Image-Guided Robotic Radiosurgery for Treatment of Recurrent Grade II and III Meningiomas. A Single-Center Study

Güliz Acker[1,2,5], Franziska Meinert[1,2], Alfredo Conti[1,2,6], Markus Kufeld[2], Claudius Jelgersma[1,2], Phuong Nguyen[1,2], Anne Kluge[2,3], Mathias Lukas[4,5], Franziska Loebel[1,2], Diana Pasemann[2,3], David Kaul[3], Volker Budach[2,3], Peter Vajkoczy[1,2], Carolin Senger[2,3]

■ OBJECTIVE: **Stereotactic radiosurgery (SRS) has been increasingly applied for malignant meningiomas as an alternative to conventionally fractioned radiation therapy. We performed a retrospective analysis of an institutional patient cohort with malignant meningiomas treated by image-guided SRS.**

■ METHODS: **All patients with atypical or anaplastic meningiomas who were treated by SRS using CyberKnife (CK) were identified. Local failure and regional and/or distant recurrences were evaluated together with toxicity and overall survival.**

■ RESULTS: **We identified 127 treated lesions (105 atypical and 22 anaplastic) in 35 patients. The mean time interval between the last surgery and subsequent CK-SRS was 30.8 ± 24.5 months. Most lesions (83.5%) were treated using single-fraction CK-SRS. The median planning target volume of all 127 lesions was 1.71 cm^3 (range, 0.06–22.5 cm^3). The median follow-up period was 23 months (range, 2.1–60.3 months). The estimated local control rates were 97%, 77%, and 67% at 12, 36, and 60 months, respectively, in atypical meningiomas and 66% each at 12 and 24 months in anaplastic meningiomas. The regional progression-free survival was 93%, 73%, and 59% at 12, 36, and 60 months, respectively, in atypical lesions and 93% and 46% at 12 and 24 months in anaplastic lesions. The estimated distant tumor progression-free interval in atypical lesions was 80%, 44%, and 44% at 12, 36, and 60 months, respectively, and 49% and 24% at 12 and 24 months, respectively, in anaplastic lesions. Age was identified as a risk factor for local failure.**

■ CONCLUSIONS: **Although the real boundaries of efficacy of SRS have to be further evaluated in a prospective trial, it seems that aggressive treatment by high-dose single or multisession SRS of recurring malignant meningiomas provides satisfactory local control rates.**

INTRODUCTION

Atypical and anaplastic meningiomas (classified as World Health Organization [WHO] grade II and III, respectively) represent approximately 10%–20% and 5% of all meningioma. Because of high recurrence rates, these tumors require frequent retreatments, including repeat surgery and radiotherapy, with survival that is often disappointing.[1-3] Conventionally fractionated external beam radiation therapy (EBRT) is widely accepted as an adjuvant treatment after subtotal resection or as a salvage treatment at local or distant progress.[4] Stereotactic radiosurgery (SRS) has been increasingly used for atypical or anaplastic meningioma as an alternative to EBRT, with comparable local control rates.[2,3,5-9] SRS allows the application of high single radiation doses to small or medium-sized volumes

Key words
- CyberKnife
- Malignant meningiomas
- Radiosurgery

Abbreviations and Acronyms
CK: CyberKnife
CT: Computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
EBRT: External beam radiation therapy
EQD_2: Biological equivalent dose with 2 Gy per fraction
GTV: Gross tumor volume
MRI: Magnetic resonance imaging
PTV: Planning target volume
SRS: Stereotactic radiosurgery
WHO: World Health Organization

From the [1]Department of Neurosurgery and Center for Stroke research Berlin (CSB), [2]Charité CyberKnife Center, and Departments of [3]Radiation Oncology and [4]Nuclear Medicine, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany; [5]Berlin Institute of Health (BIH), Berlin, Germany; and [6]Department of Neurosurgery, University of Messina, Messina, Italy

To whom correspondence should be addressed: Alfredo Conti, M.D., Ph.D. [E-mail: alfredo.conti@charite.de]

Citation: World Neurosurg. (2019) 131:e96-e107. https://doi.org/10.1016/j.wneu.2019.07.058

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

with steep dose gradients at tumor margins. This strategy leads to a protection of critical organs and tissues at risk for late radiation damage and also to shorter treatment courses. Reported series on SRS of grade II and III meningiomas using Gamma Knife radiosurgery (Elekta, Stockholm, Sweden) report reasonable local control rates,[7,8,10-17] but the full range of the efficacy of SRS is still unknown. Also CyberKnife (CK)-SRS (Accuray Inc., Sunnyvale, California, USA) has been explored in some patients.[9,18,19] Image guidance offers the potential to deliver high doses of radiation in both single or multiple sessions (typically 3–5). Thus, the aim of this study was to analyze the local control and response pattern of patients with grade II and III meningiomas after CK treatment at our institution.

METHODS

Study Design

Retrospective analysis of patients' data was approved by the local ethical committee (EA1/233/18). We identified all patients with meningioma who were treated by nonisocentric image-guided robotic radiosurgery in our center between January 2011 and September 2018. We gathered data about patients' characteristics regarding disease grade; treatment modalities performed; clinical outcome; and local, regional, and overall tumor control; as well as acute and long-term treatment morbidity. We also analyzed the dose-volume parameters, including treatment dose, fractionation scheme, gross tumor volume (GTV), planning target volume (PTV), prescription dose, mean dose, new conformality index, and PTV coverage.

CK Treatment

All patients included in the study had ≥1 tumor resection before SRS. The patients were referred for CK irradiation either immediately after surgery or at the time of local or distant progression. The decision for a CK treatment was recommended by a multidisciplinary neuro-oncology board review including the referring neurosurgeon in charge. We registered the latest available histologic diagnosis, bearing in mind that it might have changed during the period from surgery to SRS from an atypical to an anaplastic subtype. A thermoplastic mask was individually attached to each patient for treatment immobilization before high-resolution thin-slice (0.75 mm) computed tomography (CT). Scanning was performed by a 24-slice CT scanner after contrast agent injection. The treatment planning was carried out on a contrast-enhanced CT with magnetic resonance imaging (MRI) (T1-weighted magnetization-prepared rapid acquisition with gradient echo using 7 mL Gadovist, 1.0 mm slice thickness) coregistered to the CT using MultiPlan version 4.5 (Accuray Inc., Sunnyvale, California, USA).

The treatment planning, including prescription of dose, isodose lines, and fractionation scheme, was executed by a team of 2 physicians (a radiation-oncologist and a neurosurgeon) and a radiation physicist. The decision on the marginal doses and the number of fractions was dependent on various factors, such as histology, tumor volume, adjacent organs at risk (optic nerve, chiasm, and brainstem) and sometimes also the previously irradiated tumor volume.

An inverse treatment planning algorithm was used to generate steep dose gradients by means of nonisocentric beam delivery of up to 1600 incident beams, thereby allowing optimal tumor coverage and minimal dosage to organs and tissues at risk for late radiation damage.[20-24] The Ray Tracing algorithm was routinely used for this purpose. The physical treatment planning process included 1) selection of the adequate size and number of collimators, avoiding beams through the eyeballs; 2) the addition of help structures to reduce dose in specific brain regions; 3) definition of dose constraints and their weight for the target volume and critical structures; and 4) performing a high resolution dose calculation covering the whole CT scan to evaluate dose isles at distant sites of the body.

The GTV was defined as the tumor volume based on fused CT and MRI. PTV was created by expanding the GTV by 0–1 mm. Four different dose regimens were used depending on the site and size of the lesion, including single and multisession radiosurgery as defined by Barnett et al.[25]: either single-fraction SRS in the range of 15–18 Gy, 3 fractions of 7–8 Gy up to 21–24 Gy, respectively, or 4–5 fractions summing up to 20–25 Gy, always prescribed at the 70% isodose of the PTV. The biological equivalent dose with 2 Gy per fraction (EQD_2) was calculated according to the linear quadratic model assuming an α/β ratio of 10 for high-grade meningiomas. Patients routinely received 4 mg dexamethason after SRS for the prevention of side effects such as headache, nausea, or vomiting or neurologic deficits caused by postradiosurgical edema.

Follow-Up

Clinical and radiologic follow-up with contrast-enhanced MRI was carried out every 3–6 months after CK-SRS for the first 2 years and then every 6–12 months each year. We included the latest available follow-up in this analysis. The clinical status of the patients was classified using the Karnofsky Performance Status before treatment and at last follow-up; new neurologic deficits were recorded separately. Adverse effects were recorded based on Common Terminology Criteria for Adverse Events 4.0 (CTCAE).[26] The MRI scans were evaluated by the physician in charge to verify treatment response. We first evaluated the local control defined as the area of the former PTV.

We used a categorization for the treatment response of each lesion regarding size: 1) no change; 2) minimal response, defined as a volume reduction of <10%; 3) partial remission, defined as a volume reduction >10%; and 4) progressive disease, defined as a significant tumor growth. We then evaluated distant failure, which we divided in 2 categories: 1) regional failure, including novel tumors outside but in the vicinity of the irradiated volume (<1 cm) and 2) distant failure, including all the remaining new lesions. Overall survival was calculated from the first CK-SRS until this analysis (12/18). We used the Berlin-Brandenburg tumor registry to verify the death of the patients.

Statistical Analysis

Overall survival and progression-free intervals were investigated using Kaplan-Meier analysis. A minimum interval of 1 month was selected in survival table analysis to calculate progression-free intervals for 6, 12, 24, 36, 48, and 60 months, respectively. Group comparison was performed by log-rank test. To assess risk

factors potentially associated with local recurrence in atypical meningiomas, univariate and multivariate analyses were performed using Cox regression analyses; parameters with $P < 0.15$ in the univariate analysis were included in the multivariate analysis. For assessing the differences of partial remission frequency between atypical and anaplastic meningioma, a Pearson χ^2 test was performed. SPSS (version 25.0 [IBM Corp., Armonk, New York, USA]) software was used for statistical analysis. A P value ≤ 0.05 was considered as significant.

RESULTS

Patient Characteristics

We collected data of 127 lesions treated in 35 patients with histologically confirmed WHO grade II or III meningioma after surgical resection (27 atypical and 8 anaplastic). Demographic and clinical characteristics are summarized in Table 1. The mean age of patients who underwent the CK-SRS was 58.1 ± 15 years (range, 26–80 years). The female/male ratio was 1:1. A total of 21.3% of the lesions were localized at the skull base and 28.0% at the falx/sinus. From all patients, 48.6% (n = 17; 48.0% of atypical meningiomas and 5.9% of anaplastic meningiomas) were submitted to previous radiotherapy, whereas only 5.7% (n = 2) of the patients were re-irradiated after CK-SRS (Table 1). In 1 patient, the exact location of the previous irradiation (10 years before CK) was not clearly documented, and in 5 patients, other locations were subject to treatment, so that 14 of the 127 lesions were treated by previous radiation therapy. In the patient cohort, 54.3% of the patients (n = 19) received multiple tumor resections before radiosurgical treatment, with a maximum of 4 surgical procedures (Table 1). Only 16 lesions (12.6%) were treated within 7 months postoperatively, whereas the remaining lesions were irradiated by CK at progression. The median and mean time interval between the last surgery and subsequent CK-SRS was 22 and 30.8 ± 24.5 months, respectively, with a range of 2–107 months. Overall, 23% of all patients (n = 8) needed to have repeated surgery after CK-SRS for progressive disease.

Table 1. Summary of Patient Characteristics Divided Into Atypical and Anaplastic Meningioma

Patient Characteristics	Overall Cohort (n = 35)	Atypical Meningioma (n = 27)	Anaplastic Meningioma (n = 8)
Male, n (%)	17 (48.6)	12 (44.4)	5 (62.5)
Female, n (%)	18 (51.4)	15 (55.6)	3 (37.5)
Age at diagnosis (years)			
Mean ± SD	52.3 ± 16	48.3 ± 14	65.6 ± 15
Age at first CK-SRS			
Mean ± SD	58.1 ± 15	55.2 ± 14	68.0 ± 14
Years from diagnosis to CK-SRS			
Mean ± SD	5.7 ± 6	6.8 ± 6	2.2 ± 1.5
Surgery (number of patients)			
Patients with >1 surgery	19	16	3
Patients with surgery after CK-SRS	6	4	2
Other radiation treatments (number of patients)			
Without	16	13	3
Before CK-SRS	17	13	4
After CK-SRS	2	1	1

SD, standard deviation; CK, CyberKnife; SRS, stereotactic radiosurgery.

CK-SRS Treatment Characteristics

Overall, 54.3% (n = 19) of the patients received multiple CK treatments, resulting in 66 treatments covering 127 lesions (105 atypical and 22 anaplastic meningioma) (Table 2). A total of 20 patients (57%) had multiple lesions treated (16 atypical and 4 anaplastic) (Table 2). Most of the lesions (83.5%) were treated by single-fraction CK-SRS. Hypofractionation regimens used 3, 4, or 5 sessions in 13.4%, 0.8%, and 2.4%, respectively (Table 3). The median prescription dose was 16 Gy for a single fraction (range, 15–18 Gy). The median PTV for SRS was 1.44 cm^3, whereas the median PTV for multisession SRS was 5.37 cm^3. The median PTV and GTV of all 127 lesions were 1.71 cm^3 (range, 0.06–22.48 cm^3) and 1.54 cm^3 (range, 0.06–16.95 cm^3), respectively. In atypical meningioma, the median PTV was 1.55 cm^3 (range, 0.06–16.3 cm^3), the median prescribed dose was 16 Gy (range, 15–25 Gy), and the median maximum dose was 22.6 Gy (range, 13.6–35.7 Gy) (Table 4). Among WHO grade III lesions, the median tumor volume was 2.38 cm^3 (range, 0.29–22.5 cm^3), the median prescribed dose was 18 Gy (range, 15–24 Gy), and the median maximum dose was 20 Gy (range, 19.95–34.29 Gy). The mean new conformality index was 1.28 ± 0.2. Further treatment characteristics including minimum and mean dose and percentage of the PTV coverage are summarized in Table 4 divided in atypical and anaplastic meningiomas.

Follow-Up

Results of ≥1 follow-up examination including imaging data were available for 87.9% of the treatment sessions and for 88% of the lesions (112/127), with a median follow-up period of 23 months (range, 2.1–60.3 months; Table 1). Two thirds of the lesions for which the follow-up was missing (n = 10) were treated in 2018.

Tumor Control

Overall estimated median progression-free interval in our patient cohort (including local, regional, and distant tumor recurrence) was 18 months for atypical and 10 months for anaplastic lesions (log-rank test, P = 0.001; Figure 1A).

The 12-month, 36-month, and 60-month estimated local control rates in atypical meningiomas were 97%, 77%, and 67%, respectively, and the 12-month and 24-month estimated local control rates in anaplastic meningiomas were 66% each (atypical vs. anaplastic, P = 0.000; Figure 2A, Table 5). This statistic remained comparable, if only radiation-naive lesions or only salvage treatments were included in the analysis as homogenous cohorts (Figure 2A–C). The regional progression-free survival at 12, 36, and 60 months was 93%, 73%, and 59%, respectively, in atypical

Table 2. Summary of Treated Multiple Lesions and Treatments per Patient and Clinical Course After Therapy

	Overall Cohort (n = 35)	Atypical Meningioma Cohort (n = 27)	Anaplastic Meningioma Cohort (n = 8)
Karnofsky Performance Status course (treatment vs. follow-up)			
No change	29	23	6
Increase ≥10%	3	1	2
Decrease ≥10%	3	3	0
Patients treated with multiple lesions	20	16	4
Lesions per patient			
1	15	11	4
2	10	7	3
3	3	3	0
4	4	4	0
5	1	0	1
6	1	1	0
7	1	1	0
Patients with multiple treatments			
Treatments per patient			
1	16	10	6
2	11	11	0
3	4	2	2
4	4	4	0
Lesions treated per stereotactic radiosurgery session			
1	31	25	6
2	22	18	4
3	6	5	1
4	4	4	0
5	1	0	1
6	1	1	0
7	1	1	0

meningiomas and 93% and 46% at 12 and 24 months, respectively, in anaplastic lesions (atypical vs. anaplastic, P = 0.413; Table 5, Figure 3A). The estimated distant tumor progression-free interval in atypical lesions at 12, 36, and 60 months was 80%, 44%, and 44%, respectively, and in anaplastic lesions at 12 and 24 months, it was 49% and 24%, respectively (atypical vs. anaplastic, P = 0.006; Table 5, Figure 3B).

Overall absolute local control by SRS was achieved in 83% of all lesions (84% in atypical lesions and 79% in anaplastic lesions; Table 6; Figure 4) at a median follow-up period of 23 months (range, 2.1–60.3 months), whereas partial remission was observed

Table 3. Summary of the Treatment Regimes

	Atypical (n = 105)		Anaplastic (n = 22)	
	n	%	n	%
1 fraction	94	89.5	12	54.5
15 Gy	40		7	
16 Gy	49		2	
17 Gy	5		1	
18 Gy			2	
3 fractions	7	6.7		45.5
21 Gy	3			
22.5 Gy	2			
24 Gy	2		10	
4 fractions	1	1.0		
20 Gy	1			
5 fractions	5	2.9		
25 Gy	3			

in 36% of the treated lesions, with a better effect in anaplastic lesions (33% atypical and 47% anaplastic; Table 6). However, there was no significant difference between atypical and anaplastic meningiomas regarding lesions in partial or complete remission (39% vs. 47%; P = 0.632). Local recurrences occurred at a median of 19.5 months (median, 19 vs. 10.5 months in atypical vs. anaplastic meningiomas). Of all observed locally progressing

Table 4. Summary of the Treatment Characteristics Including the Planning Target Volume, Gross Tumor Volume, Minimum, Mean, and Maximum Treatment Dose and Planning Target Volume Coverage

	Atypical (n = 105), Mean ± Standard Deviation	Anaplastic (n = 22), Mean ± Standard Deviation
Volumes (cm^3)		
Planning target volume	4.7 ± 5.8	2.7 ± 3.1
Gross tumor volume	4.7 ± 4.2	2.6 ± 3
Dose (Gy)		
Minimum	18 ± 4.5	14.7 ± 1.7
Mean	23.1 ± 5.1	19.3 ± 3.5
Maximum	27 ± 6	22.8 ± 3.8
Coverage	98 ± 2.1	98.2 ± 2

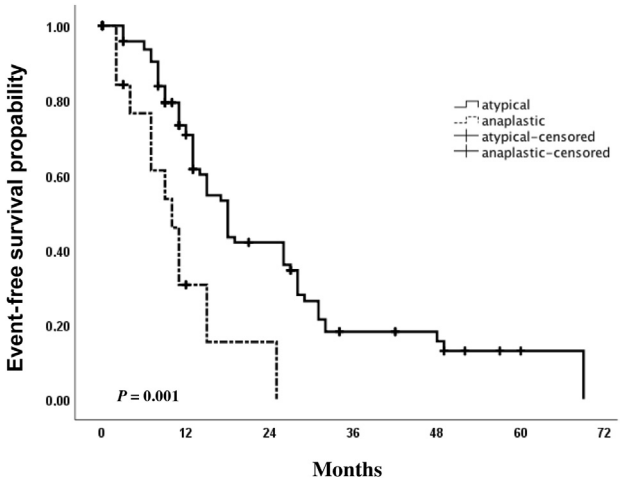

Figure 1. Kaplan-Meier curve for overall progression-free survival comparing atypical and anaplastic meningioma.

lesions, 53% were in 1 patient with atypical meningioma (10 of 19 progressing lesions).

Regional or distant tumor progress occurred in 62.5% of the lesions (66% in atypical and 47% in anaplastic lesions) (Table 7). The median time interval for regional and distant tumor recurrences was 17 months (16 vs. 15 months for atypical vs. anaplastic meningiomas) and 13 months (13 vs. 5.5 for atypical vs. anaplastic), respectively.

Factors Affecting Local Control

Multivariate Cox proportional hazards regression analysis showed older age and EQD_2 (prescription and mean dose) as risk factors for local recurrence in atypical meningiomas (Table 8). This analysis was not performed for the smaller cohort of patients with anaplastic meningioma.

Morbidity and Mortality

Karnofsky Performance Status remained stable in most patients at follow-up (29 of 35 patients; Table 2). No severe adverse events occurred (CTCAE ≥III). Thirteen patients showed a symptomatic radiation reaction presenting clinically as focal seizures in 6 patients (46.2%; CTCAE I-II); mild visual deterioration in 2 patients (15.0%; CTCAE I); dysesthesia in 2 patients (15.4%, CTCAE I); and fatigue, headache, and fine motor skill disturbance in 1 patient each (7.7% each, CTCAE I). Most of these patients ($n = 9$; 69.2%) were treated by conventional radiation therapy before first CK-SRS and 8 patients were treated repeatedly by CK-SRS. Asymptomatic radiation-induced neuroimaging changes in the white matter (edema and/or necrosis) during follow-up occurred in 4 patients (11% of 35 patients),

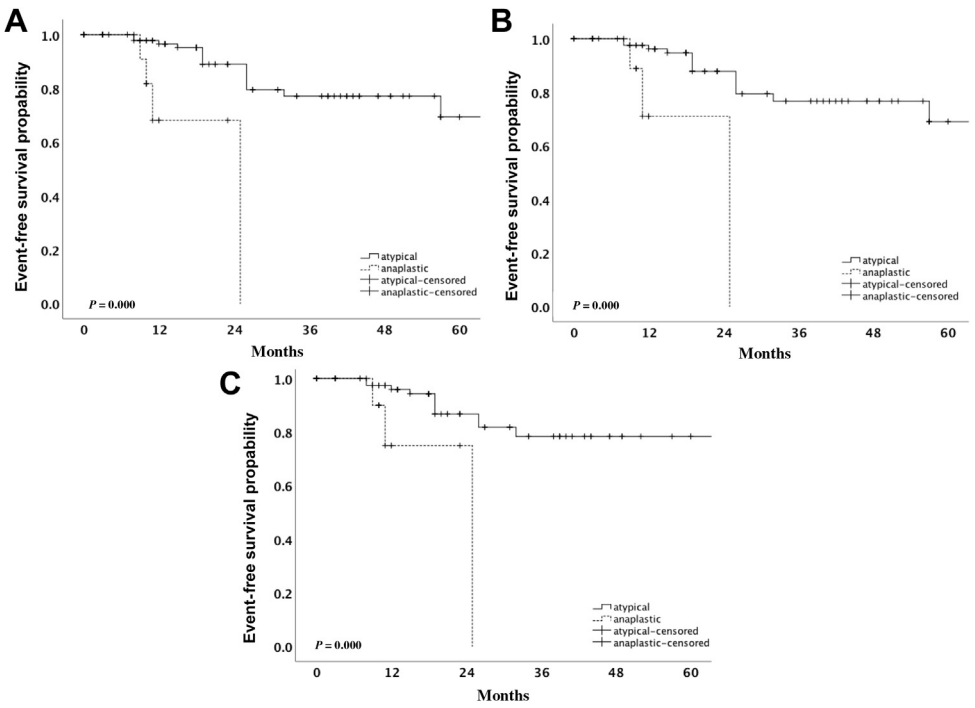

Figure 2. Kaplan-Meier curves for local progression-free survival comparing atypical and anaplastic meningioma divided in (**A**) whole cohort, (**B**) only radiation-naive lesions, and (**C**) only salvage treatments.

Table 5. Summary of Estimated Progression-Free Survival Intervals Separately for Local, Regional, and Distant Disease Progression

	Progression-Free Local (%)		Progression-Free Regional (%)		Progression-Free Distant (%)	
Interval (months)	Atypical	Anaplastic	Atypical	Anaplastic	Atypical	Anaplastic
6	99	100	99	100	95	77
12	97	66	93	93	80	49
24	89	66	83	46	61	24
36	77	0	73	0	44	0
48	77	0	66	0	44	0
60	67	0	59	0	44	0

not all of whom were radiation naive (2 were already irradiated before CK treatment conventionally and 2 received multiple CK-SRS). Seven of 35 patients (20%; 5 of 27 atypical and 2 of 8 anaplastic meningiomas) died within the follow-up period. In 4 patients, the cause of death was not monitored and 2 patients died because of tumor progression and 1 patient of a subarachnoid hemorrhage. The estimated mean overall survival was 59.8 ± 3.7 and 33.1 ± 5.0 months for atypical and anaplastic meningiomas, respectively, without reaching a level of statistical significance.

DISCUSSION

Our results show that radiosurgery can achieve reasonable local control rate with only minor radiation-related morbidity. Excellent 12-month and 24-month local control rates of 97% and 89% in atypical meningiomas and a sobering 66% for both time points in anaplastic meningiomas could be achieved. However, corresponding regional and distant progress rates were considerable, with 27% and 57% in atypical and 57% and 79% in anaplastic meningiomas. Pasquier et al.[27] analyzed 82 patients with grade II meningiomas treated by fractioned radiotherapy and reported 5-year disease-free survival of 58%, comparable to our 5-year local progression-free rate of 67% in atypical meningioma. Thus, it seems that CK-SRS can be as effective as a 6-week conventionally fractionated course of radiotherapy with a shorter overall treatment time, as supported by a recent meta-analysis comparing SRS versus stereotactic radiotherapy.[28] This recent meta-analysis reported a comparable progression-free survival at 4–10 years for both techniques (89% vs. 88.8%).[28]

Local Control

The local control of our patients seems to be slightly better than those reported by Zwang et al.[9] also using CK-SRS (atypical: 12, 36, and 60 months, 90%, 71%, and 49% vs. our series 97%, 77%, and 67%; anaplastic: 12 and 24 months, 57% and 50% vs. our series 66% each; **Table 9**).[9] In a previous study from the same group,[18] the 36-month local control was 74% for atypical meningiomas with a shorter follow-up. We can infer that our better local control might be caused by smaller median target volumes (median PTV, 3.33 vs. 1.71 cm³ in our series).[9] Di Franco et al.[19] recently reported a CK-SRS series with similar local control rates of 89% at 24 months, although they did not differentiate the tumor grading, so a proper comparison is impossible. The best treatment recommendation for these tumors might be active surveillance and aggressive radiosurgical management as soon as

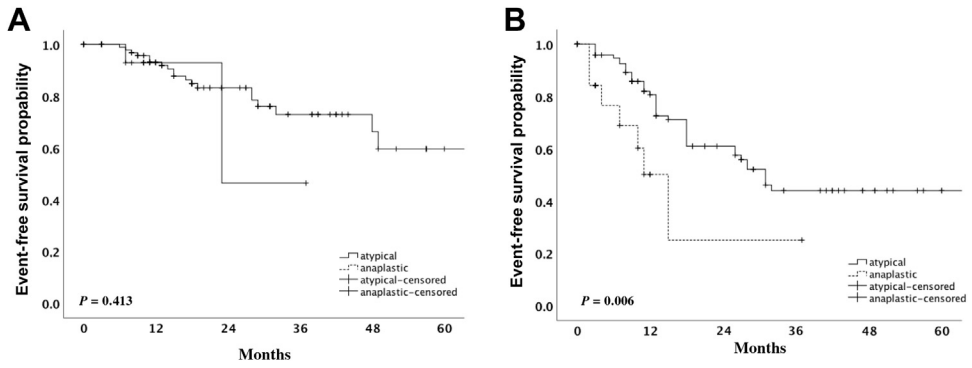

Figure 3. Kaplan-Meier curves for (**A**) regional and (**B**) distant progression-free survival comparing atypical and anaplastic meningiomas.

Table 6. Summary of Local Control per Lesion Divided in Different Response Categories

Response Categories	Local Control per Lesion (n =112 Lesions with Follow-Up)					
	Overall	%	Atypical	%	Anaplastic	%
No change	32	29	31	33	1	5
Minimal response	15	13	10	11	5	26
Partial remission	40	36	31	33	9	47
Complete remission	6	5	6	6	0	0
Local progress	19	17	15	16	4	21
Total	112	100	93	100	19	100

a small tumor node appears by means of regular cross-sectional imaging or even as adjuvant treatment postoperatively. For grade III meningiomas, adjuvant radiotherapy is generally recommended, regardless of the extent of surgical resection.[29] However, for grade II meningiomas, the postoperative management remains controversial. Depending on the extent of surgical resection, various retrospective studies showed lower recurrence rates and improved overall survival for adjuvant irradiated WHO grade II meningiomas.[30,31,32] On the other hand, many studies have found no definite advantage of adjuvant radiotherapy, emphasizing the prognostic significance of surgical resection and the risk of radiation-induced toxicity.[33,34-36] Thus, retrospective studies regarding adjuvant radiotherapy in atypical meningiomas have shown inconsistent results. The first report from the randomized trial RTOG 0539 (Radiation Therapy Oncology Group 0539)[37] supports the use of postoperative RT for newly diagnosed gross totally resected WHO grade II meningiomas based on excellent 3-year progression-free survival results. Further results from this[37] and another ongoing randomized controlled trial[38] will assist in establishing high-level evidence-based guidelines.

We used a median dose of 16 Gy in a single fraction, which seems to be a good compromise in the light of the low toxicities

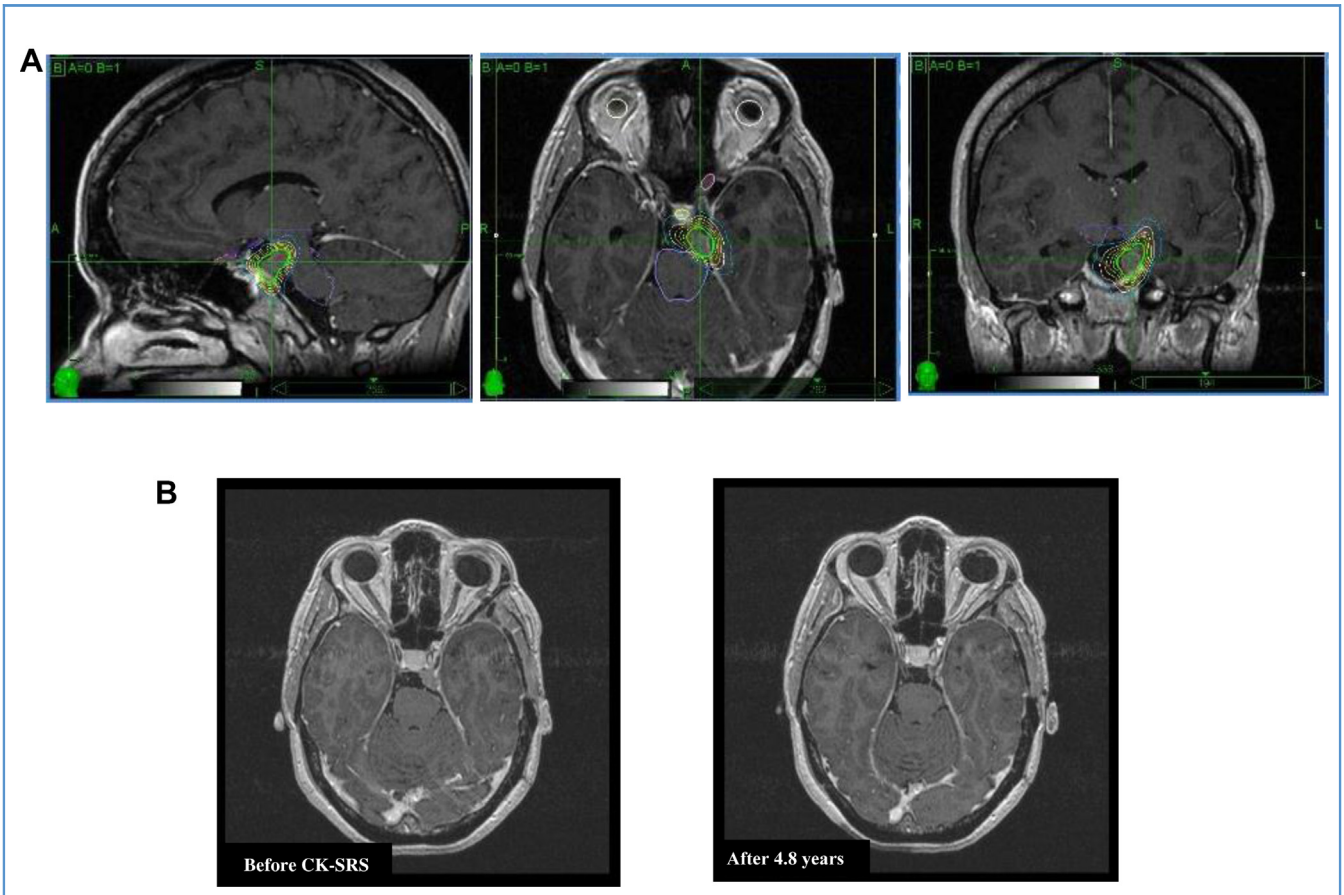

Figure 4. A representative case of a petroclival atypical meningioma (**A**) with the treatment plan and (**B**) images before and after CyberKnife radiosurgery (CK-SRS). (**A**) Magnetic resonance images in coronal (*left*), axial (*middle*) and sagittal (*right*) view with the treatment plan. Fifteen Gy in 1 fraction was prescribed to 70% isodose line (*green*) to treat planning target volume shown in red line (PTV, equal to gross tumor volume) of 0.93 cm^3. The yellow and white circle lines represent the remaining isodose lines until 20% in blue. Organs at risk are also contoured (eyes, optic tract, pituitary gland, and brainstem). (**B**) A representative magnetic resonance image in axial view 2.5 years after surgical resection before CK-SRS (*left*) and 4.5 years after CK-SRS, showing good treatment response.

Table 7. Summary of Regional and Distant Tumor Recurrences of 112 Lesions with Follow-Up

Tumor Recurrences	Overall	%	Atypical	%	Anaplastic	%
Regional	20	18	19	20	1	5
Distant	48	43	41	44	7	37
Both	2	2	1	1	1	5
No distant recurrence	42	38	32	34	10	53
Total	112	100	93	100	19	100

recorded in our series. Comparable prescription doses were used in Gamma Knife SRS series within a range of 15–16 Gy (see Table 9). Pollock et al.[8] included remarkably larger tumors with a median of 14.6 cm^3 and showed only combined local control rates for grade II and III meningiomas, which were 45% at 5 years (Table 9). Aboukais et al.[14] analyzed 27 atypical meningiomas (with larger median volumes) with a lower 3-year local control rate of 40% compared with our series. However, patients were treated with delays of up to 9 years for tumor progression after surgery. This observation also suggests a superior efficacy from early aggressive management for atypical meningiomas, as discussed earlier. Refaat et al.[15] have recently reported the largest series for atypical meningiomas ($n = 97$) with a median dose of 14.5 Gy and reported 68.9% and 57.5% local control rates at 3 and 5 years and determined doses lower and greater than 13.5 Gy and tumor size as prognostic factors for local control.

An overview of the literature is provided in Table 9; the local response rates vary between the reported studies with a tendency for dose dependency that cannot be confirmed in every study, The comparisons have to be evaluated meticulously because of heterogeneity of the treatment regimens (i.e., regarding the timing of the SRS). The role of volume as a prognostic factor for the local control after SRS has already been pointed out[8,39,40] and remains under discussion. In the series of EL-Khatib et al.,[41] it could not be confirmed for linear accelerator SRS. In our series, the PTV was also not a critical factor for local failure. Attia et al.[10] identified the conformality index as a predictor for local control in Gamma Knife–treated patients; however, the conformality index was not reported in most of the studies. In our study, age and EQD_2 were factors associated with local failure. However, other studies did not confirm age as a risk factor for the patterns of failure after SRS.[10,13] Therefore, a prospective randomized trial is needed to identify the relevant predictors for local failure and to establish best dose and treatment planning algorithms.

Distant Progression

If it is possible to achieve local control of atypical and anaplastic meningiomas, they almost invariably tend to recur distantly.[2,3,42] The 5-year recurrence rate of atypical meningiomas was reported to be up to 40% without adjuvant radiotherapy,[43,44] whereas for anaplastic meningiomas, it was up to 70%.[42] The comparison of the regional recurrence rate between SRS and EBRT is relevant for everyday clinical practice, because SRS is a focal treatment with high ablative potential within the irradiation field, but weak or null efficacy out of field. The regional control rates at 12, 24, and 60 months in our series were 93%, 83%, and 59% in atypical meningiomas and at 12 and 24 months 93% and 46% in anaplastic lesions. Zhang et al.[9] showed a 5-year regional control rate (defined as intracranial recurrence outside the treatment field) of 58%, which was similar to our cohort, with 59% regional and 44% distant control. Distant disease progression is the natural course irrespective of the local radiosurgical treatment; however, regional tumor recurrence close to the target volume might be influenced by treatment planning. The studies reported earlier did not differentiate between regional (close proximity) and real distant tumor progress. Valery et al.[45] analyzed marginal relapse

Table 8. The Univariant and Multivariate Cox Proportional Hazards Regression Analyses

	Univariant Analysis			Multivariant Analysis		
	P Value	Hazard Ratio	95% Confidence Interval	*P* Value	Hazard Ratio	95% Confidence Interval
Age	0.002	1.133	1.046–1.227	0.002	1.104	1.038–1.175
Gender	0.094	0.373	0.118–1.183	0.922	0.951	0.342–2.683
Planning target volume	0.521	0.938	0.772–1.140			
Prescribed dose	0.656	1.058	0.831–1.348			
Minimal dose	0.376	1.163	0.833–1.623			
Mean dose	0.908	1.011	0.840–1.217			
Maximal dose	0.447	0.937	0.791–1.109			
Dose mean EQD_2	0.140	1.134	0.959–1.340	0.002	1.210	1.070–1.367
Coverage	0.706	1.093	0.693–1.722			

The multivariant analysis was performed with selected variables after univariant analysis ($P < 0.15$) and demonstrated age and mean equivalent dose (EQD_2) as risk factors in atypical meningioma for local recurrence.

Table 9. Summary of Previous Literature Compared with Our Results Depending on the Dose

Reference	Technique	Number of Patients	Dose	Volume	Local Tumor Control (%)	Follow-Up, Median (Months)
Our series	CyberKnife	II: 27 III: 8	II: median, 16 III: median, 18 Overall: median, 16	II: 1.5 5 (range, 0.06—16.3) III: was 2.38 (range, 0.29—22.5)	II: 97, 77, and 67 at 1, 3, and 5 years III: 66 at 1 and 2 years	23 (range, 2.1—60.3)
Studies with similar dose						
Pollock et al., 2012[8]	Gamma Knife	II: 37 III: 13	Median, 15 (9—20)	Median, 14.6 (1.8—97.7)	II, III: 85 and 45 at 1 and 5 years, LC II, III: 76 and 40 at 1 and 5 years, PFS	38
Kim et al., 2012[16]	Gamma Knife	II: 25 III: 10	Mean, 16 (12—21)	Mean, 3.5 (0.3—25.3)	II, III: 78, 53, and 36 at 1, 2, and 3 years, LC II, III: 35 and 10 at 1 and 2 years, LC	33
Aboukais et al., 2015[14]	Gamma Knife	II: 27	Mean, 15.2 (12—21)	Mean, 5.4 (0.192—14.2)	II: 75, 52, and 40%at 1, 2, and 3 years, LC II: 75, 48, and 33 at 1, 2, and 3 years, RC	56.4
Refaat et al., 2017[15]	Gamma Knife	II: 75	Mean marginal, 16 (12—21)	Mean, 3.5 (0.3—25.3)	II: 68.9 and 55.7 at 3 and 5 years, LC	41
Studies with lower dose						
El-Khatib et al., 2011[41]	Linear accelerator	II: 14 III: 7	Median, 14 (10—15)	Median, 4.8 (0.51—51.4)	II: 91, 81, and 81 at 3, 5, and 10 years, TCR III: 77, 60, and 60 at 3, 5, and 10 years, TCR	60.3
Attia et al., 2012[10]	Gamma Knife	II: 24	Median, 14 (10.5—18)	Median, 6.2 (0.168—44.08)	II: 75, 51, and 44 at 1, 2, and 5 years, LC	42.5
Kuhn et al., 2013[13]	Gamma Knife	II: 41 III: 48	Median (with I), 12 (8.8—20)	Median (with I), 3.25 (0.0367—414.7)	II, III: 72.3, 57.7, and 52.9 at 1, 3, and 5 years, LC II, III: 62.5, 37.1, and 29.7 at 1, 3, and 5 years, PFS	34.2
Studies with higher dose						
Ferraro et al., 2014[17]	Gamma Knife	II: 31 III: 4	Median, 18 (14—24)	Median, 3.90 (0.19—33.1)	II: 95.7 and 70.1 at 1 and 3 years, PFS III: 0 and 0 at 1 and 3 years, PFS	34.5
Zhang et al., 2016[9]	CyberKnife	II:44 III:9	II: Median, 20 (15—35) III: Median, 20 (12—40)	II: Median, 3.33 (0.33—26.0) III: Median, 3.36 (0.13—35.3)	II: 90, 71, and 49 at 1,3 and 5 years, LC III: 93, 57, and 50, at 1, 3, and 5 years, LC	II: 29 III:17

LC, local control; PFS, progression-free survival; TCR, tumor control rate.

rates in grade II meningiomas. These investigators reported a local control rate of 71% at 3 years, marginal control rate of 74% at 2 years, and distant control rate of 81% at 2 years. In our series, we achieved a slightly better local control at 3 years and with 83% a remarkably better marginal control rate at 2 years. Valery et al.[45] observed only a trend toward better marginal control with higher doses and recommended enlarging the target volume along the dural insertion. Despite significant better local control and less distant disease progress of grade II compared with grade III meningiomas, the regional control did not differ in our study. The fact that there is no difference between both grades, although the local control rates are different, may be explained by a more generous contouring of grade III tumors as a result of more irregular margins caused by invasiveness of these tumors. Our findings support the enlargement of tumor margins in grade II and III meningiomas to aim at better regional control.

For a comparison of progression-free survival, it is of major interest to consider under which histologic guidelines the diagnosis was made. In our series, only 3 of 27 patients with atypical meningiomas were diagnosed before WHO 2007 classification[46] and the remainder were diagnosed under the 2007 WHO classification. In addition, 10%–30% of atypical meningiomas undergo malignant transformation to grade III tumors.[6,42] Most of our patients with tumor progression were not reoperated on before CK treatment, and thus, a potential malignant transformation before CK-SRS cannot be excluded for our patients with atypical meningioma. This explanation might be the cause for treatment failure in some cases. In our patient cohort, 23% of the patients ($n = 8$) needed further surgery after radiosurgical treatment for progressive disease. These facts underline the high complexity of the management of these diseases and the need for a multidisciplinary treatment approach, resulting in consensus guidelines. Concerning the dismal survival (in our study, the estimated mean overall survival was 60 ± 3 and 33 ± 5 months for atypical and anaplastic meningiomas, respectively), the concept of aggressive multimodal treatment is the only reasonable therapeutic attempt at treatment, until further systemic therapies such as immunotherapy or molecular targeted therapies are established.

Toxicity

The complication rate in our cohort was lower than that in the series reported by Zhang et al.,[9] which is the largest CyberKnife series reported so far. This study reported 7.5% severe neurologic deficits. Although the dose and volume range applied in this study were higher than in our study, the investigators could not identify the biologically effective dose as a predictor for complications.[9] The role of target volume was not assessed by Zhang et al. but Stafford et al.[47] disproved an association between radiation-associated complications and target volume in a large series of 190 patients with meningioma. In our study, the incidence of severe late adverse events and brain radionecrosis by re-irradiation was not pronounced. Symptomatic adverse events were observed in 13 patients, all considered minor to moderate. Of all patients, only 4 developed asymptomatic radiation reactions during follow-up MRI scans; 2 of those were already irradiated before CK treatment and 2 had received multiple CK-SRS. Apparently, re-irradiation seems to play a role, because only 1 of 13 patients and none of 4 patients with asymptomatic radiation reactions was radiation naive before the CK-SRS causing an adverse event. In this context, Zhang et al.[9] did not detect a significant difference in progression-free survival between patients with/without previous EBRT, although Choe et al.[18] found preirradiated tumor lesions to be a negative predictor for the outcome after SRS. Stafford et al.[47] also concluded that previous radiotherapy was not associated with the development of radiation-related complications. Our study also indicates sufficient safety for SRS re-treatments, because none of the adverse effects was severe. However, this issue has to be addressed by prospective studies.

Limitations

The major limitation of our study is its retrospective design with dispersed follow-up periods. Nevertheless, our analysis provides valuable data for this patient cohort, because it represents the largest yet published lesion series for atypical and anaplastic meningiomas treated by CK-SRS with a detailed lesion-based efficacy analysis. Although surgical treatment remains the treatment of choice for the primary disease, in cases of progressive disease, multilocular reoccurrence, or inoperable lesions or for elderly or very sick patients, SRS represents a reasonable treatment that has to be analyzed from larger data sets preferably generated from prospective randomized clinical trials, probably combined with new systemic agents.

CONCLUSIONS

Although the level of evidence is still low for adequate treatment of atypical and anaplastic meningiomas, CK-SRS has proven efficacy and demands further evaluation in randomized controlled trials. Aggressive treatment for recurring malignant meningiomas by high single dose or multisession radiosurgery provides reasonable local control rates. Nevertheless, regional and distant failures do frequently occur, and the challenge is to investigate not only aggressive focal treatments using the CK-SRS approach but also combinations including new biologicals.

ACKNOWLEDGMENTS

G.A. is a participant of the BIH-Charité Clinician Scientist Program funded by the Charité Universitätsmedizin Berlin and the Berlin Institute of Health.

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Conflict of interest statement: M.L. is employed by Siemens Healthcare GmbH. The remaining authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this article.

Received 17 March 2019; accepted 6 July 2019

Citation: World Neurosurg. (2019) 131:e96-e107.
https://doi.org/10.1016/j.wneu.2019.07.058

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