Organ At Risk (OAR) Data on Clinical Toxicity in The Treatment of Bulky Adrenal Metastases With Stereotactic Ablative Radiotherapy (SABR)

Tanju Berber (✉ tanjuberber@hotmail.com)

Okmeydani Training And Research Hospital Radiation Oncology Department

Özge Kandemir Gürsel

Okmeydani Training And Research Hospital Radiation Oncology Department

Berna Akkuş Yıldırım

Okmeydani Training And Research Hospital Radiation Oncology Department

Aysun Arslantaş Erken

Okmeydani Training And Research Hospital Radiation Oncology Department

Selvi Tabak Dinçer

Okmeydani Training And Research Hospital Radiation Oncology Department

Necla Gürdal

Okmeydani Training And Research Hospital Radiation Oncology Department

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Abstract

Aim

Effectiveness of the treatment was investigated in terms of treatment responses and side effects with OAR in oligometastatic patients whose adrenal metastases were treated with SABR.

Methods

Patients who underwent radiosurgery for adrenal gland metastasis in our clinic were evaluated retrospectively for the patient, tumor, treatment characteristics, survival outcomes, and dosimetric parameters with toxicity.

Results

Of the 22 patients in our study. The primary tumor site was the lung in 20 (90.9%) of 22 patients, while ten (45.5%) of the patients had isolated adrenal metastasis. The median dose was 30 Gy (R:18–50) with a median fraction of five (R:3–10). The median PTV volume was 55 cc. (IQR:44-120cc). From the first diagnosis to adrenal gland radiotherapy, the median time was 6.9 months. The median follow-up was 7 months (R:2–48), and the median survival was 9.5 months (R:2–48). The local control rate was 72.7% in the 6th month, 63.6% in the 1st year, and 59.0% in the 2nd year, and overall survival was 72.7%, 50%, and 31.8%, respectively. The median overall survival was 9.5 months for all patients ($p = 0.049$) and 6.5 months in the presence of diffuse disease. Deaths of patients due to distant progression were also found to be significant ($p = 0.03$). Patients with isolated adrenal metastasis survived for 14.4 months after the treatment; while extra-adrenal metastasis lived for a median of 6.6 months ($P = 0.01$).

Conclusion

SABR in patients with oligometastatic adrenal disease not only provides symptom control but may also provide prolonged survival with minimal toxicity.

Introduction

Since the adrenal gland is a rich region for blood supply, it often develops metastasis[1]. Different types of cancers can metastasis to the adrenal gland, which is most frequently seen with lung cancers. Even though they are often asymptomatic, they can lead to pain complaints. When patients with adrenal metastasis are left untreated, their lifespan is approximately 3 months[2].

With the development of imaging techniques, many more adrenal metastases can be detected compared to previous times[3]. Treatment of adrenal gland metastases for curative purposes is traditionally considered to be surgery. In some surgical series, its contribution to survival in isolated metastases has been demonstrated[4–6]. However, in approximately 85% of patients, recurrence can reoccur even if R0 resection is performed[7]. Additionally, many patients cannot undergo surgery due to the tumor and patient characteristics[8].

Recently, there have been studies suggesting that curative treatments can contribute to survival, particularly in oligometastatic (1–5 metastases) disease[9, 10]. There is a need to evaluate the effectiveness of the treatments that have been recently developed in new studies with oligometastatic patients[11–13].

Radiotherapy applications aim to shift from palliative treatments to radiosurgery procedures in parallel with technical and technological developments in adrenal malignancies. Radiosurgery aims to achieve not only symptom control but also local

control in oligometastatic or oligoprogressive disease. With radiosurgery techniques, it can be considered that treatment results comparable to those in surgery can be obtained, such as in lung cancer, by giving much higher BED doses than in conventional radiotherapy in adrenal metastases [14].

Although the SABR-COMET[10] study uses 8 fractions (60 Gy) regimes, 5 fraction regimes (35 Gy/5 Frx ($BED_{10} = 59.5$ Gy) can be used in practice, although there is currently no consensus or guideline. However, some studies argue that doses above 100 Gy[15, 16] of ablative BED_{10} dose may be more effective in local control. Since the adrenal region is a region with a high blood supply, we can provide local control at lower radiotherapy doses radiobiologically. However, this region is perhaps one of the most sensitive areas in terms of OAR. While the dose that can be applied to the right adrenal gland is safe in terms of OAR, the same doses may not be safe at all in terms of left-side constraints. However, as is known, dose constraints of adrenal metastases could not be determined in a phase 2 study. For this reason, dose constraints are being tried to be determined by several experiences. For this reason, in addition to determining effective doses and constraints according to which region it is in adrenal gland metastases, the adequacy of doses should be investigated according to the histological type of metastasis.

The goal of the current study, adrenal metastases were investigated in terms of treatment responses with dosimetric parameters and side effects and the primary histology of oligometastatic or oligoprogressive patients treated with SABR.

Materials And Methods

Patient Characteristics

Patients who underwent radiosurgery for adrenal gland metastasis in our XXXXXXXXXXXXXXXX clinic between 2013 and 2019 were retrospectively evaluated for disease-related treatment characteristics and toxicities and included in the study. Radiosurgery practice in adrenal gland metastases was generally applied to patients who were not candidates for surgery and had progression in the adrenal gland, although systemic control was generally achieved with chemotherapy in oligometastatic or oligoprogressive disease. Ethical approval for this study was obtained from XXXX (Date: 18. February 2020, No: 61).

All patients with adrenal gland metastases treated with SABR were included regardless of metastases in other regions. The exclusion criterion for the study was radiosurgery applications for other primary malignancies of this region. Patients were evaluated on tumor boards and were treated with radiosurgery instead of surgery. All patients had a histological diagnosis of primary tumors but not metastases because of the patient's poor performance. Decisions for adrenal metastases were decided made with MRI and PET/CT images. Before SABR, patients had received chemotherapy, and they progressed. The pretreatment patient and tumor characteristics are presented in Table 1.

Table 1
Patient and Treatment Characteristics

Characteristics (N = 22)	Median (range) or No. (%)
Age, years	63 (41–81)
Sex (No. male/female)	17/5
PTV Tm	55518,8 (13218,4-391148,6)
RX	78,0 (68,0–88,0)
PTV Mean Dose	3147,5 (2001,6-4313,8)
CI	1,15 (0,94 – 1,55)
HI	1,27 (0,07 – 1,47)
Coverage	97,87 (33,33–99,04)
Chemotherapy	14 (63,6)
Time to RT, month	8 (0–57)
Dose, Gy	30 (18–50)
BED ₁₀ , Gy	48 (28–80)
Other SRS	
None	13 (59.1)
exist	9 (40.9)
Pre RT eGFR	89 (32–123)
Post RT eGFR	89 (35–111)
Tumor histology	
Lung	20 (90,9)
Breast	1 (4,5)
Endometrial	1 (4,5)

Follow-up and Primary and Secondary Endpoints

Tumor response was evaluated with the Response Evaluation Criteria for Solid Tumors (RECIST) system [17]. Acute and late toxicity was assessed using the Common terminology criteria for adverse events CTCAE (version 5.0)[18]. The patients were first examined through PET-CT or MRI three months after the treatment. All patients were evaluated with MRI for at least every 6 months until May 2020 and with PET-CT in cases when it was impossible to decide with MRI.

The one-year local control rate and toxicity were accepted as the primary endpoints. Increasing the tumor diameter and its viability in PET-CT by 20% or more were accepted as recurrence. Disease-free survival and overall survival were determined as the secondary endpoints.

Radiotherapy Specifications

Eighteen patients were treated on the CyberKnife® (Accuray Inc., Sunnyvale, CA, USA) radiosurgery system with 6-MV X-rays under a respiratory gating system, with the remaining patients treated on a Varian® Trilogy linear accelerator platform under a 4D CT gating system. In patients treated with CyberKnife® the images during inspiration and expiration were used to create gross tumor volume (GTV), and internal target volume (ITV) was formed with a 10 mm margin to the PTV for the x-site spine

in 15 patients and three of the patients treated with internal fiducial markers near the adrenal tumors using a real-time tumor-tracking radiotherapy (TRT) system. For four patients, IGTV was created with a 4D RPM respiratory monitoring system, and they were given treatment with the Varian device. PTV was given as a 3–5 mm margin after the formation of ITV according to gross tumor volume. No margin was given for the clinical target volume (CTV). The dose and fractionation were selected depending on the location of the tumor. Treatment was prescribed so that 95% of the planning target volume received at least 100% of the prescribed dose. Ninety-nine percent of the PTV was prescribed to receive 90% of the dose.

Statistical Design

All-time-related events (failure or death) were calculated from the date of the first SABR to the date of death or censoring at the last clinical follow-up and analyzed with the Kaplan–Meier and Cox proportional hazard methods. Significance was considered at $p < 0.05$, and all significance levels were 2-sided. IBM® SPSS® Statistics, version 23 was used for all statistical analyses.

Results

Seventeen of the 22 patients in our study were male, and the median age was 63 (R: 41–81) years. The primary tumor site was the lung in 20 (90.9%) of 22 patients, while ten (45.5%) of the patients had isolated adrenal metastasis. The median PTV volume was 55 cc. (IQR (interquartile range): 44–120 cc). PTV volumes below or above 55.5 cm³ and 100 cm³ were statistically significant ($p = 0.658$ and $p = 0.170$, respectively), and no significance was found. The conformity index (CI) was 1.15 (R: 0.94–1.55), the homogeneity index (HI) was 1.27 (R: 0.7–1.47), and the coverage was 97.87% (33.33–99.04). From the first diagnosis to adrenal gland radiotherapy, the median time was 6.9 (IQR: 0.5–14) months. The median dose for SABR was 30 Gy (IQR: 25–30), with a median fraction of five (IQR: 5–5), and the median BED₁₀ dose was 48 Gy (IQR: 43.2–56.58). A median BED₁₀ dose below or above this value did not affect survival ($p = 0.335$). The median prescribed BED₁₀ value was calculated as 50.2 Gy in patients whose local control was achieved and 44.1 Gy in patients whose local control could not be achieved ($p = 0.390$). The median receipt isodose curve was 78% (R: 68.0–88.0). The median follow-up was 7 months (R: 2–48), and the median survival was 9.5 months (R: 2–48). The local control rate was 72.7% in the 6th month, 63.6% in the 1st year, and 59.0% in the 2nd year, and overall survival was 72.7%, 50%, and 31.8%, respectively. The median overall survival was 9.5 months for all patients ($p = 0.049$) and 6.5 months in the presence of diffuse disease.

Only in 4 patients (18.1%) was the time between chemotherapy and SABR four weeks. After treatment, 14 (63.6%) patients received chemotherapy due to systemic progression at any time. Patient and treatment characteristics are summarized in Table 1.

As the first response was evaluated in the third month, the local control rate was 81.8%. The local control rate was 72.7% in the 6th month, 63.6% in the 1st year, and 59.0% in the 2nd year. However, our distant progression rate was unfortunately 68.2%. The results of the patients are presented in Table 2.

Table 2
Treatment Results

Findings (N = 22)	Median (range) or No. (%)
Time to Follow up, month	7 (0–48)
Time to Survival, month	9.5 (0–48)
Isolated metastasis	10 (45,5)
Local control	18 (81.8)
Local Progression	5 (22.7)
Distant Progression	15 (68,2)
Time to Distant Progression, month	3 (0–9)
Adverse Event Grade 3–4	2 (9.0)
RECIST criteria	
Complete Response (CR)	9 (40,9)
Partial Response (PR)	6 (27,3)
Stable Disease (SD)	3 (13,6)
Progression Disease (PD)	4 (18,2)
Last Status	
Ex	15 (68,2)
Alive	7 (31,8)

Overall survival was 72.7% in the 6th month, 50% in the 1st year, and 31.8% in the 2nd year. The median overall survival was 9.5 months.

The patients who had isolated metastasis and who were treated with SABR lived for a median of 16.7 months (95% CI, 10.3 to 23.0). The median survival was 6.5 months in the presence of diffuse disease (95% CI, 2.9 to 10.2). The median overall survival for all patients was 9.5 months (95% CI, 5.7 to 13.6). The p-value was 0.049, which was significant (Fig. 1).

After the treatment, our oligometastatic patients lived for 14.4 months (95% CI, 9.2 to 19.5), and other oligoprogressive patients lived for a median of 6.6 months (95% CI, 3.8 to 9.3) ($P = 0.01$) (Fig. 2).

The median survival was 8.7 months (95% CI, 5.6 to 11.7) for patients developing distant progression and 16.7 months (95% CI, 11.9–21.5%) for those without distant progression. There was a statistically significant difference between the survival time of the group with and without distant progression ($p = 0.03$) (Fig. 3).

Adverse Events

Grade 1–2 nausea and dyspepsia complaints developed in two patients (9.0%) in the acute period.

When the EGFR values of patients were calculated before and after the treatment, the median pre-radiotherapy value was 89 (R: 32–123), and the median postradiotherapy value was 89 (35–111). (Table 3)

Table 3
Detailed Kidney Volumes and Pre-RT/Post-RT eGFR Levels

Patient	EGFR Pre RT	EGFR Post RT	Toxicity Pre RT	Toxicity Post RT	Renal mean
1	69	47	grd1	grd2	L 149 R 497
2	88	92	grd1	grd1	L 744 R 100
3	85	87	grd1	grd1	L 369 R 553
4	50	35	grd2	grd2	L 933 R 54
5	108	73	grd1	grd1	L 341 R 80
6	96	90	grd1	grd1	L 308 R 1956
7	92	87	grd1	grd1	L 357 R 633
8	85	72	grd1	grd1	L 784 R 172
9	32	35	grd2	grd2	L 354 R 115
10	97	94	grd1	grd1	L 372 R 98
11	57	52	grd2	grd2	L 1037 R 528
12	84	90	grd1	grd1	L 582 R 84
13	83	95	grd1	grd1	L 742 R 142
14	92	94	grd1	grd1	L 209 R 330
15	95	98	grd1	grd1	L 1067 R 364
16	80	90	grd1	grd1	L 293 R 943

Patient	EGFR Pre RT	EGFR Post RT	Toxicity Pre RT	Toxicity Post RT	Renal mean
17	91	92	grd1	grd1	L 474 R 851
17	101	86	grd1	grd1	L 984 R 1048
18	123	111	grd1	grd1	L 391 R 335
19	72	55	grd1	grd2	L 2268 R 532
20	64	79	grd1	grd1	L 175 R 491
21	92	89	grd1	grd1	L 279 R 778
22	89	95	grd1	grd1	L 441 R 678

One patient (4.5%) who underwent irradiation to the bilateral adrenal gland after the treatment received steroid therapy due to adrenal insufficiency (Grade 2).

One patient with grade 4 toxicity (4.5%) underwent surgery with signs of ileus in the late period. A duodenal ulcer developed in 1 patient, who was medically treated (grade 2). Fifteen patients (68.2%) died. Two of them (13.3%) died due to adrenal gland symptoms.

Detailed metastasis locations and all OAR data of all patients are given in detail in Table 4.

Table 4
OAR Data For Larger Adrenal Gland Metastasis Patients

Patient	Lesion	Other Adr Tx	Laterality	Dued. 0.5 cc	Dued. 1 cc	Dued 2 cc	Dued max	Bowell 1 cc	Bowel max	Renal mean	Liver mean
1	1	Synchronous	R	1022	860	680	1705	470	563	L 149 R 497	581
1	2	Synchronous	L	1022	860	680	1705	470	563	L 149 R 497	581
2	3	None	L	772	718	654	1015	3397	3728	L 744 R 100	454
3	4	None	R	2153	1796	1367	3018	3097	3223	L 369 R 553	514
4	5	None	L	1429	1378	1312	1581	3076	3129	L 933 R 54	402
5	6	None	L	551	468	399	800	1127	1829	L 341 R 80	175
6	7	None	R	2516	2393	2226	2874	3106	3178	L 308 R 1956	451
7	8	None	R	1271	1231	1173	1493	2139	2650	L 357 R 633	887
8	9	None	L	791	767	728	885	2571	2946	L 784 R 172	321
9	10	None	L	492	480	457	561	3630	2264	L 354 R 115	152
10	11	None	L	947	915	883	1082	3057	3219	L 372 R 98	247
11	12	None	L	917	884	838	1060	3023	3130	L 1037 R 528	451
12	13	None	L	366	354	338	415	1705	1901	L 582 R 84	150

Patient	Lesion	Other Adr Tx	Laterality	Dued. 0.5 cc	Dued. 1 cc	Dued 2 cc	Dued max	Bowell 1 cc	Bowel max	Renal mean	Liver mean
13	14	None	L	1012	964	904	1084	3678	3830	L 742 R 142	371
14	15	None	R	1854	1728	1587	2191	1893	2326	L 209 R 330	656
15	16	None	L	1790	1749	1700	1954	2577	2781	L 1067 R 364	452
16	17	None	R	2309	2261	2175	2441	2472	2594	L 293 R 943	840
17	18	Metachronous	L	1122	1078	1032	1288	796	909	L 474 R 851	884
17	19	Metachronous	R	2866	2760	2606	2059	2522	3004	L 984 R 1048	1147
18	20	None	L	665	619	590	747	1111	1211	L 391 R 335	566
19	21	None	L	1538	1307	1042	2006	3247	3305	L 2268 R 532	250
20	22	None	R	477	450	375	511	1424	1544	L 175 R 491	514
21	23	None	R	2591	2572	2548	2647	2643	2733	L 279 R 778	1002
22	24	None	R	709	688	735	942	1307	1644	L 441 R 678	714

Discussion

Radiotherapy treatments for adrenal gland metastases have been performed for symptomatic improvements, such as pain palliation until today[19]. However, in recent years, in parallel with the developments in radiosurgery, publications are suggesting that, with curative purpose in the adrenal gland, it can contribute to promising local control and even survival, particularly in oligometastatic disease[10, 20–23]. However, although the doses we administered came from important

studies such as SABR COMET[10], in these studies, SABR was applied to adrenal gland metastasis only for a few patients. Moreover, there are no randomized studies on which dosing regimen might be more effective even in lung cancers where SABR is applied relatively frequently, let alone establishing an effective dose/fractionation scheme for adrenal metastases, which is currently used as a fairly new ablative method. Moreover, due to the blood supply structure of the adrenal gland, effective ablative doses may be lower than other parts of the body according to radiobiological principles. However, the biggest problem in applying SABR to these regional metastases right is now not that the exact effective dose is not known but that the limits of OAR doses to organs such as the liver, kidneys, bowel, and duodenum that are adjacent to this region are not exactly known. Doses and fractionations in SABR applications in adrenal gland metastases are unlikely to vary depending on the OAR levels of this region, depending on whether the metastasis is right or left. For this reason, along with the local control rates obtained in fairly large adrenal gland metastases according to the literature, we essentially followed and examined our doses of OAR, which had not been studied much before, and its clinical implications.

Adrenal gland metastases are a very poor prognostic condition, considering their causing deterioration in the quality of life depending on their symptoms and their negative impact on survival times. Patients with good performance status can undergo surgery, and some studies have shown prolonged lifespan after adrenalectomy[4, 6, 24]. However, most patients do not have a level of performance that can support surgical treatment, and surgery cannot be performed for reasons such as location and tumor size[21, 25, 26]. In the review studies comparing radiosurgery to adrenalectomy, it should not be forgotten that SABR patients are generally patients with worse prognostic factors (2-year OS 44% vs 19%)[27].

In general, those with adrenal gland metastasis are elderly patients. Cassamassima et al. found the mean age of patients with adrenal gland metastasis to be 62 years, and in our study, the median age was 63 years[20]. We often encounter adrenal gland metastases early after a cancer diagnosis. In the study of Lam et al., this period was reported as 7 months, whereas in our study, the median time was 8 months (R: 0–58) [2].

With the newly developed radiosurgery techniques, a high dose can be achieved in the tumor, and protection of the surrounding organs can be much better than in the past. However, since there is not enough literature in this regard, there is no certainty about dosage. Generally, the doses used in the literature range from 16 to 60 Gy at the 1–10 fraction[21, 22, 27–30]. In our study, the median dose was 30 Gy (R: 18–50), and the median fraction was 5 (R: 3–10), depending on the patient characteristics and the tumor. Since the PTV volumes are quite large according to the literature[16], they are also slightly more recessive in our SABR doses than in other studies. Our median BED₁₀ value was 48 Gy. The median prescribed BED₁₀ value was 50.2 Gy for patients for whom local control was achieved and 44.1 Gy for those for whom local control could not be achieved. However, the difference was not found to be statistically significant. The reason for this may be the low number of our patients.

Although according to the literature[16], we have already treated large-volume metastases with relatively lower doses as mandatory, the local control rate of 22 patients was 81.8% for the first control. The local control rate was 72.7% in the 6th month, 63.6% in the 1st year, and 59.0% in the 2nd year, which was similar to the rates in many studies[20–23, 29, 31–34]. According to the RECIST criteria, complete response (CR) 9 (%40,9), partial response (PR) 6 (%27,3), stable disease (SD) 3 (%13,6), and progression disease (PD) 4 (%18,2) were determined as the first response and were similar to the literature[21, 23].

Because of recurrence under chemotherapy, only 4 patients received chemotherapy four weeks before SABR. For this reason, the bias that contributed to local control in these patients should not be concluded.

Some studies have demonstrated significance between tumor volume and survival[21, 35] In our study, PTV volume below and above the median value of 55.5 cm³ or below and above the value of 100 cm³ was not found to be statistically significant. However, parallel to the increase in PTV volume, the value of p = 0.658 decreased to the value of p = 0.170. This may indicate that no statistical significance was obtained due to the small number of patients.

Distant progression occurred in 15 (68.2%) of our patients, and only 5 (22.7%) developed local progression. Three of the 5 patients (60%) who showed local progression developed distant progression at the same time. The patients who developed distant progression lived a median of 8.7 months, and patients without distant progression lived 16.7 months. The reflection of this on statistics is significant with $p = 0.03$. For this reason, these patients need additional systemic treatment.

Patients who had isolated metastasis and who were treated with SABR had a median life of 16.7 months, whereas, with the presence of diffuse disease, they lived for 6.5 months ($p = 0.049$). This shows that patients with oligometastatic disease, especially those with isolated metastasis, should receive aggressive treatment¹¹.

Our patients with oligometastatic (1–5) metastases also lived for 14.4 months after the treatment, and the other patients lived for a median of 6.6 months ($p = 0.01$). Again, it should be concluded that these patients, like others with isolated metastases, need aggressive treatment and should be treated with local aggressive therapies.

When evaluated in terms of side effects, the toxicity of grade 3–4 and above developed in only 2 (9%) patients. This may be due to our strict obedience to dose constraints and our low median BED₁₀ value of 48 Gy.

When the EGFR values of patients were calculated before and after the treatment, the median pre-radiotherapy value was found to be 89 (R: 32–123), and the median postradiotherapy value was 89 (35–111). The values decreased slightly, but this was not reflected in the median value.

A review of several studies evaluated SABR of adrenal metastases providing good local control with a manageable toxicity profile and with improved local control similar to our study[36].

Limitation

Most SABR studies on the adrenal gland have been conducted with a small number of cases[21, 22, 34, 37–39]. However, the most important deficiency of our study is its retrospective design with a small sample size. The fact that patients are referred to us quite late in terms of radiosurgery, and therefore the patients with the largest volume of adrenal gland metastases in the literature, is that ablative doses remain slightly lower than in the literature due to the fear of side effects in practice. A real SABR dose fractionation schedule for adrenal gland metastases and a randomized trial for a safe OAR are needed.

The advantage of our study is that all organ at-risk areas were contoured and evaluated by a single physician. Even though there are large-volume adrenal metastases, it was also noteworthy that we provided a fairly high rate of local control and acceptable toxicity rates in the clinic. Moreover, the fact that 90% of our patients have lung cancer in monobloc form shows that even with a large volume, these doses can be safely administered in metastases from the lung to the adrenal gland.

Conclusion

While only palliative doses could be given with radiotherapy in the adrenal gland metastases in the past, treatment for curative purposes can be given with radiosurgery techniques that have developed in parallel with the technology at present. Maintaining local control of the adrenal metastasis region, especially in patients with isolated metastasis or oligometastatic disease, can not only provide symptom control but also provide prolonged survival with minimal toxicity if attention is given to the OAR dose constraints according to the location.

Abbreviations

BED:

Biological effective dose

CI:

Confidence interval

COPD

Chronic obstructive pulmonary disease

CR:

Complete response

CT:

Computed tomography

CTV:

Clinical target volume

FDG-PET:

Fluoro-deoxy-glucose positron emission tomography

Fr:

Fraction

GTV:

Gross tumor volume

Gy:

Gray

ITV:

Internal target volume

KPS:

Karnofsky performance score

LC:

Local control

NSCLC:

Non-small cell lung cancer

OAR:

Organ at risk

OS:

Overall survival

PFS:

Progression-free survival

PTV:

Planning target volume

RX

Receipt

SBRT/SABR

Stereotactic body radiotherapy/Stereotactic ablative radiotherapy

Declarations

Institutional review board statement: This study and all relevant procedures were performed in accordance with the Helsinki Declaration after obtaining the ethical board approval from xxxxxxxxxxxxxxxxxxxxethics committee. Ethical approval for this study was obtained from XXXX (Date: 18. February 2020, No: 61). This is a retrospective study. Patient data were taken from the files.

Informed consent statement: The patients were not required to give informed consent for this study because the study utilized the anonymous retrospective data obtained after each patient accepted the treatment by written consent.

Conflict-of-interest statement: All authors declare no conflicts of interest.

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Authors' contributions: Designed and supervised the study T.B. :Concept:T.B.; resources: T.B.O.K.G,B.A.Y.,A.A.E; materials:T.B,S.T.D,N.G.; data Collection and/or processing: T:B.O.K.G.,A.A.E., analysis and/or interpretation: T.B,O.K.G.,B.A.Y.; literature search: T.B,S.T.D.; writing manuscript: T:B.B.A.Y.; critical review: T:B,O.K.G.; other: T:B

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Figures

Figure 1

Survival of Diffuse Metastases and Isolated Metastases

Figure 2

Survival of Oligometastases and Oligoprogressive Patients

Figure 3

Local Progression or Distant Progression Determining Survival with SBRT