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Adjuvant therapy after resection of brain metastases

Frameless image-guided LINAC-based radiosurgery and stereotactic hypofractionated radiotherapy

Up until now, whole-brain radiation therapy (WBRT) has been the standard adjuvant therapy following resection of brain metastases, since it decreases the rate of local and distant recurrence in the brain [16]. WBRT with the addition of a boost to the resection cavity has been shown to increase local control (LC) rates. Since no survival benefit has been demonstrated for WBRT in addition to surgery or SRS, there is interest avoiding the potential neurocognitive sequelae associated with this treatment [12]. Recently, several retrospective reports have demonstrated that stereotactic radiosurgery (SRS) or stereotactic hypofractionated radiotherapy (SHRT) directed at the resection cavity can reduce local failure rates [19, 25]. Most patients were treated with frame-based stereotactic systems such as the Gamma Knife (Elekta, Stockholm, Sweden) or dedicated stereotactic LINAC systems [7, 10, 15]. Frameless image-guided intracranial stereotactic LINAC radiosurgery for brain metastases has recently been introduced and clinical outcomes are comparable to those after frame-based radiosurgery techniques [4, 11]. Here we report on clinical outcome and LC in patients who underwent adjuvant frameless image-guided LINAC-based SRS and SHRT after resection of brain metastases.

Materials and methods

Patients and study design

This retrospective study was approved by the local ethics committee. Between March 2009 and February 2012, 44 surgical cavities in 42 patients were treated with frameless image-guided LINAC-based SRS or SHRT. Of these patients, 35 had total gross resection of the metastasis, which was confirmed by MRI within 24 h after surgery. Patients with one or two further brain metastases were included and treated by SRS. Patients with prior WBRT were excluded. For each patient, the Radiation Therapy Oncology Group recursive partitioning analysis (RTOG RPA) classification and Graded Prognostic Assessment (GPA) scores were calculated [24]. Acute and late toxicities were evaluated using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 grading system. Clinical status evaluation and imaging examinations were performed at 3–6-month intervals. To assess local recurrence, new distant brain metastases and radionecrosis, all posttreatment MRIs were reviewed by a radiation oncologist, a neuroradiologist and a neurosurgeon. Radionecrosis was scored according to Late Effects in Normal Tissue—Subjective, Objective, Management and Analytic (LENT-SOMA) criteria [20].

Frameless SRS and SHRT procedures

All patients were immobilized using a thermoplastic stereotactic frameless head mask (BrainLAB, Feldkirchen, Germany). Postoperative helical CT images of 1.5-mm slice thickness were obtained and fused with postoperative T1 contrast-enhanced MPRAGE and T2-3D sequences that were not older than 2 weeks prior to irradiation. The clinical target volume (CTV) was defined as the resection cavity including the surgical defect and any contrast enhancement, plus a 2-mm margin in all directions. For definition of planning target volume (PTV), a 1-mm margin was added to the CTV in all directions. Planning was carried out using the BrainLAB® iPlan planning system versions 4.1 and 4.5 (BrainLAB). All patients were irradiated with a single isocenter.

Tab. 1 Patient characteristics

Patient characteristic	Finding
Median age in years (range)	67 (40–79)
Gender	
– Female	19
– Male	23
KPS median (range)	80 (60–100)
Primary tumor	
– NSCLC	19 (45%)
– Melanoma	9 (21%)
– GI cancer	6 (14%)
– Breast cancer	5 (12%)
– Gynecological cancer	2 (5%)
– CUP	1 (3%)
RPA classification	
– 1	13 (31%)
– 2	25 (60%)
– 3	4 (9%)
GPA score	
– 0–1	6 (14%)
– 1.5–2.5	26 (62%)
– 3.0–4.0	10 (24%)
Single BM	16 (38%)
Solitary BM	17 (40%)
2–3 BM	9 (22%)
Synchr./metachr. BM	10/32 (24/76%)
SRS	23 cavities
– PTV (median and range)	11 cm^3 (2–17 cm^3)
– CI median (range)	1.29 (1.02–1.7)
– CI mean (SD)	1.31 (0.18)
SHRT	21 cavities
– PTV (median and range)	22 cm^3 (14–44 cm^3)
– CI median (range)	1.2 (1.05–1.7)
– CI mean (SD)	1.2 (0.17)
– Fractionation	6×4 Gy 6/29%
	4×6 Gy 5/24%
	10×4 Gy 10/47%

KPS Karnofsky Performance Score, *NSCLC* non-small cell lung cancer, *GI* gastrointestinal, *CUP* cancer of unknown primary origin, *RPA* recursive partitioning analysis, *GPA* Graded Prognostic Assessment, *BM* brain metastases, *Single BM* only one BM but other sites of distant disease, *solitary BM* one BM as sole site of distant disease, *synchr. BM* synchronous BM detected during primary staging, *metachr. BM* metachronous BM detected during restaging, *SRS* stereotactic radiosurgery, *SHRT* stereotactic hypofractionated radiotherapy, *PTV* planning target volume, *CI* conformity index, *SD* standard deviation.

Dose–volume histograms (DVH) were calculated for the target volumes and organs at risk. We used a conformity index (CI) defined according the following formula: (1+ volume of tissue outside PTV receiving at least the prescribed dose/volume of PTV receiving at least the prescribed dose). For SRS planning we evaluated the normal brain volume irradiated with 12 Gy ($V_{12\,Gy}$) or 10 Gy ($V_{10\,Gy}$), according to previously published reports [3, 13]. For SHRT planning we evaluated the volume of normal brain irradiated with more than 4 Gy ($V_{4\,Gy}$) per fraction [8]. The prescribed SRS dose range was 17–18 Gy for PTVs with a volume ≤10 cm^3. Dose was prescribed in order to cover at least 95% of the PTV. For larger cavities, the dose concepts of SHRT were 4×6 Gy, 6×4 Gy and 10×4 Gy. The fractionation scheme of 4×6 Gy was used for smaller PTVs with a volume ≤20 cm^3. Initially, the dose concept of 6×4 Gy was used for PTVs >20 cm^3, but in order to increase the equivalent dose in 2-Gy fractions (EQD2), 40 Gy was applied in 10 fractions. All treatments were delivered using the Novalis TX® LINAC (Varian Medical Systems Inc., Palo Alto, CA, USA and BrainLAB) in the 6-MV stereotactic mode. Patient setup was performed using the ExacTrac system (BrainLAB). ExacTrac delivers the patient setup error in six dimensions. In this study, the tolerances for the patient setup were 0.8 mm for the three translational axes (longitudinal, lateral and vertical) and 1.0° for the three rotational axes (pitch, roll and couch rotation).

Treatment was delivered using conformal dynamic arcs, intensity-modulated radiation therapy (IMRT) field techniques and hybrid arcs (dynamic arcs and IMRT fields).

Statistics

The analyzed endpoints were LC, distant brain control (DC) and overall survival (OS). LC was defined as the absence of new nodular contrast enhancement adjacent to the resection cavity on MRI. Local recurrence (LR) was defined as new contrast-enhancing lesions within 3 mm of the resection cavity, i.e. within the PTV. New distant brain metastases were defined as new contrast-enhancing lesions outside the PTV. All time-to-event endpoints were measured from the beginning of radiotherapy to either the last follow-up MRI (for recurrence rates), the beginning of salvage radiotherapy (for salvage therapy) or the date of death for OS. Survival rates were calculated using the Kaplan–Meier product limit methodology. Comparison of survival rates according to treatment (SRS vs. SHRT) was performed using a two-sided log-rank test. All analyses were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Patient characteristics are shown in **Tab. 1**. In 7 patients (16%) the postoperative MRI showed residual tumor after resection. At the time of irradiation, extracranial disease was present in 60% of patients. The median time from surgery to irradiation was 40 days (range 15–73 days).

Treatment parameters

Of the 44 surgical cavities in the 42 patients in the current study, 23 lesions (52%) were treated with SRS. The median dose prescription to the PTV margin was 17 Gy (range 16–18 Gy) with maximum and minimum median PTV doses of 17.7 Gy (range 17–20.4 Gy) and 16.8 Gy (range 14.6–18 Gy), respectively. One patient received 16 Gy to the PTV margin because the lesion was near critical structures. The median $V_{10\,Gy}$ and $V_{12\,Gy}$ values were 24.3 cm^3 (range 0.6–45.0 cm^3) and 18.0 cm^3 (range 0.4–28.9 cm^3), respectively. The median PTV for SHRT was 22.3 cm^3; the $V_{4\,Gy}$/fraction was 5.9 cm^3. Mean patient setup errors for SRS and SHRT are summarized in ◘ **Tab. 4**.

Local and distant brain control

The median follow-up was 9.6 months (range 0.9–27.4 months). The median follow-up of living patients (23) was 10.8 months (range 2.4–27.4 months). Radiological follow-up data were not available for 4 patients. Median time to local brain recurrence was 7.3 months (range 3.5–9 months). Median time to any intracranial failure (local or distant) was 5.9 months. LC rates after 6 and 12 months were 91 and 77%, respectively. No statistically significant difference in LC rates between the SRS and SHRT treatments was observed (◘ **Fig. 1**). A total of 4 patients presented local recurrence: 1 patient after SRS treatment with 17 Gy and 3 patients after SHRT treatment with 4×6 Gy, 6×4 Gy and 10×4 Gy. Details of patients with local recurrence are summarized in ◘ **Tab. 2**. Of the 7 patients with residual tumor after surgery, 6 presented no local recurrence; radiological follow-up data were not available for 1 patient. DBC rates at 6 and 12 months were 61 and 33%, respectively. A total of 23 patients (61%) developed brain metastases at new sites during the follow-up period. Tumor growth along the surgical access route was observed in 2 patients, sug-

Abstract · Zusammenfassung

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Adjuvant therapy after resection of brain metastases. Frameless image-guided LINAC-based radiosurgery and stereotactic hypofractionated radiotherapy

Abstract

Background. Tumor bed stereotactic radiosurgery (SRS) after resection of brain metastases is a new strategy to delay or avoid whole-brain irradiation (WBRT) and its associated toxicities. This retrospective study analyzes results of frameless image-guided linear accelerator (LINAC)-based SRS and stereotactic hypofractionated radiotherapy (SHRT) as adjuvant treatment without WBRT.
Materials and methods. Between March 2009 and February 2012, 44 resection cavities in 42 patients were treated with SRS (23 cavities) or SHRT (21 cavities). All treatments were delivered using a stereotactic LINAC. All cavities were expanded by ≥2 mm in all directions to create the clinical target volume (CTV).
Results. The median planning target volume (PTV) for SRS was 11.1 cm^3. The median dose prescribed to the PTV margin for SRS was 17 Gy. Median PTV for SHRT was 22.3 cm^3. The fractionation schemes applied were: 4 fractions of 6 Gy (5 patients), 6 fractions of 4 Gy (6 patients) and 10 fractions of 4 Gy (10 patients). Median follow-up was 9.6 months. Local control (LC) rates after 6 and 12 months were 91 and 77%, respectively. No statistically significant differences in LC rates between SRS and SHRT treatments were observed. Distant brain control (DBC) rates at 6 and 12 months were 61 and 33%, respectively. Overall survival (OS) at 6 and 12 months was 87 and 63.5%, respectively, with a median OS of 15.9 months. One patient treated by SRS showed symptoms of radionecrosis, which was confirmed histologically.
Conclusion. Frameless image-guided LINAC-based adjuvant SRS and SHRT are effective and well tolerated local treatment strategies after resection of brain metastases in patients with oligometastatic disease.

Keywords
Toxicity · Metastases · Survival · Organs at risk · Quality of life

Adjuvante Therapie nach Resektion von Hirnmetastasen. Rahmenlose bildgesteuerte LINAC-basierte Radiochirurgie und stereotaktische hypofraktionierte Strahlentherapie

Zusammenfassung

Hintergrund. Stereotaktische Radiochirurgie (SRS) des Tumorbettes nach Resektion von Hirnmetastasen ist eine neuartige Strategie, um eine adjuvante Ganzhirnbestrahlung (WBRT) mit ihren Toxizitäten aufzuschieben oder zu vermeiden. Die vorliegende Studie untersucht retrospektiv die Resultate rahmenloser bildgesteuerter SRS und stereotaktischer hypofraktionierter Radiotherapie (SHRT) als adjuvante Behandlung ohne WBRT.
Material und Methoden. Zwischen März 2009 und Februar 2012 wurden 44 Resektionshöhlen von 42 Patienten mit SRS (23 Kavitäten) oder SHRT (21 Kavitäten) bestrahlt. Alle Behandlungen wurden mit einem stereotaktischen Linearbeschleuniger durchgeführt. Alle Kavitäten wurden um ≥2 mm zum klinischen Zielvolumen vergrößert.
Ergebnisse. Das mediane Planungszielvolumen (PTV) für SRS betrug 11,1 cm^3. Die mediane Verschreibungsdosis für SRS auf den Rand des PTV lag bei 17 Gy. Das mediane PTV für SHRT ergab 22,3 cm^3. Es wurden Fraktionierungen von 4-mal 6 Gy (5 Patienten), 6-mal 4 Gy (6 Patienten) und 10-mal 4 Gy (10 Patienten) eingesetzt. Die mediane Nachkontrolldauer betrug 9,6 Monate. Die lokale Kontrollrate nach 6 und 12 Monaten betrug 91 bzw. 77%. Es wurde kein statistisch signifikanter Unterschied der lokalen Kontrolle zwischen SRS und SHRT festgestellt. Die Kontrollraten bezüglich weiterer zerebraler Metastasen nach 6 und 12 Monaten waren 61 bzw. 33%. Das Gesamtüberleben nach 6 und 12 Monaten lag bei 87 bzw. 63,5%, mit einem medianen Gesamtüberleben von 15,9 Monaten. Eine symptomatische und histologisch gesicherte Radionekrose zeigte sich bei einer Patientin, die mit SRS behandelt worden war.
Schlussfolgerungen. Rahmenlose bildgesteuerte adjuvante SRS und SHRT mit einem Linearbeschleuniger sind wirksame und gut verträgliche lokale Behandlungen nach Resektion von Hirnmetastasen in oligometastatischen Patienten.

Schlüsselwörter
Toxizität · Metastasen · Überleben · Risikoorgane · Lebensqualität

Tab. 2 Characteristics of patients with a local recurrence

Patient no.	1	2	3	4
Primary tumor	Esophageal cancer	Rectal cancer	Melanoma	Rectal cancer
Dose (Gy)	6×4 Gy	1×17 Gy	10×4 Gy	4×6 Gy
Resection status	R0[a], piecemeal	R0[a], piecemeal	R0[a], piecemeal	R0[a], piecemeal
PTV size (cm^3)	25.8	8.1	30	16.5
Time to recurrence (months)	8.7	6	9	3.5
Salvage treatment	WBRT	SRS	Surgery + SRS	Surgery + WBRT

WBRT whole brain radiation therapy, *SRS* stereotactic radiosurgery, *PTV* planning target volume. [a]R0 status was assessed by postoperative MRI.

Tab. 3 Summary of published frameless image-guided series

Author	Technique	No. cavities	Follow-up (months, median)	Dose (Gy, median)	Margins	Local control (%)	Median OS (months)
Soltys et al. [23]	CK	72	8.1	18.6	No margin[a]	86	15.1
Rwigema et al. [21]	CK	77	13.8	18	1 mm	74	14.5
Choi et al. [6]	CK	120	11	20 (1–5 fractions)	2 mm	89	17
Wang et al. [26]	CK	37	5.5	3×8 Gy	2–3 mm	80	5.5
Prabhu et al. [18]	LINAC	64	9.7	18	2 mm	83	13.4
Kelly et al. [11]	LINAC	18	12.7	18	No margin	89	Not reached
Steinmann et al. [25]	LINAC	33	10.7	10×4 Gy 7×5 Gy 5×6 Gy	4 mm	76	20.2
Present study	LINAC	44	9.6	17 10×4 Gy 4×6 Gy 6×4 Gy	3 mm	77	15.9

OS overall survival, *CK* Cyberknife® (Accuray, Sunnyvale, CA, USA), *LINAC* linear accelerator. [a]Only a minority of cases with 2-mm margins.

Tab. 4 Patient setup accuracy

	Lat. (mm)	Long. (mm)	Vert. (mm)	Pitch (°)	Roll (°)	Rotation (°)
SRS mean (SD)	−0.03 (0.25)	0.00 (0.36)	0.01 (0.26)	0.13 (0.27)	0.00 (0.25)	0.03 (0.24)
SHRT mean (SD)	0.05 (0.32)	0.00 (0.38)	−0.05 (0.30)	−0.06 (0.35)	0.02 (0.24)	−0.05 (0.26)

SRS stereotactic radiosurgery, *SHRT* stereotactic hypofractionated radiotherapy, *SD* standard deviation, *lat* lateral axis, *long* longitudinal axis, *vert* vertical axis, *pitch* angulation to lateral axis, *roll* angulation to longitudinal axis, *rotation* angulation to vertical axis.

gestive of leptomeningeal seeding. Median survival after regional recurrence was 6.4 months. OS at 6 and 12 months was 87 and 63.5%, respectively, with a median OS of 15.9 months (**Fig. 2**). At the last follow-up, 19 of the 42 patients had passed away. Salvage radiotherapy was applied in 16 patients (38%), 15 patients received WBRT and 1 patient was treated using radiosurgery. The median estimated time to salvage irradiation was 13.4 months.

Toxicity

Symptomatic and pathologically proven radionecrosis occurred in 1 patient treated by SRS. This patient received a single dose of 17 Gy. The PTV, $V_{12\,Gy}$ and $V_{10\,Gy}$ values were 13.3 cm^3, 21.5 cm^3 and 29.6 cm^3, respectively. The most frequent acute toxicities were mild headaches and nausea. No acute grade 2 or higher toxicity was observed.

Discussion

In patients with limited brain metastases, the positive effects of WBRT in decreasing the rate of intracranial progression do not translate into survival or quality of life benefits [22]. Up until now, no prospective study including a quality of life assessment has investigated stereotactic irradiation of the resection cavity as an alternative to upfront WBRT after surgery. In light of these findings, it is our practice to omit or defer WBRT in favor of SRS or SHRT in postoperative patients with a limited number of brain metastases. In our study, the LC rates after 6 and 12 months were 91 and 77%, respectively, with a median follow-up of 9.6 months. These results are comparable to the LC rates of 75–90% achieved previously with adjuvant WBRT [17].

Frameless image-guided SRS and SHRT

Noninvasive patient immobilization and frameless image guidance as applied in SRS of brain metastases are techniques that have been recently introduced. A number of reports regarding the accuracy of image-guided methods have demonstrated that submillimeter accuracies can be achieved and that accuracy is comparable to the traditional frame-based approach [5, 9]. In our experience, mean patient setup errors for the SRS and SHRT treatments were comparable to published reports. The number of reports exploring the efficacy and morbidity associated with frameless image-guided SRS and SHRT of the resection cavity is limited ([6, 11, 18, 21, 23, 25, 26], **Tab. 3**). The SRS studies suggest that LC rates of 74–89% can be obtained using a radiosurgical

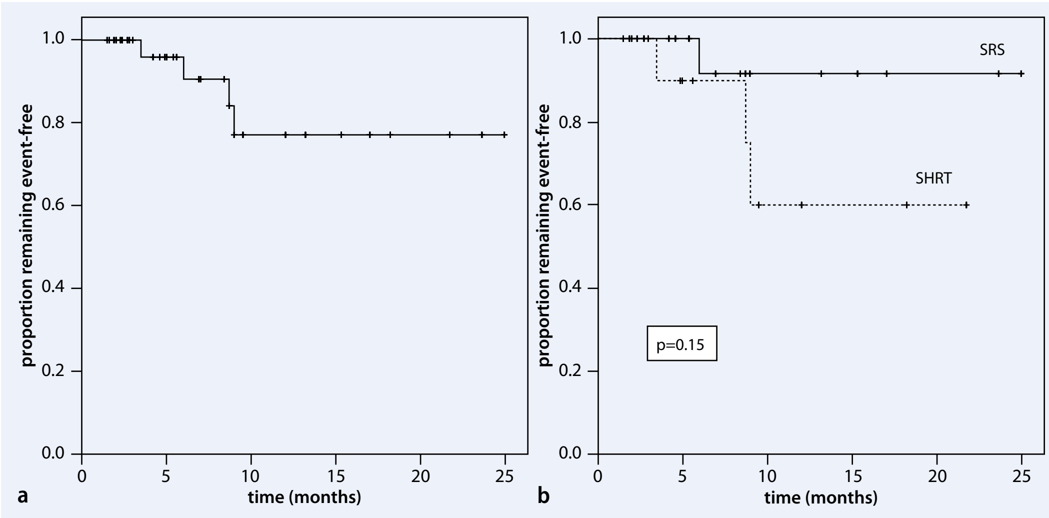

Fig. 1 ◀ Local control. **a** All patients, **b** patients stratified by treatment. *SRS* stereotactic radiosurgery (**solid line** in **b**), *SHRT* stereotactic hypofractionated radiotherapy (**dotted line** in **b**)

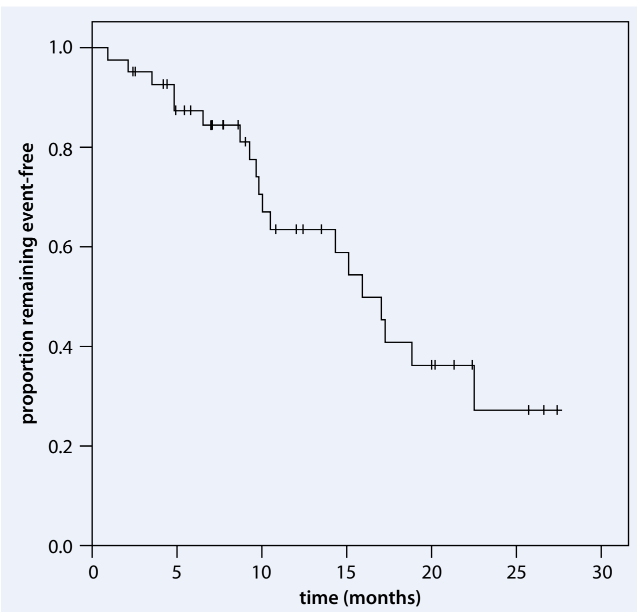

Fig. 2 ◀ Overall survival of all patients

dose of 18 Gy [12, 18, 21, 23]. However, the SRS dose to the resection cavity in the absence of WBRT remains a topic of investigation. In multivariate analysis, smaller PTV volumes and marginal doses <18 Gy were predictive for reduced LC [18]. In our analysis, we observed only a single recurrence in the SRS group, with a dose of 17 Gy and a PTV volume of 11.1 cm^3. The SHRT studies suggest that LC rates of 76–89% can be obtained using regimens of 3–10 fractions with total doses ranging from 20 to 40 Gy [6, 25, 26]. However, it is difficult to compare the results of these studies due to the large hetereogeneity of the fractionation regimens. A recent report comparing different dose concepts in SHRT showed that EQD2s of ≥35 Gy seem to be the most effective concept in patients with primary or recurrent limited primary brain metastases [14]. We compared SRS to different hypofractionated regimens and failed to find any fraction-ation-associated differences in LC due to the high diversity of dose concepts. However, in our study the LC rate in the SHRT group was 60% and in 2 out 3 patients with recurrence, the EQD2 was <35 Gy.

The importance of other key issues, such as target volume definition and the use of margins, also has to be established.

Target volume

At present, there are no well established guidelines concerning the definition of the target after surgical resection of brain metastases. There are no prospective data showing that the inclusion of the surgical track has an impact on LC. However, surgical resection seems to be crucial in terms of local recurrence incidence rates. Patel and colleagues reported that resection of the tumor in a piecemeal fashion significantly increased the incidence of local recurrence in comparison with en bloc resection [17]. The resection of metastatic lesions in contact with or involved with the cerebrospinal fluid (CSF) pathway is associated with a significantly higher incidence of leptomeningeal seeding than resection of tumors separated from the CSF pathway by brain parenchyma [1]. The addition of margins around the surgical cavity remains controversial. Neuropathological studies have shown that infiltration may be responsible for the presence of clinically undetectable cancer islands showing a maximum infiltration depth of 1–3 mm [2].

Toxicity

Choi and colleagues reported the first prospective data showing that the addition of a 2-mm margin to the resection cavity resulted in a decreased local failure rate at 12 months from 16 to 3%, without increasing toxicity [6]. In our series, we observed symptomatic and pathologically proven radionecrosis in 1 patient treated by a single fraction of 17 Gy. Clinical data on the toxicity profile of postoperative hypofractionated SRS and SHRT remain limited. Wang and colleagues reported a combined rate of all toxicities (radionecrosis, prolonged steroid use and new-onset seizures) of 9% using Cyberknife® (Accuray, Sunnyvale, CA, USA) hypofractionated SRS with 3 fractions of 8 Gy daily [26]. No toxicity grade 2 or higher was reported by Steinmann and colleagues using three different fractionation concepts with SHRT to the resection cavity [25]. For most lesions, 40 Gy in 10 fractions was applied according to the guidelines reported in the previous phase II trial of SHRT, which recommended that the $V_{4\,Gy}$ per fraction for normal brain should not exceed 20 cm^3 [8]. In our SHRT treated patient group, the median normal brain $V_{4\,Gy}$/fraction was 5.9 cm^3 and we did not observe acute grade 2 or higher toxicity.

Conclusion

Frameless image-guided LINAC-based adjuvant SRS and SHRT is a safe and effective treatment after resection of brain metastases in patients with oligometastatic disease. The system's accuracy is comparable to that of frame-based systems. In the current study, we found SHRT to be comparable to single-fraction SRS in terms of local tumor control and toxicity. This treatment strategy and its correlation with quality of life should be explored by additional studies.

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Conflict of interest. J. Broemme, J. Abu-Isa, R. Kottke, J. Beck, R. Wiest, M. Malthaner, D. Schmidhalter, A. Raabe, D.M. Aebersold and A. Pica state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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