Neuro-Oncology Advances

3(1), 1–10, 2021 | https://doi.org/10.1093/noajnl/vdab114 | Advance Access date 20 August 2021

Multimodal therapy of cavernous sinus meningioma: Impact of surgery and ^{68}Ga-DOTATATE PET-guided radiation therapy on tumor control and functional outcome

Indrawati Hadi,[†] Annamaria Biczok,[†] Nicole Terpolilli, Jun Thorsteinsdottir, Robert Forbrig, Nathalie L. Albert, Petar Yanchovski, Barbara Zollner, Raphael Bodensohn, Stefanie Corradini, Peter Bartenstein, Claus Belka, Jörg-Christian Tonn, Christian Schichor,[‡] and Maximilian Niyazi[‡]

Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany (I.H., P.Y., B.Z., R.B., S.C., C.B., M.N.); Department of Neurosurgery, University Hospital, LMU Munich, Munich, Germany (A.B., N.T., J.T., J.-C.T., C.S.); Department of Neuroradiology, University Hospital, LMU Munich, Munich, Germany (R.F.); Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany (N.L.A., P.B.); German Cancer Consortium (DKTK), partner site Munich, Munich, Germany (C.B., J.-C.T., M.N.)

[†]*I.H. and A.B. contributed equally as first authors.*

[‡]*M.N. and C.S. contributed equally as last authors.*

Corresponding Author: Maximilian Niyazi, MD, MSc, Department of Radiation Oncology, University Hospital, LMU Munich, Marchioninistrasse 15, 81377 Munich, Germany (maximilian.niyazi@med.uni-muenchen.de).

Abstract

Background. Functional preservation in patients with WHO grade I meningioma involving the cavernous sinus (CSM) is crucial for long-term tumor control. Concise data on the functional outcome of an interdisciplinary, multimodal treatment are scarce. We analyzed functional outcome and tumor control in CSM patients following maximal safe resection (MSR), fractionated stereotactic radiotherapy (FSRT), or combination of them, retrospectively.

Methods. Patients with WHO grade I CSM treated between 2003 and 2017 were included. Prior to FSRT, a ^{68}Ga-DOTATATE PET/CT was performed for radiation planning. Progression-free survival (PFS) was analyzed using Kaplan–Meier method and log-rank test was performed to test differences between groups. Visual function was analyzed at baseline and follow-up.

Results. Eighty-five patients were included. MSR alone was performed in 48 patients (group A), MSR followed by FSRT in 25 patients (group B), and FSRT alone in 12 patients (group C). Intracranial tumor volumes were higher in A and B compared to C (median 9.2/10.8/4.3 ccm for A/B/C, $P = .023$). Median follow-up was 47/46/45 months and PFS at 5 years 55.7%, 100%, and 100% in A/B/C, respectively ($P < .001$). Optic nerve compression was more common in A (91.7%) and B (84.0%) than C (16.7%), $P < .001$. Post-therapeutic new onset or deterioration of double vision was observed in 29% (A), 17% (B), and 0% (C).

Conclusion. Personalized treatment strategies for CSM are essential to control space-occupying or functionally compromising lesions. The additional potential side effect of radiotherapy seems to be justified under the aspect of longer tumor control with low functional risk. Without space-occupying effect of CSM, FSRT alone is reasonably possible.

Key Points

- Personalized treatment strategies for CSM are essential.
- Additional potential side effect of radiotherapy seems to be justified under the aspect of longer tumor control with low functional risk.
- Without space-occupying effect of CSM, FSRT alone is possible.

Importance of the Study

Our study shows the importance of personalized therapy management for CSM patients. For space-occupying and functional compromising CSM maximal safe resection followed by FSRT seems to provide a better tumor control without additional severe radiotherapy adverse events. FSRT alone is a reasonable therapeutic option in the absence of space-occupying effect.

Meningioma is the most frequent primary intracranial tumor, originating from arachnoid cap cells of the dura mater and comprising up to 30% of all intracranial tumors.[1] The therapeutic management of CSM includes surgery alone, combined surgery, and radiation therapy (RT)/radiosurgery or RT/radiosurgery alone.

Although these modern treatment modalities provide excellent outcome in meningiomas grade I, even in the case of benign histology and reasonable resection rates, there is still a risk of recurrence of up to 20%.[2] This leads to more aggressive therapy concepts (surgical or radiotherapeutic), which on the other hand are counteracted by the risk of functional deficits. This problem becomes particularly evident in patients suffering from a meningioma involving the cavernous sinus (cavernous sinus meningiomas [CSM]). CSM is a specific subgroup of tumors, which originates either from the cavernous sinus, or invades it from the anterior clinoid and inner sphenoid ridge. CSM are rare and represent only 1% of all meningiomas.[3]

Especially, because CSM develop close to vascular and nerve structures (eg, internal carotid artery [ICA], the sympathetic plexus, and cranial nerves [CN] III, IV, and VI and the first 2 branches of the CN V), gross total resection (GTR) is nowadays not advisable due to the risk of severe morbidity (eg, diplopic images, field of vision impairment). The same risk constellation also applies to irradiation of the cavernous sinus. Therefore, the management of CSM poses significant challenges and requires a multidisciplinary decision-making process.

To find an answer to this complex decision situation, we investigated the functional outcome and long-term tumor control in a large, homogeneous patient cohort with exclusively WHO grade 1 tumors, whose tumor involving the cavernous sinus was treated either by surgery only or by RT or a combination of both, according to an interdisciplinary decision. To achieve additional therapeutic safety, all radiation therapies were planned based on ^{68}Ga-DOTATATE PET data.

Patients and Methods

Patients

Patients with WHO grade I meningioma who had been treated with surgery or RT between 2003 and 2017 were identified from the institutional database (including department of neurosurgery and radiation oncology). In this study, we only included patients whose tumor involved the cavernous sinus—either localized exclusively in the sinus or additionally extending beyond it into the suprasellar region/the area of the medial sphenoidal wing or the plica petroclinoidea. Overall, 118 patients were identified who met these inclusion criteria. The treatment concept was based on an interdisciplinary tumor board decisions in all patients. There were 33 patients with previous meningioma treatments, hereditary syndromes (eg, neurofibromatosis type II), multiple lesions, atypical or anaplastic meningioma, or patients who were lost of follow-up. These patients were excluded from the analysis. Of the remaining 85 patients, 48 patients underwent surgery alone (group A), 25 patients were treated with maximal safe resection (MSR) followed by fractionated stereotactic radiotherapy (FSRT) (group B), and 12 patients underwent FSRT alone (group C). A CONSORT (Consolidated Standards of Reporting Trials) diagram of our cohort is presented in Supplementary Figure 1.

Medical charts and surgical reports were retrospectively searched for age at first diagnosis, sex, presenting symptoms particularly: visual pathway impairment, diploic vision, pituitary insufficiency, vascular adverse events, or cognitive impairments (in terms of memory or concentration deficits). Each patient gave informed consent prior to the treatment. This retrospective analysis was approved by the ethics committee of the LMU Munich on record number 17-334.

Radiographic Grading

In order to further stratify treatment risks, we defined 3 groups based on standard imaging MRI (contrast-enhanced T1 and high-resolution T2), obtained for treatment planning.

(1) infiltration of anterior third of CS
(2) infiltration of 2/3rd of CS
(3) infiltration of whole CS

Stratification was performed by a neuroradiologist, blinded for the clinical course. Volumetric analysis was obtained from gadolinium-enhanced MRI prior to FSRT and preoperative imaging. Total and intracranial volume was measured separately in all groups using the Oncentra treatment planning system (OTP MasterPlan, Elekta, Crawley, UK).

^{68}Ga-DOTATATE PET/CT

PET/CT scans for RT treatment planning (Biograph 64; Siemens Healthcare, Erlangen, Germany) were acquired 60 minutes after intravenous injection of approximately 150 MBq ^{68}Ga-DOTATATE. Contrast-enhanced CT scans (1.5 mL/kg body weight Iopromide; Ultravist-300, Bayer Healthcare,

Leverkusen, Germany) were obtained for anatomic localization and attenuation correction. Subsequently, the PET scan was acquired by static emission data for 10 minutes. PET images were reconstructed using an iterative algorithm (ordered-subset expectation maximization: 4 iterations, 8 subsets). Contrast-enhanced CT data were reconstructed with a slice thickness of 2.0 mm (axial). The reconstructed PET/CT and fused images were analyzed on the manufacturer's imaging software (syngo.via; Siemens Healthcare).

Tumor Resection

Microsurgical resection was performed as primary treatment modality for patients with space-occupying tumors, neurological impairment due to compression of the brainstem, optic nerve involvement, or symptomatic tumors (eg, seizures). Primary goal of surgery was maximum safe decompression of neurological structures at risk (optic system, adjacent brain parenchyma). Additionally, the resection inside the cavernous sinus was performed as radically as was acceptable from a functional point of view.

To improve the extent of MSR, intraoperative tools such as ultrasound, neuromonitoring, neuronavigation, or cavitron ultrasonic surgical aspirator (CUSA) were used. In case of CSM, extending towards orbital structures, intraoperative computed tomography was used to achieve the best possible extent of resection as previously described by our group.[4]

Fractionated Stereotactic Radiation Therapy

FSRT was performed either in the postoperative setting or as monotherapy in patients who did not undergo surgery. Patients underwent postoperative FSRT within 6 months after surgery, based on an interdisciplinary tumor board decision. Resection status, intraoperative findings, pre-/postoperative MRI, and performance status of the patients were taken into consideration to decide on the most suitable therapy for the patients. Our interdisciplinary tumor board usually recommends postoperative FSRT in case of subtotal resection (STR) confirmed on a postoperative MRI after 3 months, initial space-occupying effects of CSM, compression of critical structures (eg, optic pathways, brainstem), and favorable performance status.

Prior to FSRT, a ^{68}Ga-DOTATATE PET/CT was obtained for each patient to support target delineation of postoperative changes (scar formation). FSRT monotherapy was applied in cases in which no space-occupying tumor extension beyond the cavernous sinus threatened to cause functional deterioration of the patient. An MRI of the brain with 1 mm slice thickness T1-weighted gadolinium-enhanced and T2-weighted was carried out as a part of RT planning. The ^{68}Ga-DOTATATE PET/CT and MRI were merged with 1 mm slice thickness native CT simulation imaging. Patients have been immobilized with a noninvasive thermoplastic double-layered mask system. Gross tumor volume (GTV) was defined as fusion of the contrast-enhancing lesion in T1w + Gd MRI and the ^{68}Ga-DOTATATE enhancement to identify the dural tail or any bone infiltration. The GTV was expanded 2 mm solely along the dura and the area of the skull base to create the clinical target volume (CTV). A uniform 3 mm expansion of the CTV was used to obtain the planning target volume (PTV). RT was delivered in 1.8 Gy single dose to a total dose of 54.0 Gy. Total dose was reduced to 52.2 Gy, in case that CSM was located in close proximity to the optical system.

Oncentra treatment planning system (OTP MasterPlan, Elekta, Crawley, UK) was used for stereotactic RT, Hyperion for intensity-modulated radiotherapy (IMRT), and Monaco (Elekta, Crawley, UK) for volumetric-modulated arc therapy (VMAT).

RT was delivered using a linear accelerator (LINAC) with a photon energy of 6 MV. Image guidance was performed using a cone beam CT or with the Brainlab ExacTrac positioning system since November 2014. Furthermore, the robotic couch HexaPOD evo RT system (Elekta, Crawley, UK) was employed to correct sub-millimetric translational and rotational errors in 6 degrees of freedom.

Follow-Up

The first follow-up was 3 months after the end of treatment with MRI, and further follow-up with MRI was conducted annually. ^{68}Ga-DOTATATE PET/CT was performed in case of suspected recurrence on MRI. The date of the last follow-up was March 2020.

Neurological status assessment focusing on ophthalmological findings (visual acuity, visual field, and the presence of double vision) was performed at baseline and at each follow-up after treatment.

Statistical Analysis

Patient demographics were calculated using descriptive statistics as absolute and relative frequencies. To evaluate the differences in the baseline characteristics, Kruskal–Wallis test was used for continuous variables, Pearson's chi-square test and Cramer's V were performed for categorical variables.

Primary endpoint of the study was progression-free survival (PFS), which was calculated from the first therapy until signs of radiographic progression, defined as newly detected contrast enhancement or an increase of >25% in residual tumor volume on MRI according to the Response Assessment in Neuro-Oncology (RANO) criteria or date of last follow-up.[5] PFS was analyzed using the Kaplan–Meier method. The log-rank test was used to test differences between the groups. All patients, who were alive and without signs of tumor progression at the last follow-up, were censored for survival analysis. Significance was assumed at $P < .05$. Statistical analyses were done using IBM SPSS Statistics, Version 25 (IBM, Armonk, NY, USA).

Results

Patients' Characteristics

We analyzed 85 patients with CSM, who were treated between 2003 and 2017 and fulfilled the aforementioned

criteria. The median age of patients at the time of first diagnosis was 56 years (range, 32–79 years). Twenty-one patients were male (24.7%) and 64 patients (75.3%) were female. Median follow-up was 47 months (95% CI: 36–58 months). The median total GTVs of the CSM on MRI were 11.8 ccm (range, 1.17–111.2 ccm) for group A, 15.3 ccm (range, 4.9–94.1 ccm) for group B, and 8.9 ccm (range, 2.8–33.0 ccm) for group C, $P = .100$. The median intracranial CSM volumes on MRI were 9.2 ccm (range, 0.3–109.7 ccm) for group A, 10.8 ccm (range, 2.1–32.9 ccm) for group B, and 4.3 ccm (range, 1.2–15.7 ccm) for group C, $P = .023$. Space-occupying effects of the CSM were found in 26 patients (54.2%) of group A, 14 patients (56.0%) of group B, and 2 patients (16.7%) of group C, $P = .051$. The CSM compressed the optic nerve in 91.7% patients of group A, 84.0% patients of group B, and 16.7% patients of group C, $P < .001$.

Patient characteristics are summarized in Table 1.

FSRT Parameters

Patients in groups B and C were treated with a dose of 1.8 Gy per fraction up to a median total dose of 54.0 Gy (range, 52.2–54.0 Gy). RT was performed mostly using an IMRT or VMAT technique (76% in group B and 83.4% in group C). The median irradiated GTV was 12.4 ccm (range, 3.2–44.6 ccm) in group B and 12.6 ccm (range, 2.51–33.74 ccm) in group C. The median PTV had a size of 54.2 ccm (range, 18.7–175.34 ccm) in group B and 42.3 ccm (range, 12.0–114.78 ccm) in group C. FSRT parameters are shown in Table 1.

Progression-Free Survival

With a median follow-up of 47/46/45 months in groups A/B/C, respectively, local progression was reported in 18 patients (37.5%) of group A (according to the abovementioned RANO criteria). The initial resection status of these patients was STR in 10 patients (55.5%), GTR in 5 patients (27.8%), the resection status was unknown in 3 patients (16.7%).

No progression was found in the 2 other groups. The median PFS of group A was 69 months, while the median PFS for groups B and C were not reached. The Kaplan–Meier analysis showed 5-year PFS estimates of 55.7%, 100.0%, and 100.0% for groups A, B, and C, respectively (Figure 1). The 10-year PFS rates were 19.2% and 100.0% for groups A and B, and not yet reached for group C. FSRT alone as well as in combination with surgery improved PFS significantly ($P < .001$) compared to surgery alone.

Functional Outcomes

Certain CN deficits were reported by patients at the baseline, including double vision in 19 patients (22%), visual field restriction in 35 patients (41%), visual impairment of the right eye in 32 patients (38%), and visual impairment of the left eye in 33 patients (39%).

Stable neurological status or improvement was described by the majority of patients after all treatment approaches. Improvement or stabilization of double vision was observed in 71%, 83%, and 100% for groups A, B, and C, respectively. Similarly, improvement of visual field restriction was also observed in 91%, 83%, and 100% for groups A, B, and C, respectively.

Cognitive impairment in terms of memory or concentration deficits was reported in 3 patients (6%) of group A at baseline. There was no aggravation of cognitive impairment after treatment of CSM in each group. Hypopituitarism was reported in 2 patients (4%) of group A at baseline and was stable after tumor resection. Hypopituitarism was observed in 3 patients (12%) of group B: 1 patient developed hypopituitarism after CSM resection, 1 patient developed hypopituitarism after resection and worsened 5 years after therapy combination with FSRT, hypopituitarism was described in the third patient after resection followed by FSRT. Pituitary insufficiency was found in 1 patient (8%) of group C in 3 years after FSRT. Vascular adverse events were observed in 2 patients (8%) of group B: 1 patient developed cerebral infarction postoperatively with incomplete right-sided hemiparesis, 1 patient developed carotid stenosis 12 years after surgery and FSRT.

Using chi-square and Cramer's V statistical methods, we analyzed the correlation between treatment modality and functional outcomes. There was a trend towards increased visual impairment of the right eye after surgery alone (39% after surgery alone vs 0% after FSRT or combined modality, $P = .084$), however, not reaching statistical significance. Otherwise, we did not find any significant differences between the 3 groups regarding functional outcomes, in particular, no additive functional risks arose from the combined therapy in group B.

Functional status before and after the treatments of CSM according to each treatment modality is summarized in Table 2.

Treatment Failure

Local progression was described in 18 patients, who underwent surgery alone (group A). The median time to recurrence was 51 months (range, 8–158 months). Two patients underwent re-resection and 16 patients were treated with salvage FSRT. FSRT was delivered in a single dose of 1.8 Gy to a median total dose of 54.0 Gy (range, 52.2–54.0 Gy). The median GTV was 19.8 ccm (range, 10.9–134.3 ccm) and the median PTV was 150.1 ccm (range, 18.8–454.4 ccm). Regarding visual function at recurrence, 1 patient reported worsened double vision, 2 patients had a decreased visual field restriction, 6 patients reported aggravated visual impairment of the right eye, and 3 patients described visual impairments of the left eye. Treatment management and visual function before secondary treatment are summarized in Table 3.

Discussion

In this study, we present the long-term outcome of a large cohort of patients with CSM WHO grade I, who were treated using a multidisciplinary treatment approach with either surgery alone, combined surgery, and ^{68}Ga-DOTATATE PET-guided RT or ^{68}Ga-DOTATATE PET-guided RT alone.

Table 1. Patients' Characteristics

Characteristics	A. Surgery Only n = 48	B. Surgery + FSRT n = 25	C. FSRT Only n = 12	P-values
Sex				
Male	11 (22.9%)	4 (16.0%)	6 (50.0%)	.073
Female	37 (77.1%)	21 (84.0%)	6 (50.0%)	
Median age, yr	54	60	65	.061
Range	32–79	39–78	50–74	
Median follow-up, mo	47	46	45	.712
95% CI	15–79	39–53	25–65	
Median total volume of CSM on MRI, ccm	11.8	15.3	8.9	.100
Range	1.17–111.2	4.9–94.1	2.8–33.0	
Median intracranial CSM volume on MRI, ccm	9.2	10.8	4.3	**.023**
Range	0.3–109.7	2.1–32.9	(1.2–15.7)	
Intracranial space-occupying effect of CSM				
Yes	26 (54.2%)	14 (56.0%)	2 (16.7 %)	**.051**
No	22 (45.8%)	11 (44.0%)	10 (83.3 %)	
Compression of optic nerve				
Yes	44 (91.7%)	21 (84.0%)	2 (16.7 %)	**<.001**
No	4 (8.3%)	4 (16.0%)	10 (83.3 %)	
Laterality of CSM				
Right	24 (50.0%)	10 (40%)	2 (16.7%)	.138
Left	23 (47.9%)	13 (52%)	8 (66.7%)	
Bilateral	1 (2.1%)	2 (8%)	2 (16.7%)	
Orbital infiltration				
Yes	33 (68.7%)	20 (80.0%)	5 (41.7 %)	.066
No	15 (31.3%)	5 (20.0%)	7 (58.3%)	
Infiltration of CS based on radiographic grading				
Anterior third	9 (18.7%)	2 (8.0%)	1 (8.3%)	.618
2/3rd of CS	10 (20.8%)	4 (16.0%)	3 (25.0%)	
Whole CS	29 (60.4%)	19 (76.0%)	8 (66.7%)	
Resection				
Complete	19 (39.6%)	0 (0%)	0 (0%)	**<.001**
Incomplete	25 (52.1%)	25 (100%)	0 (0%)	
No resection	0 (0%)	0 (0%)	12 (100%)	
Unknown	4 (8.3%)	0 (0%)	0 (0%)	
Total dose of irradiation				
1.8–52.2 Gy		9 (36.0%)	1 (8.3%)	
1.8–54.0 Gy		16 (64.0%)	11 (91.7%)	
Median total dose		54.0 Gy	54.0 Gy	
Technique of FSRT				
3D RT		6 (24.0%)	2 (16.7%)	
IMRT		12 (48.0%)	8 (66.7%)	
VMAT		7 (28.0%)	2 (16.7%)	
GTV, median (ccm)		12.4	12.6	
Range		3.2–44.6	2.51–33.74	
PTV, median (ccm)		54.2	42.3	
Range		18.7–175.34	12.0–114.78	

CI, confidence interval; CS, cavernous sinus; CSM, cavernous sinus meningioma; FSRT, fractionated stereotactic radiotherapy; GTV, gross tumor volume; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; PTV, planning target volume; RT, radiation therapy; VMAT, volumetric-modulated arc therapy.
P-values marked with bold indicate statistically significant differences between the groups.

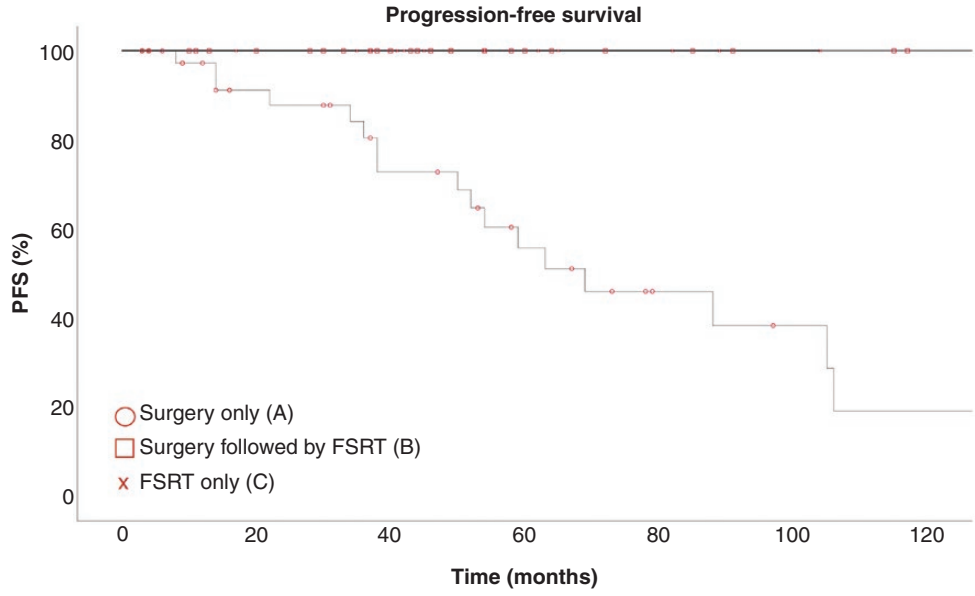

Figure 1. Kaplan–Meier plots of progression-free survival (PFS) for all patients with CSM treated with surgery only (A), combined modality of surgery and FSRT (B), and FSRT only (C). Five-year PFS rates were 55.7%, 100.0%, and 100.0% for A, B, and C, respectively. Ten-year PFS rates were 19.2% and 100.0% for A and B, and not yet reached for group C. B and C improved PFS significantly ($P < .001$) compared to A. CSM, cavernous sinus meningioma; FSRT, fractionated stereotactic radiotherapy.

Table 2. Functional Status Before and After Treatment of CSM

Functional Outcomes	A. Surgery Only n = 48			B. Surgery + FSRT n = 25			C. FSRT Only n = 12		
	Before	Stable/Improved	Worsened	Before	Stable/Improved	Worsened	Before	Stable/Improved	Worsened
Double vision	7 (15%)	5 (71%)	2 (29%)	6 (24%)	5 (83%)	1 (17%)	6 (50%)	6 (100%)	0 (0%)
Visual field restriction	22 (46%)	20 (91%)	2 (9%)	6 (24%)	5 (83%)	1 (17%)	7 (58%)	7 (100%)	0 (0%)
Visual impairment right eye	18 (38%)	11 (61%)	7 (39%)	8 (32%)	8 (100%)	0 (0%)	6 (50%)	6 (100%)	0 (0%)
Visual impairment left eye	17 (35%)	14 (82%)	3 (18%)	12 (48%)	12 (100%)	0 (0%)	4 (33%)	4 (100%)	0 (0%)
Cognitive impairment	3 (6%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypopituitarism	2 (4%)	2 (100%)	1 (2%)	0 (0%)	0 (0%)	3 (12%)	0 (0%)	0 (0%)	1 (8%)
Vascular adverse events	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	0 (0%)

CSM, cavernous sinus meningioma; FSRT, fractionated stereotactic radiotherapy.

Management of CSM remains a challenge for modern neuro-oncologists. CSM are usually indolent and benign tumors, however their growth could be unpredictable.[6,7] CSM, which are confined only to the CS, without extracavernous extension could be diagnosed as incidental finding. But they could also cause minor as well as major symptoms. A prospective study of 53 patients with confined CSM and median follow-up of 10 years demonstrated that watch and wait or simple symptomatic treatment (short course of steroid or carbamazepine) could primarily be performed to relieve the symptoms.[7] However, in case of CSM with extracavernous extension, a complete removal of the tumor inside the CS is, as already addressed, often challenging due to its associated severe surgery-associated risk of morbidity.[8–10] A large prospective observational study of 100 patients with CSM treated with surgery alone showed that a complete removal of the tumor could only be achieved in 12% of cases. Furthermore, the mortality rate was 5% and severe hemiplegia was reported in 2% of the patients. Deterioration of neurological deficits (vision disorder, ocular motility, or trigeminal function) was described in 19%–29% of the patients and the complication rate was significantly higher if surgery was performed inside the CS.[10] A more recent study showed a higher complete tumor resection rate of 41.5%.[11] A similar result was obtained in our cohort, where a gross tumor resection was achieved in 39.6% of the patients in the surgery alone group.

Table 3. Management of Secondary Treatment After Recurrence and Visual Function Before Secondary Treatment

Management of Secondary Treatment After Recurrence			
Parameters	Number of Patients n = 18		
Treatment			
Resection	2 (11%)		
FSRT	16 (89%)		
FSRT			
Dose per fraction (Gy)	1.8		
Median total dose (Gy)	54.0		
Range total dose (Gy)	52.2–54.0		
Median GTV (range) in ccm	19.8 (10.9–134.3)		
Median PTV (range) in ccm	150.1 (18.8–454.4)		
Visual Function Before Secondary Treatment			
	Baseline	Stable/ Improved	Worsened
Double vision	2 (11%)	1 (6%)	1 (6%)
Visual field restriction	8 (44%)	6 (33%)	2 (11%)
Visual impairment right eye	6 (33%)	0 (0%)	6 (33%)
Visual impairment left eye	5 (28%)	2 (11%)	3 (17%)

FSRT, fractionated stereotactic radiotherapy; GTV, gross tumor volume; PTV, planning target volume.

Even though a complete resection is associated with higher morbidity, it is also correlated with a lower recurrence rate of CSM than subtotal tumor removal.[8–10] Sekhar et al reported that patients with GTR presented a much lower progression rate (5%) compared to 20% recurrence rate in patients with incomplete resection.[12] A high probability of tumor recurrence (13% at 3 years; 38% at 5 years) was also found in another study after partial tumor resection.[13] The current study showed a consistent result, as 37.5% of the patients who underwent surgery alone experienced a progression after a median follow-up of 51 months. This was attributable to the fact that 55.5% of patients with a recurrence underwent STR.

Several studies demonstrated that difficulties in achieving a complete resection in CSM resulted in an inferior 5-year PFS in patients who underwent surgery alone.[8,9,14] Our results are in line with these studies, with a 5-year PFS of 55.7% after surgery alone, compared to 100.0% after combined treatment (STR and FSRT), and 100.0% after FSRT alone. In particular, accurate decompression of tumor components in close vicinity of relevant tissue at risk (eg, the brainstem or optic pathways) facilitated maximum dose application during RT. Compression of the optic nerve leading to severe visual impairment was observed more frequently in patients in both surgical groups. Immediate surgical decompression of the optic nerve, including bone removal of the optic canal, was necessary prior to FSRT to prevent further visual deterioration.

Notably, volumetric analysis on gadolinium-enhanced MRI showed a significant smaller intracranial tumor volume in patients treated with FSRT alone in comparison to groups A and B. Due to this significant space-occupying effect in both surgical groups, surgical MSR was necessary to allow postoperative FSRT and relieve symptoms associated with the mass effect created by the tumor. Therefore, our study suggests a MSR followed by RT to optimize long-term neurological performance, corroborating results of other groups, pointing in a similar direction.[15] We could not find a significant difference in total tumor volume, due to higher ratio of orbital involvement in patients treated with FSRT alone.

Regarding RT, 2 methods are commonly utilized to treat CSM: either stereotactic radiosurgery (SRS), delivered with Gamma Knife/CyberKnife or a conventional LINAC) or FSRT. Both modalities were used as combined treatment after incomplete resection as well as sole therapy. SRS was performed to treat small volume CSM with a maximum diameter of 3 cm.[14,16,17] Various published SRS series treated CSM with a median tumor volume range from 4 up to 14 ccm.[13,14,18,19] On the contrary, FSRT is recommended for larger lesions, tumors compressing the optic pathway, or tumors with irregular borders.[16,20–22] FSRT has been preferred over SRS in our cohort due to larger GTVs (median ranged from 12.4 to 12.6 ccm) and PTVs (median ranged from 42.3 to 54.2 ccm). Furthermore, in 37 patients who underwent FSRT (as combined or sole therapy), orbital infiltration was found in 25 patients (67.6%) and the infiltration of whole CS was found in 27 patients (72.9%). These factors aggravated the implementation of SRS and made FSRT the optimal choice for our patients.

Most of the patients were treated using IMRT/VMAT technique, as both are considered superior to a 3D conformal RT technique in terms of PTV coverage, particularly for irregular shaped target volumes.[23] Furthermore, due to the complexity and shape of CSM, we also utilized ^{68}Ga-DOTATATE PET to provide additional information about the tumor extension.[20,24,25] Additionally, as our group has already shown previously, PET imaging delivers valuable additional information to differentiate residual tumor tissue from postoperative scar formation, which might also be helpful in FSRT treatment planning.[24,26]

The current study demonstrated excellent local tumor control in patients, who underwent surgery followed by FSRT or FSRT alone. No progression was found in both groups after a median follow-up of 45–46 months. Previous studies also reflected similar findings with local PFS rates of 93%–99% after 3 years,[27–29] 92%–100% after 5 years,[14,21,30,31] and 81%–92.8% after 8–10 years.[32,33]

Regarding the neurological outcomes, 61%–82% of patients with certain CN deficits at baseline described an improvement or unaltered neurological status after surgery alone. In the surgery alone group, worsening of double vision was found in 29% of patients, worsening of visual field restriction in 9%,

worsening of visual impairment of the right eye in 39%, and worsening of visual impairment of the left eye in 18%. These results were in line with the aforementioned study by Sindou et al, which reported 19% deterioration for vision and 29% for ocular motility as long-term outcome in 100 patients treated with surgery alone.[10] Compared to other groups, there was a trend towards increased visual impairment of the right eye after surgery alone. We could not detect any imbalance of tumor location at baseline between all groups. Although this result might be caused by a bias in this retrospective analysis, it indicated that surgery combined with FSRT or FSRT alone might lead to a better functional outcome than surgery alone. In the group of patients, who underwent surgery and FSRT, an improvement or stabilization of visual deficits was reported in 83%–100% of patients. After FSRT alone, all patients who had CN deficits at baseline reported a better or stable neurological outcome. Compared with previous results, Brahimi et al reported an improvement of at least 1 symptom in 71% of patients after FSRT for skull base meningioma.[34] Other studies described an improvement in neurological status of patients who underwent FSRT ranging from 20% to 80%. These heterogeneous results might be caused by the different criteria and definitions, which were implemented to evaluate clinical response in each study.[17,27,28,31,35] We did not observe any significant difference in terms of late-onset cognitive impairments, pituitary insufficiency, and vascular adverse events between the 3 groups due to low overall incidence. However, it is noteworthy that in case of complex-shaped and/or larger CSM, proton-based FSRT should be considered in order to decrease dose to critical structures and the risk of long-term radiation-induced toxicity.[36,37] In contrast to photon, proton therapy (PT) provides a characteristically unique dose deposition with a steep dose gradient, known as Bragg peak. This enables lower dose exposition to organs at risk (OAR), such as the optical tract, brain stem, and hippocampi; these results have been derived from several comparative studies.[38–40]

Hence, with its excellent effectiveness and functional outcomes, our results support the pivotal role of MSR followed by FSRT or FSRT alone in the treatment of CSM. These results are in line with other studies. The authors are aware of some limitations of the study, inherited by the retrospective study design and a potential imbalance between the 3 groups. These drawbacks might lead to difficulties in drawing conclusion for clinical practice. Indeed, we believe that our analyses could be a foundation of prospective randomized trials in the future.

Conclusion

FSRT alone or the combined modality approach of microsurgical maximal safe tumor resection with FSRT improved PFS significantly compared to surgery alone. Surgical MSR is necessary in patients with severe compression of the optic nerve and space-occupying tumors in order to facilitate FSRT. Interdisciplinary collaboration is important to optimize the multidisciplinary therapy of CSM.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

cavernous sinus | meningioma | neuro-oncology | radiation therapy | stereotactic fractionated radiotherapy

Funding

Not applicable.

Acknowledgments

Not applicable.

Conflict of interest statement. The authors declare that they have no competing interests.

Authorship Statement. I.H., A.M.B., N.T., J.T., C.S., and M.N.: design of the work. I.H., A.M.B., N.T., J.T., R.F., P.Y., and B.Z.: data acquisition, analysis. I.H., A.M.B., N.T., J.T., R.F., P.Y., B.Z., R.B., S.C., C.B., C.S., M.N., and N.A.: interpretation of data, drafted the work or substantially revised it, approved the submitted version, have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

Ethics Approval and Consent to Participate

The institutional review board approved this analysis on July 5, 2017, and all patients signed informed consent (UE nr. 17-334).

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Zhao L, Zhao W, Hou Y, et al. An overview of managements in meningiomas. *Front Oncol.* 2020;10:1–12.
2. Gallagher MJ, Jenkinson MD, Brodbelt AR, Mills SJ, Chavredakis E. WHO grade 1 meningioma recurrence: are location and Simpson grade still relevant? *Clin Neurol Neurosurg.* 2016;141:117–121.
3. Alzhrani G, Derrico N, Abou-Al-Shaar H, Couldwell WT. Management of cavernous sinus meningioma presenting with cerebrovascular insufficiency secondary to cavernous carotid artery occlusion: report of 2 cases. *Oper Neurosurg (Hagerstown).* 2019;16(4):503–513.
4. Terpolilli NA, Rachinger W, Kunz M, et al. Orbit-associated tumors: navigation and control of resection using intraoperative computed tomography. *J Neurosurg.* 2016;124(5):1319–1327.
5. Huang RY, Bi WL, Weller M, et al. Proposed response assessment and endpoints for meningioma clinical trials: report from the Response Assessment in Neuro-Oncology Working Group. *Neuro Oncol.* 2019;21(1):26–36.
6. Bindal R, Goodman JM, Kawasaki A, Purvin V, Kuzma B. The natural history of untreated skull base meningiomas. *Surg Neurol.* 2003;59(2):87–92; discussion 92.
7. Amelot A, van Effenterre R, Kalamarides M, Cornu P, Boch AL. Natural history of cavernous sinus meningiomas. *J Neurosurg.* 2019;130(2):435–442.
8. DeMonte F, Smith HK, Al-Mefty O. Outcome of aggressive removal of cavernous sinus meningiomas. *J Neurosurg.* 1994;81(2):245–251.
9. De Jesús O, Sekhar LN, Parikh HK, Wright DC, Wagner DP. Long-term follow-up of patients with meningiomas involving the cavernous sinus: recurrence, progression, and quality of life. *Neurosurgery.* 1996;39(5):915–919; discussion 919.
10. Sindou M, Wydh E, Jouanneau E, Nebbal M, Lieutaud T. Long-term follow-up of meningiomas of the cavernous sinus after surgical treatment alone. *J Neurosurg.* 2007;107(5):937–944.
11. Nanda A, Thakur JD, Sonig A, Missios S. Microsurgical resectability, outcomes, and tumor control in meningiomas occupying the cavernous sinus. *J Neurosurg.* 2016;125(2):378–392.
12. Sekhar LN, Patel S, Cusimano M, Wright DC, Sen CN, Bank WO. Surgical treatment of meningiomas involving the cavernous sinus: evolving ideas based on a ten year experience. *Acta Neurochir Suppl.* 1996;65:58–62.
13. Marta GN, Correa SF, Teixeira MJ. Meningioma: review of the literature with emphasis on the approach to radiotherapy. *Expert Rev Anticancer Ther.* 2011;11(11):1749–1758.
14. Leroy HA, Tuleasca C, Reyns N, Levivier M. Radiosurgery and fractionated radiotherapy for cavernous sinus meningioma: a systematic review and meta-analysis. *Acta Neurochir (Wien).* 2018;160(12):2367–2378.
15. Walsh MT, Couldwell WT. Management options for cavernous sinus meningiomas. *J Neurooncol.* 2009;92(3):307–316.
16. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol.* 2016;17(9):e383–e391.
17. Correa SF, Marta GN, Teixeira MJ. Neurosymptomatic cavernous sinus meningioma: a 15-years experience with fractionated stereotactic radiotherapy and radiosurgery. *Radiat Oncol.* 2014;9:27.
18. Hung YC, Lee CC, Guo WY, et al. Gamma knife radiosurgery for the treatment of cavernous sinus meningiomas: post-treatment long-term clinical outcomes, complications, and volume changes. *J Neurooncol.* 2019;143(2):261–270.
19. Kano H, Park KJ, Kondziolka D, et al. Does prior microsurgery improve or worsen the outcomes of stereotactic radiosurgery for cavernous sinus meningiomas? *Neurosurgery.* 2013;73(3):401–410.
20. Milker-Zabel S, Zabel-du Bois A, Henze M, et al. Improved target volume definition for fractionated stereotactic radiotherapy in patients with intracranial meningiomas by correlation of CT, MRI, and [^{68}Ga]-DOTATOC-PET. *Int J Radiat Oncol Biol Phys.* 2006;65(1):222–227.
21. Milker-Zabel S, Zabel-du Bois A, Huber P, Schlegel W, Debus J. Intensity-modulated radiotherapy for complex-shaped meningioma of the skull base: long-term experience of a single institution. *Int J Radiat Oncol Biol Phys.* 2007;68(3):858–863.
22. Kondziolka D, Levy EI, Niranjan A, Flickinger JC, Dade Lunsford D. Long-term outcomes after meningioma radiosurgery: physician and patient perspectives. *Skull Base Surg.* 1999;9(4):310.
23. Baumert BG, Norton IA, Davis JB. Intensity-modulated stereotactic radiotherapy vs. stereotactic conformal radiotherapy for the treatment of meningioma located predominantly in the skull base. *Int J Radiat Oncol Biol Phys.* 2003;57(2):580–592.
24. Rachinger W, Stoecklein VM, Terpolilli NA, et al. Increased ^{68}Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. *J Nucl Med.* 2015;56(3):347–353.
25. Zollner B, Ganswindt U, Maihöfer C, et al. Recurrence pattern analysis after [^{68}Ga]-DOTATATE-PET/CT -planned radiotherapy of high-grade meningiomas. *Radiat Oncol.* 2018;13(1):110.
26. Ueberschaer M, Vettermann FJ, Forbrig R, et al. Simpson grade revisited – intraoperative estimation of the extent of resection in meningiomas versus postoperative somatostatin receptor positron emission tomography/computed tomography and magnetic resonance imaging. *Neurosurgery.* 2020;88(1):140–146.
27. Brell M, Villà S, Teixidor P, et al. Fractionated stereotactic radiotherapy in the treatment of exclusive cavernous sinus meningioma: functional outcome, local control, and tolerance. *Surg Neurol.* 2006;65(1):28–33; discussion 33.
28. Litré CF, Colin P, Noudel R, et al. Fractionated stereotactic radiotherapy treatment of cavernous sinus meningiomas: a study of 100 cases. *Int J Radiat Oncol Biol Phys.* 2009;74(4):1012–1017.
29. Alfredo C, Carolin S, Güliz A, et al. Normofractionated stereotactic radiotherapy versus CyberKnife-based hypofractionation in skull base meningioma: a German and Italian pooled cohort analysis. *Radiat Oncol.* 2019;14(1):201.
30. Metellus P, Batra S, Karkar S, et al. Fractionated conformal radiotherapy in the management of cavernous sinus meningiomas: long-term functional outcome and tumor control at a single institution. *Int J Radiat Oncol Biol Phys.* 2010;78(3):836–843.
31. Combs SE, Farzin M, Boehmer J, et al. Clinical outcome after high-precision radiotherapy for skull base meningiomas: pooled data from three large German centers for radiation oncology. *Radiother Oncol.* 2018;127(2):274–279.
32. Maguire PD, Clough R, Friedman AH, Halperin EC. Fractionated external-beam radiation therapy for meningiomas of the cavernous sinus. *Int J Radiat Oncol Biol Phys.* 1999;44(1):75–79.
33. Dufour H, Muracciole X, Métellus P, Régis J, Chinot O, Grisoli F. Long-term tumor control and functional outcome in patients with cavernous sinus meningiomas treated by radiotherapy with or without previous surgery: is there an alternative to aggressive tumor removal? *Neurosurgery.* 2001;48(2):285–294; discussion 294.
34. Brahimi Y, Antoni D, Srour R, et al. Efficacy and tolerance of intensity modulated radiation therapy for skull base meningioma. *Adv Radiat Oncol.* 2019;4(4):587–595.
35. Brahimi Y, Antoni D, Srour R, et al. Fractionated stereotactic radiation therapy in the management of benign cavernous sinus meningiomas: long-term experience and review of the literature. *Strahlenther Onkol.* 2006;182(11):635–640.

36. El Shafie RA, Czech M, Kessel KA, et al. Clinical outcome after particle therapy for meningiomas of the skull base: toxicity and local control in patients treated with active raster scanning. *Radiat Oncol*. 2018;13(1):54.
37. Rogers L, Barani I, Chamberlain M, et al. Meningiomas: knowledge base, treatment outcomes, and uncertainties. A RANO review. *J Neurosurg*. 2015;122(1):4–23.
38. Florijn MA, Sharfo AWM, Wiggenraad RGJ, et al. Lower doses to hippocampi and other brain structures for skull-base meningiomas with intensity modulated proton therapy compared to photon therapy. *Radiother Oncol*. 2020;142:147–153.
39. Adeberg S, Harrabi SB, Bougatf N, et al. Dosimetric comparison of proton radiation therapy, volumetric modulated arc therapy, and three-dimensional conformal radiotherapy based on intracranial tumor location. *Cancers (Basel)*. 2018;10(11):401.
40. Poel R, Stuessi Lobmaier A, Andratschke N, et al. Dosimetric comparison of protons vs photons in re-irradiation of intracranial meningioma. *Br J Radiol*. 2019;92(1100):20190113.