates and pain relief. Recent advances in stereotactic radiotherapy made it possible to safely apply larger doses of radiation to the adrenal tumors with a limited number of fractions. SBRT is a novel modality and being used with increased frequency in radiation oncology practice with accumulating experience nowadays. The biologically equivalent doses (BED) delivered by SBRT are much higher than doses delivered by normal fractionated radiotherapy. SBRT is a non-invasive treatment alternative to surgery in selected patients.[17-19] There are few studies reporting the treatment results of SBRT in adrenal gland metastases. To our knowledge, there are no standard prescription doses, and fractionation regimens and the reported studies are heterogeneous concerning patient selection (primary tumors, previous treatments, performance status and disease extension) and prescribed radiation dose and fractionation schedules.[19] The radiation doses in the published studies ranged from 16 to 60 Gy and were delivered in 1 to 10 fractions.[2,12,17,19-23] In our study, the median prescription dose was 30 Gy (range,18-45 Gy) administered in median 3 fractions (range, 3–5 fractions) determined according to patient and tumor characteristics.

There are several reasons for the difference in survival obtained with surgery and other local ablative therapies. The patients selected for surgery are generally in good performance status, have no major co-morbidities, and, most of the time, have controlled extra-adrenal disease when compared with the patients had other local ablative treatments, namely the SBRT.[3] A recent analysis demonstrated 2-year OS rates in favor of surgery when compared to SBRT (44% vs. 19%).[3]

A recent study in 30 patients who underwent SBRT for adrenal metastases of different primary tumors reported 1-year OS, LC, and distant control rates as 44%, 55%, and 13%, respectively. No grade II or greater toxicity was observed.[19] Another study by Franzese et al. found similar outcomes with 28.5 months median OS and 65.5% and 40.7% 1-year and 2-year LC rates, respectively.[12] Scorsetti et al. reported the results of 34 patients with adrenal metastasis who were treated with SBRT.[24] They delivered a median dose of 32 Gy in 4 fractions. Local control rates were 66% at 1 year, and 32% at 2 years after a median follow-up time of 41 months. The median time to local progression was 19 months, and the median survival time was 22 months. No grade III toxicity was observed. In our patients, the median follow-up time from SBRT was 11 months (1-34 months). Median overall survival after SBRT was 12 months, and 1.2-years survival rates were 49.7%, 21%, respectively.

Local control rates in the literature vary among studies. While Casamassima et al. reported a 90% local control rate at 2 years [21], Chawla et al. reported a 55% 1-year local control rate.[19] We found 6-months, 1-year and 2-year local failure-free survival rates to be 78.6%, 66.5% and 66.5%, respectively, which was in accordance with the literature.

Lower doses seem to be associated with poor tumor control rates, as reported by Chawla et al. The differences in local control rates may be explained by differences in dose and fractionations used in SBRT. There are significant differences in the prescribed BED. While maximum delivered BED was 137 Gy (36 Gy in 3 fractions) in the study of Casamassima et al., it was only between 22 Gy (16 Gy in 4 fractions) and 75 Gy (50 Gy in 10 fractions) in the study of Chawla et al.[19,21] Several studies demonstrated that a BED10 value <60Gy was predictive of lower 1-year LC rates [17,19,24] while several other studies identified that BED10 value >85Gy correlated with better LC.[20,21,25] Other series have suggested that a BED value >100 Gy is necessary to achieve optimal local control.[26,27] Rudra et al. treated 13 patients with SBRT and noticed that the local failures were observed in three patients with the lowest BED10 values, with a mean BED value of 43.2 Gy.[18] In our study, we did not find any relation between BED10 value (100 Gy> and 100 Gy≤) and treatment results.

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Holy et al. reported a median progression-free survival (PFS) of 4.2 months in 18 NSCLC patients who were treated with SBRT. However, in 13 patients with isolated adrenal gland metastases, the PFS was markedly longer and reported as 12 months. After a median follow-up of 21 months, 10 of these 13 patients achieved local control, and the median overall survival was 23 months.[23] These results were similar to the results obtained by surgery. Porte et al. reported PFS of 13 months with surgical resection of solitary adrenal metastasis.[28] In different SBRT series, one-year LC rates reported ranged between 44% to 100% depending on the radiation doses and the fractionation scheme.[21,23,29] Although isolated adrenal gland involvement was not found as a prognostic factor for local control in our study, we found it as a prognostic factor for overall survival after SBRT in both univariate and multivariate analyses. While overall survival was nine months for oligometastatic patients, the overall survival was 34 months for patients with isolated adrenal gland metastasis (HR 3; 95% CI 1.06-8.55 p=0.04).

Bilateral adrenal gland metastasis was associated with significantly worse PFS and OS. This is probably related to the aggressiveness and high tumor burden of the disease in these patients in comparison to the patients with unilateral metastasis.[11] In univariate analysis, we found that patients treated for bilateral adrenal gland metastasis had worse survival as compared with the patients treated for unilateral adrenal gland metastasis. However, this significance was not observed in the multivariate analysis.

In general, SBRT to the adrenal gland is well tolerated with acceptable acute toxicity. The most commonly reported acute toxicities are nausea, vomiting 6% to 40%,[17,18,20,22-24] and fatigue 38% to 88%.[18,20,22] We observed mostly nausea, vomiting, and abdominal pain (grade I or II) and no grade III/IV acute toxicity. All patients tolerated the treatment well. Grade III/IV late gastrointestinal or renal toxicities were not observed, as in the other studies reported in the literature.[12,23,30,31]

Our study has several limitations. Our study was a retrospective study with a limited number of patients. The patient population was heterogeneous, consisting of several different primary tumors. In addition, the treatment parameters, i.e. the radiation doses and fractionations, were heterogeneous. Different systemic chemotherapy schemes administered to our patients was another important confounding factor.

Our study confirmed the efficacy of SBRT in the treatment of adrenal gland metastases with high local control rates and acceptable acute and late toxicity. Our findings were comparable to the results reported in the literature.

Conclusion

Recently with the technological improvements in radiation oncology, it is possible to deliver stereotactic ablative radiation doses to the adrenal gland metastases. SBRT is a well-tolerated treatment in patients with adrenal metastases and provides good local control rates. Survival is particularly encouraging for patients with a solitary metastasis in the adrenal gland. High local control rates with low toxicity make this treatment an alternative to surgery, especially in patients with solitary metastases.

Ethics Committee Approval: This study was approved by the local ethics committee of the hospital (2019/514/154/16).

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