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Stereotactic radiotherapy for brain metastases in patients with non-small cell lung cancer: CyberKnife-M6 experience

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► ***Original article***

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ABSTRACT

Background: We assessed local control and survival in non-small cell lung cancer (NSCLC) patients with limited brain metastases (BM) who underwent stereotactic radiotherapy (SRT) using the CyberKnife-M6 (CK-M6) system as well as the treatment efficacy. ***Materials and Methods:*** Twenty NSCLC patients with 40 BM were treated between 2018 and 2020. Median age was 61 years (46-80 years). Surgery was performed for nine lesions in eight cases. Median lesion size was 10 mm (2–38 mm). Resection cavities and intact metastases contoured as gross target volume. Planning target volume (PTV) was created with a margin of 0–2 mm. A median of 18 Gy (18–20 Gy) in one fraction was applied to 19 lesions, and 25 Gy/5 fractions (24–30 Gy/3–6 fx) to 21 lesions. Median treatment time was 20 min (13–35 min). ***Results:*** The median follow-up duration was nine months (1–15 months) in March 2021. Prescription isodose covering 95% of PTV was 85,9% (80% –92,7%). During the follow-up, local and intracranial control rates in evaluated patients were 88% (15/17) and 70,5% (12/17), respectively. Asymptomatic radionecrosis was observed in 23.5% (4/17) of patients at a median of 8 months (6–12 months). The median survival was 13 months (1–25 months). In univariate analysis, factors positively affecting survival were Karnofsky performance status, RPA, and DS-GPA classification ($p < 0,05$). ***Conclusion:*** Promising local control and survival in patients and treatment time demonstrated that CK-M6 based SRT was effective, safe and comfortable in the treatment of NSCLC with BM.

INTRODUCTION

Brain metastases (BM) are observed at a rate of 20% – 40% in cancer cases and adversely affect survival [1]. BM from lung cancer account for 50% of the cases with BM. To reduce neurocognitive side effects, instead of whole-brain radiotherapy (WBRT), surgery and upfront stereotactic radiotherapy (SRT) have become the standard treatment approaches in limited BM [2, 3]. In a prospective European Organisation for Research and Treatment of Cancer (EORTC) study, the local control rate was found to be increased (69% vs 41%) with stereotactic radiosurgery (SRS) compared with that from surgery. However, there was no difference in overall survival (OS) [4]. In addition, SRT is an alternative treatment method for patients who are not suitable for surgery due to tumor location or medical conditions.

SRT is called SRS when used in a single fraction (fx), and hypofractionated SRT (hSRT) when applied in 1–5 fx. SRT has the advantages of being more effective radiobiologically, providing better local control, and increasing treatment compliance and comfort in patients who are not suitable for long-term radiotherapy (RT) applications due to age and comorbidities [5]. SRT can be applied with Gamma-Knife (GK), CyberKnife (CK) and linear accelerator (LINAC)- based devices.

The importance of prognostic factors such as recursive partition analysis (RPA), disease-specific graded prognostic assessment (DS-GPA), baseline score for BM (BSBM) and score index for stereotactic radiotherapy (SIR) has been demonstrated in patients with BM receiving SRT [6-9]. A wide variety of prognostic factors including age, Karnofsky performance status (KPS), extracranial disease status, number of BM, largest brain lesion volume, location of BM, and receiving WBRT or not have been used for these classifications. RPA class 1-2 versus class 3 and higher GPA score reflect a more favorable baseline. In a study by Fessart *et al.,* CK-based SRT was shown to be effective with high local control and low toxicity for 100 patients with BM with lung cancer, and the GPA score in terms of survival and the number of BM for local control was found to be significant [10].

CK is a frameless robotic treatment system developed for SRT applications [11]. Thanks to the 6 MV energy LINAC placed on the robotic movable arm, isocentric, non-isocentric, and non-coplanar treatments can be performed under image guidance using diagnostic X-rays. The CK system increases patient comfort and treatment results with conformal dose distribution with submillimetric accuracy, and reduces damage to healthy tissues.

Next-generation CyberKnife Model 6 (CK-M6) device (Accuray, Sunnyvale, CA, USA) includes fixed

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collimator as well as IRIS variable collimator and InCise2 multileaf collimator (MLC) system. It offers faster optimization and better plan quality with the updated treatment planning system (TPS) including VOLO optimizer (Precision 2.0, Accuray, Sunnyvale, CA, USA) [12]. In addition, the respective numbers of node positions, beams, segments (MLC only) and monitor units have been reduced and the treatment is completed in a shorter time.

The balance between local control and radionecrosis is an important issue in SRT applications for BM. Although local control is improved with the use of SRT compared with that from conventional RT, radionecrosis is more common as a late side effect depends on dosimetric factors and presence of comorbidities [13]. Various planning parameters are used for radionecrosis risk estimation. The 50% –80% isodose line is typically chosen for the prescribed dose in CK-based planning [14]. Xuyao *et al.* demonstrated that healthy brain tissue was preserved more with faster dose fall-off in plans using 60% –65% isodose line compared with 70% –80% isodose line, but dose homogeneity of planning target volume (PTV) decreased, and monitor units and treatment time increased [14]. Zindler *et al*. defined the maximum dose allowed in PTV as 140% (70% isodose line) of the prescription dose [15]. Cut-off values of 10 or 12 Gy for SRS (V_{10Gy}, $V_{12\,Gy}$) and 18 Gy for SRT ($V_{18\,Gy}$) have been reported as key parameters for healthy brain tissue excluding the target volume [3].

In this study, we aimed to evaluate the efficacy, local control, dosimetric factors, side effects, and survival in non-small cell lung cancer (NSCLC) patients with limited BM who underwent CK-M6-based SRT.

MATERIALS AND METHODS

Patients with histologically confirmed NSCLC, age ≥ 18 years, KPS ≥ 60, 1–3 BM, the largest metastasis or cavity size ≤ 4 cm, and able to adapt to treatment were included in the study. Written informed consent was obtained from all patients. The study was approved by the local ethics committee (no: 2018-7/6).

Study population and preparation

Twenty patients and 40 targets with intact metastases or surgical cavity treated with SRT from October 2018 to October 2020 were included in this study. Postoperative SRT was applied 2–3 weeks after surgery for cavity reduction. Cranial magnetic resonance imaging (MRI) with 1.0 mm slice thickness (Achieva 3.0 T Tx; Philips Medical Systems, Best, The Netherlands) was performed for treatment planning. Patients were fixed with a noninvasive cranial mask in the supine position on the same day and simulation images were captured with a slice thickness of 1.0 mm using a computed tomography (CT) scanner (Lightspeed RT16, GE Healthcare Technologies, Waukesha, WI). MRI and CT images transferred to TPS were fused. Organs at risk (OAR) were automatically contoured. Visible gross target or cavity volume (GTV) was contoured using T1-weighted contrast-enhanced MRI slices. PTV margins of 0–1 mm for intact metastases and 2 mm for cavity volume were added by isotropic expansion. In target volumes close to the OAR, the PTV margin was modified. The treatment dose and fx number were chosen considering tumor size and proximity to critical organs. SRS dose was prescribed under the guidance of Radiation Therapy Oncology Group (RTOG) 90-05 study [16]. The American Association of Physicists in Medicine Task Group (AAPM TG) 101 guidelines were considered for dose restrictions for OAR such as the brainstem, spinal cord, optic nerves, chiasma, eyes, lenses, pituitary gland and cochlea [17]. Whole brain minus GTV (WB-GTV) was considered the dosimetric parameter for healthy brain tissue and cut-off values of V_{10Gy} (<12 cm^3) and V_{12Gy} (<10 cm^3) for SRS and V_{18Gy} (<30 cm^3) for hSRT were used. Dose -limiting shells were created around the PTV (1-, 5-20 mm away) to achieve an optimal dose distribution in a healthy brain tissue. Ray tracing algorithm was used for fixed collimator, and finite size pencil-beam algorithm was used for MLC collimator (Precision 2.0, Accuray, Sunnyvale, CA, USA). The VOLO optimizer was used to create treatment plans with a high resolution calculation method through inverse optimization and a non-isocentric algorithm. The maximum accepted number of nodes was 170. The treatment plan was created to cover 95% of the prescribed dose of PTV. In cases with multiple metastases, a single plan was created if the targets were ≤ 3 cm close to each other (figure 1). Patients were treated consecutively or every other day on the CK-M6 device. kV image pairs were usually taken on an interval between 20 and 60 s based on patient positioning stability.

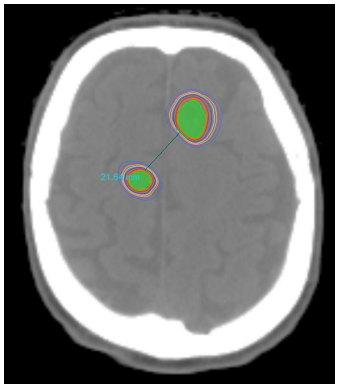


Figure 1. A single isocentric plan for multiple targets in a case with a distance of less than 3 cm between targets (In this figure, the distance between targets is 21.64 mm).

Quality assurance

For successful treatment with CK, it is very important to deliver the dose with millimetric accuracy within ± 5% of the target. SRT is a very complex treatment method and patient-specific

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quality assurance measurements should be verified prior to the treatment. In this study, under the guidance of AAPM-TG 135, end-to-end testing was performed using Gafchromic EBT3 film dosimetry (Ashland Specialty Ingredients Technology, USA) [18]. For absolute point dose measurements, 30×30 cm^2 water-equivalent solid RW3 slab phantoms (PTW, Freiburg, Germany), calibrated PinPoint ionization chamber with 0.015 cm^3 precision volume (Model 31014; PTW, Freiburg, Germany) and PTW Unidos electrometer (PTW, Freiburg, Germany) were used. CT images were taken with a slice thickness of 1.0 mm and transferred to water-equivalent solid RW3 slab phantom CT images. Isodose curves were created on ion chamber-sensitive volumes. Point dose measurement was taken for each plan. The dose difference calculated by TPS in PinPoint mean dose and PinPoint sensitive volume was ±3%.

Treatment and follow-up

Patients were given prophylactic dexamethasone before treatment. Patients were followed up with cranial MRI second month after treatment, every three months for one year, then at decreasing intervals. Response evaluation was performed in accordance with the Response Evaluation Criteria in Solid Tumours, 1.1 criteria [19]. Prognostic evaluation was performed with the classification of RPA and DS-GPA [6, 7]. Acute and late side effects were evaluated according to the Common Terminology Criteria for Adverse Events, v5.0. During the follow-up, SRT was applied in case of local recurrence or new limited cranial metastases.

Statistical analysis

Statistical analysis was performed using SPSS 21 (SPSS Inc, Chicago, IL, USA). Survival analysis was carried out from the beginning of SRT using the Kaplan-Meier test. Log-rank test was used in univariate analysis. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 40 targets in 20 patients were included in the present study. Patients characteristics are summarized in table 1. Data regarding age, lesion size, prescription dose, and so on are reported hereafter in terms of median, and the ranges are specified in brackets. The median age was 61 years (46-80 years) and the most common histological diagnosis was adenocarcinoma. One patients with limited BM at diagnosis with small-cell carcinoma included in the study. Primary lung lesion was treated with surgery in five cases, and with RT in five cases, and various-line chemotherapy was given to 15 cases. Before SRT, 30 Gy WBRT was applied to five patients, two of whom were postoperative.

Systemic therapy was given to 11 patients (55%) following SRT.

Table 1. Clinical characteristics. LCNEC (large cell neuroendocrin carcinoma), NSCLC (non-small cell lung cancer), SCLC (small cell lung cancer), SRT (stereotactic radiotherapy), KPS (Karnofsky performance status), RPA (recursive partitioning analysis), DS-GPA (Disease specific graded prognostic assessment).

Features	N (%)
Age, years, median (range)	61 (46-80)
Male/Female	18/2
Histology	
Adenocarcinoma	12 (60)
Squamous cell carcinoma	2 (10)
Others [AdenoSCC (1), LCNEC (1), NSCLC (3), SCLC (1)]	6 (30)
Primary stage at diagnosis	
I	3 (15)
II	2 (10)
III	12 (60)
IV	3 (15)
Primary stage before SRT	
I	1 (5)
II	3 (15)
III	8 (40)
IV	8 (40)
KPS before SRT, median (range)	80 (50-90)
RPA classification	
1	5 (25)
2	12 (60)
3	3 (15)
DS-GPA score	
0-2	10 (50)
2,5-4	10 (50)
Number of brain metastases, median (range)	2 (1-5)
Single metastases (n, %)	8 (40)
Multiple metastases (n, %)	12 (60)
Brain metastases localization	
Cerebellum	9 (22.5)
Occipital	8 (20)
Frontal	7 (17.5)
Parietal	7 (17.5)
Temporal	7 (17.5)
Temporoparietal	2 (5)

BM were present in 11 cases at the time of diagnosis, and developed metachronously in nine cases in 19 months (2-65 months). Before the study, the number of BM was 1 (1-4 BM), while it increased to 2 (1–5 BM) with MRI before SRT. Nine BM in eight patients were removed by macroscopic total excision. The interval from diagnosis or recurrence to SRT for intact metastases was 40 days (13-155 days), while it was 47 days (20-204 days) in operated patients from surgery to SRT. The interval of planning MRI to SRT was 4 days (1–19 days). The RPA class was 2 (1 to 3) and the DS-GPA score was 2 (0,5 to 4), before SRT.

The median lesion size was 11 mm (2-38 mm), 10 mm (2-32 mm) and 21 mm (18-8 mm) and the bigger lesion ratio (i.e., > 2 cm) was 22,5% (9/40), 13% (4/31) and 55% (5/9), for all metastases, intact metastases and cavitary lesions, respectively (table 2). The GTV and PTV volumes were 0.76 cm^3 (0.01–

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17.9 cm^3) and 1.16 cm^3 (0.05-26.76 cm^3), respectively. For a total of 40 lesions, the prescription dose was 24 Gy/3 fx (18-30 Gy/1–6 fx) and the biologically effective dose (BED_{10Gy}) was 50,4 Gy (37.5-60.0). Eight patients underwent irradiation for a single lesion. In 12 cases with multiple lesions, 2 lesions (2–5 lesions) per patient and a total of 32 lesions received 20 Gy/1 fx (18-30 Gy/1–5 fx) SRT. In three cases, there were 1–2 intact metastases in additon to cavitary lesion and were simultaneously irradiated. SRT was applied to two cavities in one patient.

Patients were evaluated in March 2021. Median follow-up and OS were 9 months (1-15 months), and 13 months (1-25 months) from beginning of SRT, respectively. At the first evaluation performed 2 months (2-3 months) after SRT, objective/stable response was found in 88% (15/17) for patients and 84% (27/32) for lesions. Five lesions in two patients showed progressive disease. Three patients were not evaluated, and two of them died in the first or third months. At the second evaluation, performed 5 months (4-8 months) after SRT, six patients died in 3 months (1-6 months). The objective/stable response was 83% (10/12) for patients and 87% (20/23) for lesions. Three lesions in two patients were progressive. In the time of the third evaluation, performed 12 months (9-14 months) after SRT, a total of nine patients (45%) died at a 4 months (1-13 months). The objective/stable response was 67% (6/9) for patients and 73% (11/15) for lesions. The cause of death was lung infection (n=2), systemic progression (n=4), and COVID-19-related pneumonia (n=1), and it was unknown in two cases.

Local, distant and combined brain recurrence were observed in 1, 3, and 1 patients, respectively. The target size was 10 mm (2.5-18 mm) in five relapsed patients who received 18-27 Gy/1-3 fx. The BED_{10Gy} was 51,3 Gy (50.4–60.0) for these recurrent patients, and not different for unrecurrent patients (48 Gy, rang: 37.5-60.0). Progression was considered to be associated with the presence of intact metastases for these cases. Leptomeningeal metastases were noticed after two months in one patient (5%) who underwent 20 Gy/1 fx SRS for three metastases. This patients died in four months after SRS despite receiving salvage WBRT and chemotherapy. No recurrence was observed in any of the eight patients who received cavitary irradiation. At the time of analysis, the local control rate was 88% (15/17) and the intracranial control rate was 70.5% (12/17) for all patients. In one patient who received 20 Gy/1 fx SRS due to right parahippocampal metastasis, recurrence was observed in nine months and 24 Gy/3 fx re-SRT was performed. WBRT (30 Gy/10 fx) was given to two patients who progressed. The other patient received systemic treatment. In one case, 25 Gy/5 fx SRT was applied to new distant brain metastasis.

A median of 10 mm (7.5-15 mm) sized fixed collimator was used for 20 metastases, and MLC was used for the other 20 metastases. The median numbers of nodes and beams were 30 (17-134) and 42 (17-134) for all plans. The respective number of nodes and beams were 30 (21-134) and 64 (23-134) for plans using the fixed collimator. For MLC-based plans, the respective numbers of nodes, beams and segments were 29 (17-83), 23 (17-71), and 32 (18-80). The number of segments per beam was 1 or 2 in MLC-based plans. The median conformity index, new conformity index, and homogenity index values were 1.09 (1.01-3.14), 1.13 (1.01-3.31) and 1.16 (1.08-11.25), respectively. Prescription isodose covering 95% of PTV, coverage and monitor unit values were 85.9% (80.0-92.7), 95.17% (68-134) and 5603.1 (2395-11681.7), respectively (table 2). The dose gradient index was 5.38 (2.16-16.0) for patients with single metastasis. The planned treatment time including estimated set-up time and image interval was 20 min (13-35 min). The planned treatment time was 23 min (15-35 min) and 18 min (13-32 min) for the plans using fixed collimator and MLC, respectively. While the lesion was adjacent to the brainstem in two cases, the median OAR distance was 30 mm (7-110 mm) in the other cases. OAR doses were not exceeded in any of the cases (table 3). The median V_{10Gy}, V_{12Gy}, and $V_{18\,Gy}$ values for healthy brain tissue were 3.37 cm^3 (0.44-16.28 cm^3), 2.36 cm^3 (0.3-12.26 cm^3) and 7.16 cm^3 (2.2-31.78 cm^3), respectively. For patients with multitargets, single isocentric planning was found effective and the median V_{18Gy} was 8.96 cm^3 (4.16-23 cm^3).

Acute mucositis developed in one patient during treatment and regressed with medication. Asymptomatic radionecrosis was observed in 23.5% of patients (4/17) and 12% of lesions (4/33), respectively in a median of 8 months (6-12 months). The radionecrosis rate was 5% (1/19) in lesions treated with SRS, while it was 14% (3/21) in lesions treated with hSRT. Prescription dose was 18–30 Gy/1–6 fx, and BED_{10Gy} ranged from 37.5 to 51.3 Gy in these patients. The target size was 7, 15, 18, and 38 mm for these patients, and two patients had a history of WBRT. The V_{18Gy} value for a healthy brain tissue was 31.78 cm^3 in a patient with 38 mm lesion size who was given 30 Gy/6 fx hSRT and, who had undergone previous surgery and WBRT. For the other three cases, the dose of healthy brain tissue was below the limits and was not found to be associated with radionecrosis. Since the number is small, the relationship between radionecrosis and tumor size and dose could not be elucidated.

Owing to the small size of study and the few recurrences, statistical analysis could not be performed in terms of recurrences. Factors positively affecting OS were KPS≥80 (mean; 18.21 versus 5.60 months, p=0.017), RPA 1-2 classification (mean; RPA1: 20.80, RPA2: 12.35 and RPA3: 3.3 months,

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p=0.006) and DS-GPA score ≥2.5 (mean; 20.70 versus 9.01 months, p=0.043) in univariate analysis (figure 2). Presence of synchronous metastases was a nonsignificantly adverse prognostic factor for OS (mean; 11,72 versus 17.33 months, p=0.092). Multivariate analysis could not be performed because the size of study was small.

Table 2. Dosimetric features. GTV (gross target volume), PTV (planning target volume), BED_{10Gy} (biologically effective dose for tumor).

Features	N (%)
Lesion size, mm, median (range)	11 (2-38)
Cavity (n: 9)	21 (17-38)
Intact metastasis (n: 31)	10 (2-32)
Lesion size, mm	
≤ 10	19 (47.5)
≥ 11-20	12 (30)
≥ 21-30	6 (15)
> 30	3 (7.5)
GTV volume, cm3, median (range)	0.71 (0.01-17.9)
< 1	23 (57.5)
≥ 1- 3	9 (22.5)
≥ 3.1	8 (4)
PTV volume, cm3, median (range)	1.07 (0.05-26.76)
< 1	18 (45)
≥ 1-3	12 (30)
≥ 3,1	10 (6)
Prescription dose, Gy/fx, median (range)	24 Gy/3 fx (18-30/1-6 fx)
18 Gy/1 fx	8 (20)
20 Gy/1 fx	11 (27.5)
24 Gy/3 fx	8 (20)
25 Gy/5 fx	3 (7.5)
27 Gy/3 fx	7 (17.5)
30 Gy/5 fx	2 (5)
30 Gy/6 fx	1 (2.5)
BED_{10Gy} (Gy), Median (range)	50,4 (37.5-60)
≤ 50	14 (35)
≥ 50.1 -59	15 (37.5)
60	11 (27.5)
Collimator type	
Fixed	20 (50)
InCise multileaf	20 (50)
Number of nodes, median (range)	30 (17-134)
Number of beams, median (range)	42 (17-134)
Number of segments (n: 20), median (range)	32 (18-80)
Conformity index, median (range)	1.09 (1.01-3.14)
New conformity index, median (range)	1.13 (1.01-3,31)
Homogeneity index, median (range)	1.16 (1.08-11.25)
Prescription isodose, median, % (range)	85.9 (80-92.7)
Coverage, median, % (range)	95.17 (68-134)
Monitor units, median (range)	5603.1 (2395-11681.7)
Treatment time (minutes), median (range)	20 (13-35)

Table 3. Organ at risk (OAR) values, WB-GTV (Whole brain minus gross target volume).

OAR dose	Volume, median (range), Gy	Dmax, median (range), Gy
Chiasm (0.2 cm^3)	0.42 (0.11-2.89)	1.04 (0.08-4.86)
Right optik nerve (0.2 cm^3)	0.13 (0.02-3.04)	0.48 (0.03-5.76)
Left optik nerve (0.2 cm^3)	0.15 (0.01-5.92)	0.23 (0.03-8.44)
Brainstem (0.5 cm^3)	4.08 (0.85-23.25)	5.29 (1.24-28.81)
Spinal cord		
0.35 cm^3	1.07 (0.07-8.65)	1.18 (0.08-16.53)
1.2 cm^3	0.77 (0-5.05)	
WB-GTV (cut-off, cm^3)		
$V10_{Gy}$ (12 cm^3)	3.37 (0.44-16.28)	
$V12_{Gy}$ (10 cm^3)	2.36 (0.3-12.26)	
$V18_{Gy}$ (30 cm^3)	7.16 (2.2-31.78)	

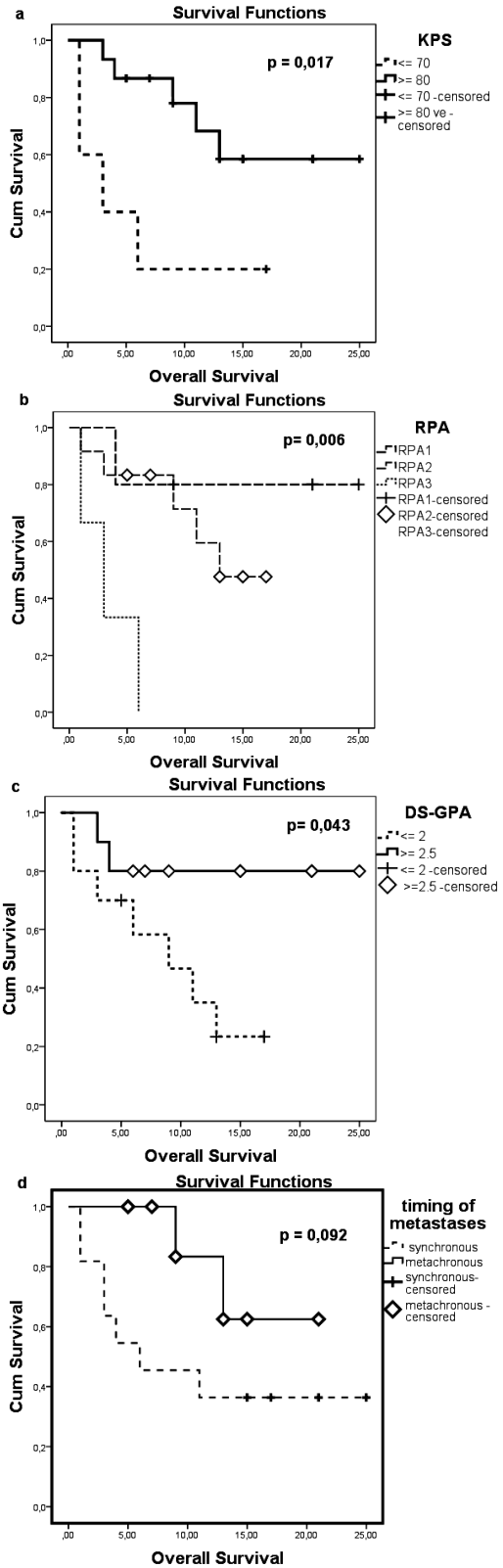


Figure 2. Overall survival according to favorable prognostic factors in univariate analysis. **a)** Karnofsky performance status (KPS) ≥ 80 (p=0, 017), **b)** Recursive partitioning analysis (RPA) 1 -2 (p=0,006). **c)** Disease-specific graded prognostic assessment analysis (DS-GPA) score ≥ 2,5 (p=0,043), **d)** Timing of metastases (presence of metachronous metastases) (p= 0,092).

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DISCUSSION

This study aimed to evaluate the efficacy of CK-M6 based SRT in NSCLC patients with limited BM.

Currently, upfront SRT is standard in patients with limited BM. Fessart *et al.* evaluated 100 lung cancer patients treated with CK-based SRT, 67% of whom had a single BM [10]. They applied 20–25 Gy/1 fx SRS or 24–36 Gy/3–5 fx hSRT to 80% isodose line. One year local control, distant brain control and grade 3–4 toxicity were reported as 79%, 43%, and 2% –3%, respectively, with a median survival of 10 months. In the multivariate analysis, GPA for OS, and the number of BM and the presence of metachronous metastases for local control were significant. CK-based SRT was found to be effective with low morbidity in this study.

In metastases larger than 3 cm, the primary treatment is surgery with a 40% local control rate [20]. Compared with observation or adjuvant WBRT, postoperative SRT alone is now the standard because of no difference in OS, better local control and fewer side effects [20, 21]. In the ESTRON study, KPS≤70, incomplete resection and large cavity volume were identified as unfavorable factors for local control and OS [22]. In the study of Atalar *et al.*, the benefit of waiting more than 1-2 weeks for cavity shrinkage was not demonstrated [23]. hSRT is also an alternative and effective treatment method in larger metastases or close to OAR that are not suitable for surgery and provides radiobiological advantage in terms of local control and toxicity [24, 25]. Lischalk *et al.* performed 35 Gy (30-40 Gy)/5 fx CK-based hSRT in 20 high-risk patients who had BM size of > 2 cm or within an eloquent cortex [24]. In their study, one-year local control, OS and symptomatic radionecrosis was 90%, 45%, and 20%, respectively and the cut-off dose for neurotoxicity was reported as 40 Gy.

In our study, a median of 13 months OS was achieved with 88% local control rate and 70.5% intracranial control rate during the follow-up period. In terms of OS, KPS≥80, RPA 1-2 classification and DS -GPA score ≥2.5 were favorable factors, while the presence of synchronous metastases was recognized as an unfavorable factor. In this study, a median of 2 [2–5] and a total of 40 BM were detected with planning MRI, an increase of 33%. Wardak *et al*. reported that 34% more metastases were seen if the planning MRI had a slice thickness of 1.0 mm [26]. In their study, the presence of large size and ≥ 4 metastases were also found to be significant in terms of additional metastases.

The balance between local control and radionecrosis is critical issue in SRT application and is associated with the treatment volume, fraction dose, fraction number, prescription isodose, PTV margin, and healthy brain dose. The maximum tolerated dose according to lesion size in cranial SRS application was demonstrated by the RTOG 90-05 study [16]. The cut-off value for large size varied as ≥2 or ≥4 cm in different studies [14, 27]. While the safe single dose for < 2 and 2–3 cm of intact metastases was 18 and 15 Gy in the ESTRON study, the dose constraints for the same cavity size were reported as 20 and 18 Gy, respectively (28). If lesion size was >3 cm, 30 Gy/5 fx was recommended. A cohort study, revealed a lesser radionecrosis (9% versus 19%) with LINAC-based hSRT (27 Gy/3 fx) compared with SRS for >2 cm diameter of BM [29]. The importance of the PTV margin in terms of local control and radionecrosis was investigated. In a study including 78 BM with ≤3 cm diameter who underwent LINAC-based 20 Gy/1 fx SRS with a 1 mm PTV margin, two-year local control rate found to be increased compared with those without margin (51% versus 20%) [30]. On the other hand, at least 2 mm margin should be given to cavitary metastases to achieve a better local control, and it has been reported that the risk of radionecrosis and leptomeningeal metastases is reduced when hSRT is used despite using a wide margin [31]. A meta-analysis of 24 studies reported better one-year local control (83% versus 77%) and lesser radionecrosis (7% versus 23%) with hSRT compared with SRS [25].

The risk of radionecrosis has been reported to increase with the healthy brain tissue (>10 cm^3) receiving 30 Gy, previous history of SRS/WBRT, use of immunotherapy, and presence of intact metastases. Zindler *et al.* emphasized that the dose gradient outside of PTV should be as sharp as possible for healthy brain sparing [15]. Lee *et al.* evaluated 15 patients who received CK-based SRS using Multiplan TPS (Accuray, Sunnyvale, CA, USA) [32]. Although a sharp dose reduction was observed outside the PTV with 50% isodose line selection, the best conformal plan was achieved with 65% isodose line. In the study of McGuinnes *et al*., including five patients with BM, a more homogeneous dose distribution was obtained with an isodose line of 86%-93% with equal coverage, suitability and OAR protection with MLC-based plans compared with fixed collimator plans [33]. Furthermore the average treatment time was reduced by 50% from 31 to 17 min, with an average 70% reduction in monitor units. For a healthy brain tissue dose below the threshold value, the risk of radionecrosis is reported as <10% in the literature [3, 27]. In our study, hSRT was preferred in lesions with large size or near the OAR. A PTV margin of 2 mm for cavity and 0–1 mm for intact metastases were considered sufficient and 88% local control obtained. Although the median cavity size was larger, none of the eight patients who received hSRT had recurrence.

The radiobiological efficacy of SRT was associated with duration of treatment and BED value [34]. In general, the treatment time depends on the prescription isodose, collimator size, number of isocenters, and number of beams, and varies as a

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function of dose rate and includes setup, imaging, robot motion, and beam delivery time, with the greatest loss seen due to internodal robot motion [34, 35]. In the study of GK-ICON- based SRS/hSRT, a median of 1 [1-7] pause was reported within a median of 23 min (4–108 min) treatment time [36]. The study affirmed that for a treatment duration >19 min, other techniques should be applied. Millar et al emphasized that BED regressed to 65% as the treatment was prolonged due to repair and repopulation of tumor cells [35]. It has been reported that BED_{12Gy} and BED_{10Gy} should be at least 40 Gy and ≥50 Gy, respectively, to achieve a one-year local control ≥ 70% in patients with BM [37, 38]. In patients with multiple BM in a diameter of ≥2 cm treated with 15 Gy/1 fx LINAC-based SRS (BED_{10Gy} =37.5), the probability of tumor control (TCP) was estimated as 42% [39]. On the other hand, the fractionation effect provides increased efficacy as well as reduces normal tissue toxicity, especially in large BM [40]. In large metastases, considering BED_{2Gy} for normal tissues, and BED_{10Gy} for lesions, the best risk-benefit ratio through BED manipulation was found to be 27 Gy/3 fx (BED_{10Gy} =51.3, TCP 55%, BED_{2Gy}=148.5) or 30 Gy/5 fx (BED_{10Gy} =48, TCP 68%, BED_{2Gy}=120) [3, 25, 27, 41].

In SRT applications, though local recurrence decreases, the toxicity increases as the conformity increases with homogeneous dose distribution. It has been shown that MLC-based plans have the advantage of increasing the conformity index, creating a single plan for irregular and multiple targets, and reducing beam-on time (BOT) by 30%-40% compared with cone-based plans [42]. With new optimization techniques such as the VOLO optimizer, it has been possible to provide monitor units, treatment time, body dose, image interval, image dose reduction, and, patient position stability [12]. In patients undergoing CK-based SRT, compared with IRIS-based sequential optimizer plans (Multiplan, Accuray, USA), in MLC-based VOLO planning, it has been reported to reduce 47% of treatment time (41.6 to 22.2 min), 70% of monitor units (33.597 to 10.335), 2% of conformity index (1.18 to 1.16) and 11% of dose gradient index (3.10 to 2.75%) (12). The dosimetric findings of 10 patients with ≥2 BM who underwent a median of 27 Gy/3 fx (21–30 Gy/3–5 fx), Han *et al.* compared LINAC-based hSRT with GK-ICON and CK-M6 plans [43]. The researchers noted that although target coverage was similar, mean dose gradient index was lower in GK-based and CK-based plans compared with LINAC based plans (3.1 versus 3.1 versus 4.1, respectively) and healthy brain dose (i.e., V_{12Gy}, V_{20Gy}) was reduced by 20%. BOT was 64, 31 and 4 min for GK-, CK- and LINAC- based hSRT, respectively. Due to the long duration of treatment with GK and the presence of residual rotational error with LINAC, it can be said that the most appropriate time-effective treatment option is CK-based SRT applications.

In our study, the median BED_{10Gy} was 50.4 Gy and there was no association with radionecrosis or recurrences. The median number of nodes, beams and treatment time was lower in MLC-based plans compared with fixed collimator plans.

The limitations of the study include small patient population with heterogeneous features such as intact and cavity lesions, use of single and multiple isocentric plans, use of different collimators, use of different dose regimens, and a short follow-up period.

CONCLUSION

In this study, we achieved 88% local control, and 70.5% intracranial control with a median survival of 13 months for 40 BM in 20 NSCLC patients treated with upfront or postoperative SRS/hSRT. Asymptomatic radionecrosis was observed at the rate of 23.5% of patients and was in agreement with the literature. With a median treatment time of 20 min, CK-M6-based SRT was found to be effective, safe and comfortable.

***Ethical statement*:** The study was approved by the ethics committee (no: 2018-7/6) of Medical Faculty of Bursa Uludag University of Turkey.

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***Author's contributions*:** SS designed the study. SGT, AK, and ZKI performed treatment planning. SS treated and follow-up the patients. SS, SGT, AK and ZKI collected the data. SS performed the statistically analysis and wrote the manuscript. All authors read and approved the final manuscript.

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