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CLINICAL ARTICLE

How to dose-stage large or high-risk brain metastases: an alternative two-fraction radiosurgical treatment approach

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OBJECTIVE The authors sought to evaluate clinical outcome in patients with large, high-risk brain metastases (BMs) treated with different dose strategies by use of two-fraction dose-staged Gamma Knife radiosurgery (GKRS).

METHODS A retrospective analysis was performed with data from 142 patients from two centers who had been treated with two-fraction dose-staged GKRS between June 2015 and January 2020. Depending on the changes in marginal dose between the first (GKRS1) and second (GKRS2) GKRS treatments, the study population was divided into three treatment groups: dose escalation, dose maintenance, and dose de-escalation.

RESULTS The 142 study patients underwent two-fraction dose-staged GKRS treatments for 166 large, high-risk BMs. The median tumor volume of 7.4 cm^3 decreased significantly from GKRS1 to GKRS2 (4.4 cm^3; $p < 0.001$), and to the last follow-up (1.8 cm^3; $p < 0.001$). These significant differences in BM volume reduction were achieved in all three treatment groups. However, differences according to the primary tumor histology were apparent: while dose maintenance seemed to be the most effective treatment strategy for BMs from lung cancer or melanoma, dose escalation was the most beneficial treatment option for BMs from breast, gastrointestinal, or genitourinary cancer. Of note, the vast majority of patients who underwent dose-staged BM treatment did not show any significant postradiosurgical complications.

CONCLUSIONS In patients with large, high-risk BMs, dose-staged GKRS treatment represents an effective local treatment method with acceptable complication risks. Different dose-strategy options are available that may be chosen according to the primary tumor histology and treatment volume but may also be tailored to the findings at GKRS2.

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KEYWORDS Gamma Knife radiosurgery; brain metastases; dose-staged GKRS; primary tumor; oncology; stereotactic radiosurgery

As the most common intracranial tumor, brain metastases (BMs) occur in up to 40% of all oncological patients.[1,2] Local treatments for BM include stereotactic radiosurgery (SRS), microsurgical resection, and whole-brain radiation therapy (WBRT).[1,3] In contrast to microsurgical resection, Gamma Knife radiosurgery (GKRS) is a noninvasive neurosurgical method, which also allows treatment in multimorbid patients with contraindications to general anesthesia during surgery.[4–6] Furthermore, SRS is the only local treatment method for multiple disseminated and thereby nonresectable BMs.[1] In general, microsurgical resection is considered the treatment of choice for BMs exceeding 2.5 or 3 cm in diameter.[6,7] However, the dose-staged technique may enable radiosurgical treatment of larger metastases. This novel method allows the application of a high cumulative dose for the treatment of complex BMs.[8–10]

The aim of this study was to evaluate clinical outcomes in patients with large or high-risk BMs who were treated with different two-fraction dose-staged GKRS regimens.

Methods

Study Population and Patient Characteristics

To investigate data from a larger cohort, patient data from two study centers were retrospectively gathered. The

ABBREVIATIONS ARE = adverse radiation effect; BM = brain metastasis; GI = gastrointestinal; GKRS = Gamma Knife radiosurgery; GKRS1 = first GKRS fraction/treatment; GKRS2 = second GKRS fraction/treatment; GPA = graded prognostic assessment; GU = genitourinary; KPS = Karnofsky Performance Status; RN = radiation necrosis; RPA = recursive partitioning analysis; RR = radiation reaction; SIR = Score Index for Radiosurgery; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

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TABLE 1. Baseline characteristics of the study population

	GKRS1 All Pts (n = 142)	Dose Escalation (n = 41, 29%)	Dose Maintainance (n = 72, 51%)	Dose De-escalation (n = 29, 20%)	p Value (btwn groups)
Age, yrs	63 (34–89)	59 (42–86)	63 (34–88)	69 (35–89)	**0.009**
Female/male ratio	68:74	18:23	38:34	12:17	0.486
KPS score, %	80 (40–100)	80 (60–90)	80 (40–100)	80 (50–90)	0.975
KPS score groups					0.869
≥80%	92 (65%)	26 (63%)	46 (64%)	20 (69%)	
<80%	50 (35%)	15 (37%)	26 (36%)	9 (31%)	
ECM at BM diagnosis					0.532
Yes	96 (68%)	26 (63%)	48 (67%)	22 (75%)	
No	46 (32%)	15 (37%)	24 (33%)	7 (25%)	
Primary tumor					0.086
Lung cancer*	67 (47%)	19 (47%)	34 (47%)	14 (48%)	
Breast cancer	21 (15%)	9 (22%)	11 (15%)	1 (3%)	
Melanoma	18 (13%)	1 (2%)	12 (17%)	5 (18%)	
GU cancer	13 (9%)	9 (22%)	3 (4%)	1 (3%)	
GI cancer	10 (7%)	1 (2%)	4 (6%)	5 (18%)	
Multiple/other	13 (9%)	2 (5%)	8 (11%)	3 (10%)	
Pre-GKRS1 CNS treatment†					0.194
None	127 (90%)	33 (81%)	68 (95%)	26 (90%)	
Resection	9 (6%)	5 (12%)	2 (3%)	2 (7%)	
GKRS	1 (1%)	—	—	1 (3%)	
Resection & GKRS	2 (1%)	1 (2%)	1 (1%)	—	
WBRT &/or fRT	3 (2%)	2 (5%)	1 (1%)	—	
Dose-staged BM localization					0.103
Multiple	16 (12%)	7 (17%)	9 (13%)	—	
Frontal	26 (18%)	5 (12%)	18 (25%)	3 (10%)	
Parietal	12 (9%)	4 (10%)	6 (8%)	2 (7%)	
Temporal	13 (9%)	5 (12%)	5 (7%)	3 (10%)	
Occipital	13 (9%)	4 (10%)	6 (8%)	3 (10%)	
Central	26 (18%)	3 (7%)	16 (22%)	7 (25%)	
Cerebellar	23 (16%)	6 (15%)	9 (13%)	8 (28%)	
Basal ganglia/brainstem/other	13 (9%)	7 (17%)	3 (4%)	3 (10%)	

ECM = extracranial metastasis; fRT = fractionated radiotherapy; pts = patients.
Values are presented as median (range) or number (%) of patients unless otherwise indicated. Boldface type indicates statistical significance.
* Included only non–small cell lung cancer patients. Small cell lung cancer patients were excluded from the study.
† Mainly performed for distant BMs.

combined data were from 142 patients who had been treated with two-fraction dose-staged GKRS between June 2015 and January 2020. The study population included patients treated at study centers in two different countries (center I: 113/142, 80%; center II: 29/142, 20%). The inclusion criteria were age > 18 years and having undergone dose-staged GKRS treatment for at least 1 high-risk BM. This study complied with the ethical principles of the Declaration of Helsinki and was approved by the institutional review board. Patient consent was not obtained due to the retrospective study design. Detailed clinical characteristics of the study patients are displayed in Table 1.

Radiosurgical Technique

Patient treatments were planned with the GammaPlan system and performed with the Leksell Gamma Knife Perfexion (Elekta AB). The planning sequences were performed on a 1.5-T or 3-T MRI and always included gadolinium contrast-enhanced T1-weighted MRI sequences in axial and coronal planes. Multiplanar T2-weighted MRI sequences were additionally performed as appropriate. The target was defined as a contrast-enhanced tumor mass on T1 sequences. The whole tumor mass was covered without an additional margin. All metastases visualized on the planning MRI were treated with GKRS.[11] As previously described, the dose-staged GKRS treatment method is applied in two reduced fractions to high-risk BMs.[9] In our study, 166 BMs from 142 patients were treated by use of two-fraction dose-staged GKRS treatment. Our study population was divided into three treatment groups: dose escalation, defined as an increase in marginal dose after the first GKRS treatment (GKRS1) to the second GKRS treatment (GKRS2); dose maintenance, defined as no differences in marginal dose between GKRS1 and GKRS2; and dose de-escalation, defined as a decrease in marginal dose from GKRS1 to GKRS2. In both study centers, all

TABLE 2. Radiosurgical parameters of the three different dose-strategy groups

	Margin Dose Changes Btwn GKRS1 & GKRS2			
	Dose Escalation (n = 53/166; 32%)*	Dose Maintainance (n = 84/166; 50%)*	Dose De-escalation (n = 29/166; 17%)*	p Value
Tumor volume, cm^3				
GKRS1	9.8 (0.9–19.1)	6.7 (0.5–17.2)	6.2 (0.9–13.5)	**<0.001**
GKRS2	5.9 (0.4–17.3)	3.7 (0.4–20.7)	3.8 (0.7–11.4)	**<0.001**
Last FU	3.1 (0.1–15.4)	1.7 (0.1–25.0)	1.1 (0.1–7.8)	0.101
Max BM diameter, cm				
GKRS1	3.0 (1.3–4.3)	2.5 (0.9–3.7)	2.4 (0.8–3.0)	**<0.001**
GKRS2	2.5 (1.0–3.8)	2.0 (0.6–3.5)	1.9 (0.7–2.7)	**<0.001**
Last FU	2.1 (0.1–4.6)	1.5 (0.1–4.2)	1.4 (0.3–4.0)	**0.010**
Isodose line, %				
GKRS1	50 (40–60)	50 (40–60)	50 (45–50)	0.658
GKRS2	50 (40–55)	50 (48–60)	50 (40–50)	**0.037**
Prescription dose, Gy				
GKRS1	12 (10–14)	14 (10–16)	14 (12–16)	**<0.001**
GKRS2	15 (12–18)	14 (10–16)	13 (10–15)	**<0.001**
Central dose, Gy				
GKRS1	24.3 (19.9–32.5)	28.0 (20.0–35.6)	28.0 (24.0–33.3)	**<0.001**
GKRS2	30.0 (24.0–36.4)	28.0 (22.2–49.3)	26.0 (20.0–31.1)	**<0.001**
Localization of dose-staged BM				0.099
Frontal	8 (15%)	22 (26%)	4 (14%)	
Parietal	10 (19%)	8 (10%)	2 (7%)	
Temporal	9 (17%)	7 (8%)	3 (10%)	
Occipital	6 (11%)	7 (8%)	3 (10%)	
Central	4 (8%)	20 (24%)	6 (21%)	
Cerebellar	9 (17%)	16 (19%)	8 (28%)	
Basal ganglia/brainstem/other	7 (13%)	4 (5%)	3 (10%)	
Primary tumor				**0.001**
Lung cancer	21 (40%)	38 (45%)	15 (53%)	
Breast cancer	13 (24%)	11 (13%)	1 (3%)	
Melanoma	1 (2%)	15 (18%)	5 (17%)	
GU cancer	15 (28%)	3 (4%)	1 (3%)	
GI cancer	1 (2%)	5 (6%)	5 (17%)	
Multiple/other	2 (4%)	12 (14%)	2 (7%)	
Time btwn GKRS1 & GKRS2, days	34 (21–62)	32 (23–74)	32 (23–42)	0.286

FU = follow-up.

Values are presented as median (range) or number (%) of BMs unless otherwise indicated. Boldface type indicates statistical significance.

* Patients with multiple dose-staged BMs in whom the GKRS2 treatment could not be performed for 2 BMs (2/168, 1%) due to local progression. Since the other BMs were treated with the dose-staged method, only these 2 BMs were excluded from this subanalysis.

three dose strategies were applied. All detailed radiosurgical parameters and localization of the dose-staged BMs in all three different dose-strategy groups for each treatment group are presented in Table 2, which shows an overview of the radiosurgical parameters. In 16/142 (11%) patients, more than 1 BM was treated with the dose-staged treatment strategy. The median time between the staged GKRS1 and GKRS2 treatments was 32 days (range 21–74 days).

Outcome Evaluation and Statistical Analysis

Actual observed survival was compared with predicted survival determined according to three different prognostic outcome scales: general and disease-specific graded prognostic assessment (GPA), recursive partitioning analysis (RPA), and Score Index for Radiosurgery (SIR).[12–14]

According to our clinical standard procedure, all radiosurgically treated patients were clinically and radiologically followed up for a 3-month interval. However, as occurs in daily clinical practice, not all patients adhered to their follow-up appointments.

Based on standard MRI sequences (FLAIR/T2-weighted, T1-weighted pregadolinium- and postgadolinium-based contrast agent) and the Response Assessment for Neuro-Oncology (RANO) criteria, progression was defined as an increase of at least 20% in the longest tumor diameter.[15] Radiation reaction (RR) was defined as progressive surrounding edema and radiation necrosis (RN) as a progressive ring-enhancing lesion with surrounding edema.[16] Intralesional hemorrhage was identified either as a novel intralesional increase of CT density compatible

TABLE 3. Predicted and observed overall survival by primary tumor

	Survival, mos		
	Predicted by Prognostic Scores	Observed	p Value
Overall (n = 140)			
GPA general	3.8 (2.6–11.0)	14.0 (8.2–19.8)	**<0.001**
GPA specific	5.5 (2.6–25.3)		**<0.001**
RPA	4.5 (2.3–7.7)		**<0.001**
SIR	6.0 (2.1–8.8)		**<0.001**
Lung cancer (n = 66)			
GPA general	3.8 (2.6–11.0)	15.2 (7.3–23.1)	**<0.001**
GPA specific	5.5 (2.6–14.8)		**<0.001**
RPA	4.5 (2.3–7.7)		**<0.001**
SIR	6.0 (2.1–8.8)		**<0.001**
Breast cancer (n = 20)			
GPA general	3.8 (2.6–11.0)	14.6 (0.0–30.2)	**0.004**
GPA specific	15.1 (3.4–25.3)		NS
RPA	4.5 (2.3–7.7)		**0.004**
SIR	6.0 (2.1–8.8)		**0.015**
Melanoma (n = 18)			
GPA general	3.8 (2.6–3.8)	8.1 (0.0–35.9)	**0.002**
GPA specific	4.7 (3.0–13.2)		**0.039**
RPA	4.5 (2.3–4.5)		**0.003**
SIR	6.0 (2.1–6.0)		**0.003**
GU cancer (n = 13)			
GPA general	3.8 (2.6–6.9)	9.0 (5.1–12.9)	**0.004**
GPA specific	7.3 (3.3–11.3)		NS
RPA	4.5 (2.3–7.7)		**0.003**
SIR	6.0 (2.1–8.8)		**0.028**
GI cancer (n = 10)			
GPA general	3.8 (2.6–3.8)	7.0 (0.0–17.2)	NS
GPA specific	4.4 (3.1–6.9)		NS
RPA	4.5 (2.3–7.7)		NS
SIR	6.0 (2.1–6.0)		NS

NS = not significant.
Values are presented as median (range) unless otherwise indicated. Boldface type indicates statistical significance. Predicted survival durations according to the different prongostic outcome scales compared with the actual observed survival duration in 140/142 (99%) patients. Two patients (1%) were excluded due to missing follow-up data. Survival after BM diagnosis was calculated for the entire study population as well as for the different primary tumor entities.

with hemorrhage or as a progressive or novel additional (T2-weighted hypointense or T1-weighted hyperintense) signal alteration.[17,18]

For the evaluation of maximum BM diameter at the last follow-up, BMs without any residual contrast enhancement or with only glial tissue changes and a minimum tumor diameter of 0.1 cm were used.

Categorical data were presented as counts and percentages, and continuous parameters as median and range. The chi-square test was used to analyze the counts. The Wilcoxon signed-rank test was used to compare the predicted survival calculated according to prognostic scores with the observed survival and to evaluate differences in BM volume. For comparison between different treatment groups, Kruskal-Wallis or Mann-Whitney U-tests were applied. Survival after the GKRS1 treatment was estimated with the Kaplan-Meier method and compared with the log-rank test. Tumor control rates at 3, 6, and 12 months were calculated with life tables. For all tests, $p < 0.05$ was considered statistically significant. Statistical analyses were carried out with IBM SPSS Statistics for Windows version 24 (IBM Corp.) and GraphPad Prism version 8.1.2 (GraphPad Software).

Results

Overall Clinical Outcome After Dose-Staged Radiosurgical Treatment

Due to missing follow-up data, 2/142 (1%) patients were excluded from the clinical outcome analyses. Overall, the majority of patients (91/140, 65%) had died at the time of last follow-up. The estimated median overall survival after BM diagnosis was 14.0 months (95% CI 8.2–19.8). Compared to the predicted survival based on prognostic scores, the observed median survival time was significantly longer in our study population (Table 3). The estimated median overall survival after GKRS1 was 11.0 months (95% CI 7.0–15.0). In our study population, the longest median survival after GKRS1 was observed in lung and breast cancer patients (Table 3). Furthermore, the estimated median survival after the radiosurgical treatment did not show any significant differences between the different dose-strategy treatment groups ($p = 0.449$).

Radiological Outcome and Complications After Dose-Staged Radiosurgical Treatment

In 142 patients, 166 BMs were treated by two-fraction dose-staged GKRS. Of patients with multiple staged BMs (16/142, 11%), the GKRS2 treatment could not be performed for 2 BMs (2/168, 1%) in 2 patients (2/142, 1%). In both cases (BM from melanoma in 1 case and from lung cancer in 1 case), emergency resection was performed before the planned GKRS2 treatment, due to intralesional hemorrhage and/or RR resulting in neurological symptoms.

Documented radiological follow-up was available for 118/166 (71%) dose-staged BMs (Fig. 1). In the vast majority of dose-staged BMs (107/118, 91%), the BM size remained stable or decreased between the GKRS1 treatment and the last follow-up (Table 4).

For all 166 dose-staged BMs, the median volume decreased significantly between the GKRS1 and GKRS2 treatments (7.4 vs 4.4 cm^3; $p < 0.001$), and further until the time of the last follow-up MRI (1.8 cm^3; $p < 0.001$; Fig. 2A). This significant decrease in BM volume was observed among all three treatment groups (Fig. 2B–D). Similar results were observed when evaluating maximum BM diameter instead of BM volume (Table 2). The BM diameter decreased significantly between the GKRS1 and GKRS2 treatments ($p < 0.001$ for all three treatment groups) and to the time of the last follow-up MRI ($p < 0.001$ for dose escalation and dose maintenance; $p = 0.017$ for dose de-escalation). Calculated tumor control rates after GKRS1 at 3, 6, and 12 months were 97%, 97%, and

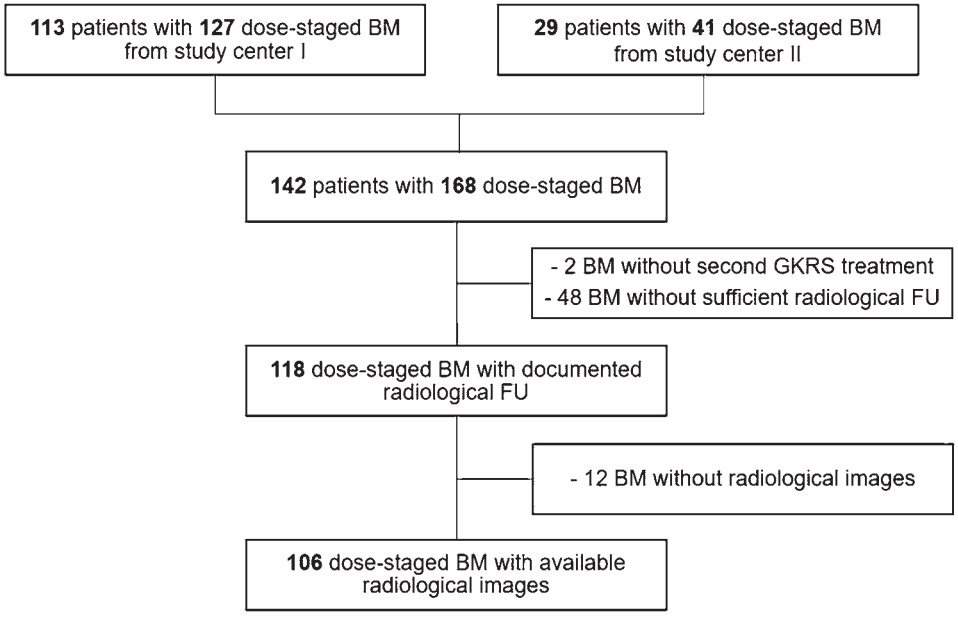

FIG. 1. Flowchart depicting the study inclusion algorithm. FU = follow-up.

92% for the dose escalation group; 97%, 95%, and 90% for the dose maintenance group; and 100%, 100%, and 91% for the dose de-escalation group, respectively.

Overall, for the vast majority (98/118, 83%) of dose-staged BMs, the treated patients did not show any significant postradiosurgical complications, including RR, RN, and intralesional hemorrhage. The remaining 17% (20/118) of dose-staged BMs were in patients diagnosed with either symptomatic RR (8/118, 7%), symptomatic RN (9/118, 7%), or intralesional hemorrhage (3/118, 3%). An additional subanalysis did not reveal any significant differences for postradiosurgical complications or local progression among the three treatment groups (RR, $p = 0.412$; RN, $p = 0.854$; local progression, $p = 0.952$; and intralesional hemorrhage, $p = 0.456$).

Outcome After Dose-Staged Radiosurgical Treatment in Relation to Primary Tumor

The influence of the types of primary tumors on patient outcomes was evaluated. Primary tumor groups comprised lung cancer, breast cancer, melanoma, and pooled gastrointestinal (GI)/genitourinary (GU) cancer. Patients with multiple or other primary tumors (13/142, 9%) were excluded from these subanalyses. Detailed outcome data are displayed in Fig. 3.

In lung cancer patients (Fig. 3A–C), the median BM volume decreased significantly between the GKRS1 and GKRS2 treatments in all three treatment groups. In addition, the median BM volume also decreased significantly from GKRS1 to the last follow-up in all three treatment groups. However, the significant volume decrease from GKRS2 to last follow-up was only observed in the dose maintenance group ($p < 0.001$; Fig. 3B). Among lung cancer patients, calculated overall local tumor control rates at 3, 6, and 12 months after GKRS1 were 98%, 98%, and 92%, respectively.

In breast cancer patients (Fig. 3D–F), the median BM volume decreased significantly from GKRS1 to GKRS2 as well as to the last follow-up in both the dose escalation and dose maintenance strategy groups. Interestingly, a further significant decrease in volume after GKRS2 to last follow-up was only observed in the dose escalation group ($p = 0.009$; Fig. 3D). Among breast cancer patients, calculated overall local tumor control rates at 3, 6, and 12 months after GKRS1 were 100%, 94%, and 85%, respectively.

In melanoma patients (Fig. 3G–I), significant volume decreases between GKRS1 and GKRS2 ($p = 0.047$) as well as to the last follow-up ($p = 0.016$) were observed in the dose maintenance group. From GKRS2 to last follow-up, a tendency toward volume decrease was seen ($p = 0.056$; Fig. 3H). In the dose de-escalation group, no significant volume decrease was observed from GKRS1 to GKRS2 or from GKRS2 to last follow-up (Fig. 3I). Among melanoma patients, calculated overall local tumor control rates at 3, 6, and 12 months after GKRS1 were 89%, 89%, and 89%, respectively.

TABLE 4. Tumor control rates at last follow-up after dose-staged treatment

BM Status at Last FU	Total (n = 118)	Dose Escalation (n = 32/118; 27%)	Dose Maintainance (n = 67/118; 57%)	Dose De-escalation (n = 19/118; 16%)
Stable/ decreased	105 (89%)	28 (88%)	60 (90%)	17 (90%)
Increased	13 (11%)	4 (12%)	7 (10%)	2 (10%)

BM status at last follow-up evaluated for 118/166 (71%) dose-staged BMs (after exclusion of patients lost to follow-up and without documented radiological follow-up data). BM volume decreased in the majority (105/118, 89%) of dose-staged BMs. These findings were observed in all three treatment groups.

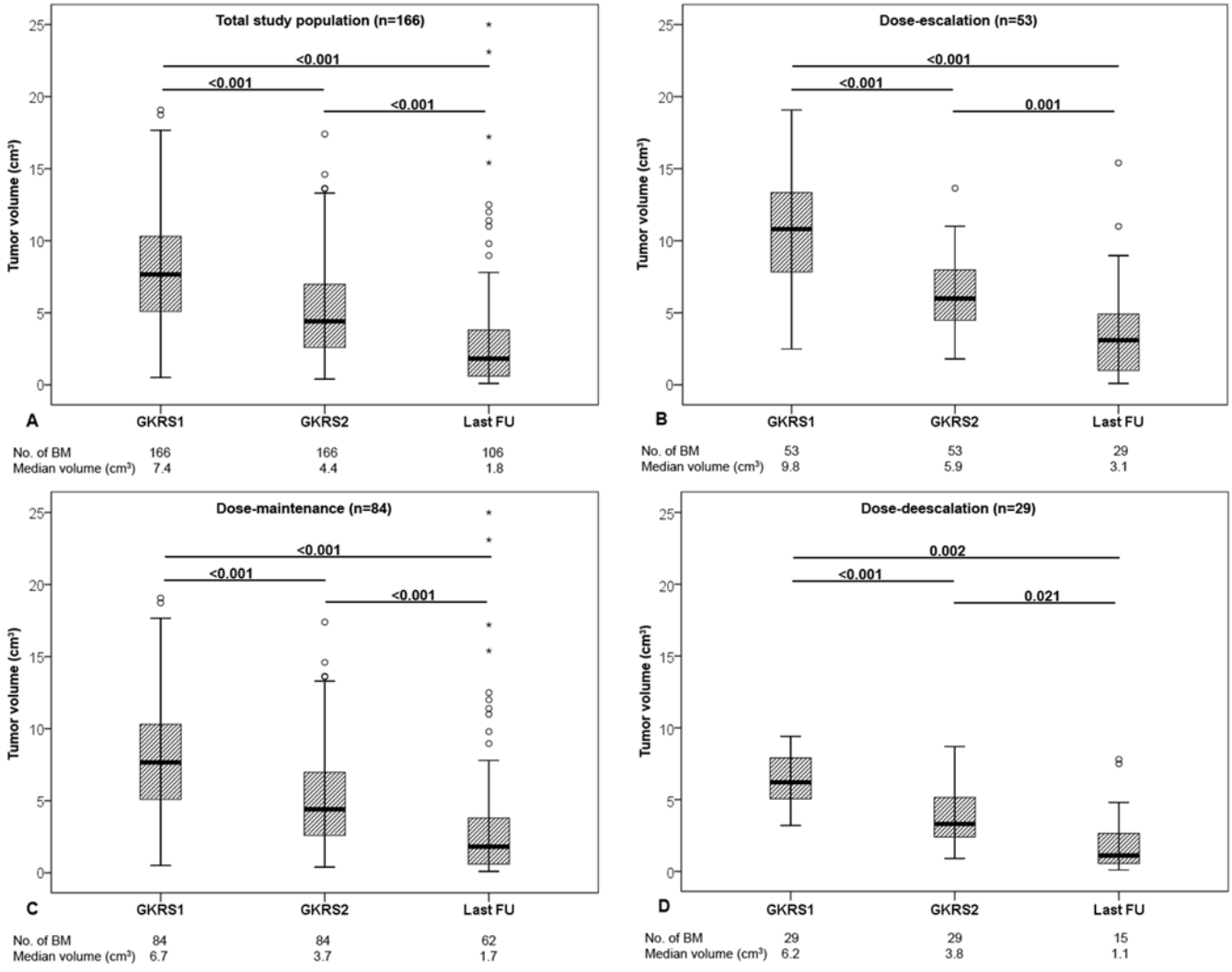

FIG. 2. Outcome after dose-staged treatment. **A:** The median volume of all dose-staged BMs at GKRS1, GKRS2, and last FU. **B–D:** The median volume of all dose-staged BMs at GKRS1, GKRS2, and last FU according to the three treatment groups (dose escalation [B], dose maintenance [C], dose de-escalation [D]).

In GI and GU cancer patients (Fig. 3J–L), only the dose escalation group showed significant decreases between GKRS1 and GKRS2 ($p < 0.001$) as well as from GKRS2 to the last follow-up ($p = 0.043$; Fig. 3J). Of note, at the time of GKRS1, patients with GI or GU cancer had a significantly worse median Karnofsky Performance Status (KPS) score compared to patients with lung cancer ($p = 0.003$), breast cancer ($p = 0.043$), or melanoma ($p = 0.004$).

Discussion

Rationale Behind Different Dose Strategies

Microsurgical resection is still considered the treatment of choice for large, symptomatic BMs.[19] However, surgical procedures are often deemed high risk in oncological patients due to the general clinical condition of the patient.[1,9,20] In recent years, SRS has emerged as an effective local treatment method with low complication rates and almost no neurotoxicity, even in patients with multiple BMs.[1,6] Still, the application of a single-fraction radiosurgical treatment for large, high-risk BMs is challenging due to a decreased responsiveness to radiation and an increased risk of complications.[19] The consequent application of a decreased radiation dose often results in poor local tumor control.[21]

To minimize neurotoxicity and to maintain the advantages of SRS, Higuchi et al. introduced a new treatment concept with three-staged fractionated SRS in 2009.[21,22] In a study by Kim et al., an optimal dose-fraction scheme for BM > 3 cm was investigated to balance local tumor control and radiation-induced toxicity.[23] Their study revealed that 27 Gy in 3 fractions might be the most beneficial regimen, compared to 24 or 30 Gy in 3 fractions. However, the decision-making regarding the dose-fraction scheme was mainly performed in the randomized study setting, without evaluation of other potentially influencing factors, such as primary tumor.[23]

Based on this treatment approach, an alternative radiosurgical treatment method with two-fraction dose-staged

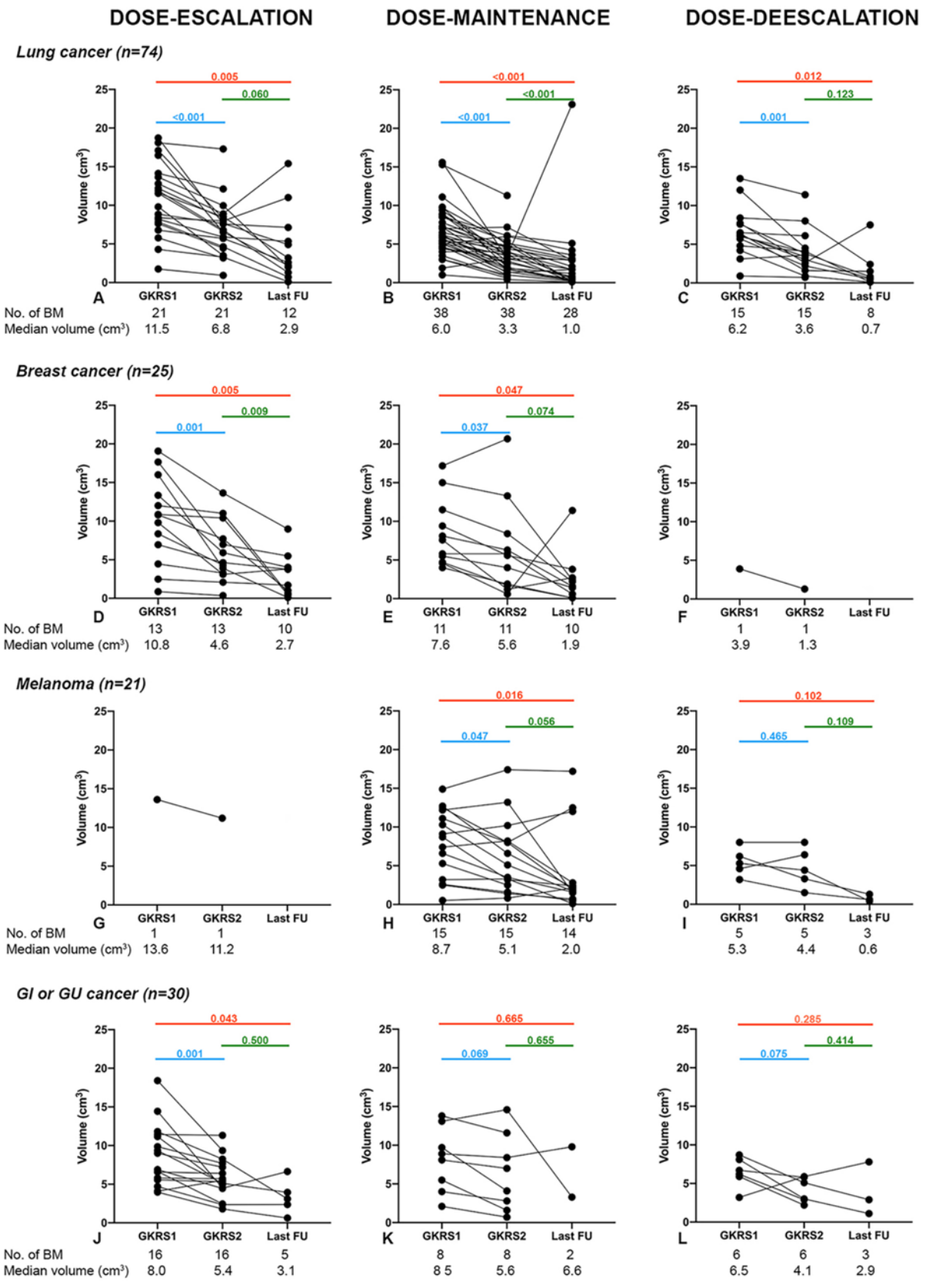

FIG. 3. Outcome after dose-staged treatment according to primary tumor and treatment groups. **A–C:** Lung cancer. **D–F:** Breast cancer. **G–I:** Melanoma. **J–L:** GI and GU cancer.

GKRS was developed.[10] As we and others have previously published, we usually perform dose-staged GKRS treatment for large or high-risk BMs in eloquent areas with an interval of 4 weeks.[9] However, data on the optimal dose-fraction strategy for large, high-risk BMs are still missing.[22,24] Previous studies have reported on different dose strategies for the two-fraction dose-staged treatment, with prescription doses ranging between 10 and 16 Gy.[9,22,24] Moreover, Serizawa et al. performed a retrospective multi-institutional study to compare three-staged and two-staged GKRS.[24] However, no significant differences in terms of overall survival, tumor progression, or radiosurgical complications were observed. Therefore, Serizawa et al. recommended the two-staged GKRS treatment regimen for the treatment of large BMs, considering the burdens on patients, the costs, and the total treatment interval.[24]

The definitions of large, high-risk BMs reported in previous studies range widely. In summary, BMs with a maximum diameter of 2 to 3 cm and upward were considered to be large and therefore eligible for two-fraction dose-staged treatment.[9,22,24] In the present study, we defined large BMs as ≥ 5 cm^3, but have treated BMs up to 21 cm^3. However, we also applied dose-staged GKRS to BMs that were localized in highly eloquent brain regions and multiple smaller BMs in close proximity to each other.[9] Depending on the clinical and radiological parameters at GKRS1, the radiological findings at GKRS2, and the expertise of the radiosurgeon, marginal doses were prescribed as appropriate. Thus, we assigned patients to the following dose-strategy treatment groups: dose escalation, dose maintenance, and dose de-escalation.

Overall, the dose escalation group showed the largest median BM volume at GKRS1. Thus, lower initial prescription doses had to be used to cover the whole tumor mass and to reduce the risk of neurotoxicity. Among these patients, 30% of BMs originated from GI or GU cancers, which are generally described to be radioresistant.[25,27] At GKRS2, the median volume of these dose-staged BMs decreased significantly, allowing the application of higher prescription doses for further treatment. The dose maintenance group results reflect the hitherto existing standard for two-fraction dose-staged treatment, whereas the dose de-escalation strategy was often applied for lung cancer BMs or in case of a progressing edema after GKRS1.[9] Thus, the decision of maintaining or changing the marginal dose between GKRS1 and GKRS2 was made individually, based on the type of primary tumor, the BM treatment volume at GKRS1, and the radiological response of the BM displayed on planning MR images at GKRS2. Consequently, our data provide the basis for an individual treatment approach that may be chosen according to the tumor histology and treatment volume but may also be tailored to the findings on the planning MR images for the second fraction at GKRS2.

Overall Clinical and Radiological Outcome

Overall, excellent local tumor control rates were achieved among all dose-strategy groups, similar to previously reported data for single-fraction as well as two-fraction radiosurgical BM treatments.[9,25,26] Of note, tumor volume of dose-staged BMs decreased significantly from GKRS1 to GKRS2 treatment, but also to the last available follow-up, regardless of the different dose-strategy groups.

The significant decrease in volume that had already occurred after GKRS1 is evidence for the key advantage of the two-fraction dose-staged GKRS method, given that the risk of RN has been reported to increase with tumor volume.[27] Thus, at the time of the GKRS2 fraction not only the treatment volume but also the volume of normal brain exposed to radiation is drastically reduced.[27]

To further evaluate the outcome of our patients, the survival after BM diagnosis was compared to the predicted survival after well-known prognostic scores.[12–14] Of note, our patients showed a significantly longer observed survival period than those predicted after analysis of all four scores.

Outcome According to Primary Tumor

It has been well established that the type of primary tumor influences the outcome of radiosurgically treated BM, yet studies investigating the differences in outcome according to the primary tumor among dose-staged BMs are scarce. However, patients with dose-staged BMs from GI cancer have been reported to have a lower volume reduction rate than BMs from other primary tumors.[25] To adjust the prescription dose at GKRS1 only according to the primary tumor seems to defeat the objective of the dose-staged treatment option for particularly large BMs. Thus, we suggest that different dose strategies should be applied for dose-staged management.

For lung cancer patients, a significant decrease in tumor volume from GKRS1 to GKRS2 and from GKRS1 to last follow-up was observed among all three dose-strategy groups. However, a further significant decrease in tumor volume after GKRS2 until last follow-up was only achieved in the dose maintenance group. Thereby, dose maintenance might represent the most effective method in patients with lung cancer BMs. These findings might be influenced by the smaller number of patients in the dose de-escalation and dose escalation lung cancer patient groups. However, there is a trend toward a further decrease of tumor volume after GKRS2 in the dose escalation group as well.

In patients with BMs from breast cancer, only the dose escalation group showed a significant further decrease after GKRS2 until the last follow-up. However, there was a trend toward the same results in the dose maintenance group. Significantly greater volume reductions in large BMs were generally achieved in patients with breast cancer than in patients with lung or GI cancer.[25] Based on these high response rates and significant tumor volume reduction after GKRS1, the dose escalation strategy may represent an optimal treatment method for large breast cancer BMs.

BMs from melanoma are more radioresistant than those from lung or breast cancer.[11,26,28] Among melanoma patients in our study, the vast majority were treated by use of a dose maintenance strategy, resulting in a significant decrease in tumor volume from GKRS1 to GKRS2 and to the last follow-up. Other dose strategies were applied in too few cases to allow a conclusion. Still, the two-fraction dose-staged treatment achieved excellent overall rates of tumor control that are in line with previously published single-fraction SRS data.[11,26,28]

Because of the small number of patients in our study, data for BMs originating from GU and GI cancer were pooled. Significant decreases in tumor volume from GKRS1 to GKRS2 and from GKRS1 to last follow-up were achieved only in the dose escalation group. However, our analysis suffers from a rather high rate of patients having been lost to follow-up or died due to peripheral disease progression before follow-up, especially in the GI cancer group. BMs from both GU and GI primary tumors are considered radioresistant. Unfavorable survival and tumor control rates after fractionated WBRT for these cancers have been described in the literature.[27,29] In contrast, SRS for these BMs, especially with higher prescription doses, has achieved excellent results.[27,29]

Postradiosurgical Complications

After radiosurgical treatment, RN, RR, and intralesional hemorrhage are possible adverse radiation effects (AREs).[9,30] Occurrences of these postradiosurgical complications are associated with several factors, including prior SRS treatment to the same lesion as well as maximum BM diameter and volume.[25,30]

As previously reported in a large study cohort with 2200 single-fraction treated BMs, the increased risk of worst-case AREs was clearly associated with increasing BM volume.[30]

As mentioned above, two-fraction dose-staged BM management allows reduction of radiation exposure of the normal brain tissue, leading to a reduction of neurotoxicity.[27] However, the evaluations of postradiosurgical complications for dose-staged BMs are still limited to smaller study cohorts. In a study by Ito et al., the cumulative incidence for RN was 4.2%. Furthermore, no significant differences in risk of AREs could be seen between different primary tumors.[25] Among all dose-strategy treatment groups, the majority of our patients did not show any significant postradiosurgical complications. Moreover, the postradiosurgical complication rates in our study were in line with those for previously reported single-fraction SRS and also dose-staged SRS complication rates.[25,30]

Study Limitations

One of our study limitations is the retrospective study design. Furthermore, the subanalyses for the origins of each primary tumor or postradiosurgical complications were limited when separating the study population into three different dose-strategy groups.

Conclusions

In patients with large or high-risk BMs, all three dose-staged GKRS treatment strategies represent effective local treatment methods with excellent local tumor control rates. Complication rates are acceptable and in line with complication rates previously reported for single-fraction methods as well as for dose-staged radiosurgery. Depending on the primary tumor origin and initial treatment volume, different dose-strategy options are suggested, although further prospective studies may be necessary. Still, our data provide the basis for an individual treatment approach that may be chosen according to the tumor histology and treatment volume but may also be tailored to the findings at GKRS2.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Frischer, Cho, Kranawetter, Untersteiner, Ilyalov. Acquisition of data: Frischer, Cho, Medvedeva, Kranawetter, Untersteiner, Hirschmann, Lepilina, Baulin, Ertl, Gatterbauer, Ilyalov. Analysis and interpretation of data: Frischer, Cho, Kranawetter, Untersteiner, Buschmann, Ertl, Marik, Dorfer, Rössler, Ilyalov. Drafting the article: Frischer, Cho, Kranawetter, Untersteiner. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Frischer. Statistical analysis: Frischer, Cho, Untersteiner. Study supervision: Frischer, Rössler, Ilyalov.

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