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$^{1*}$, Annamaria Biczok$^{2*}$, Nicole Terpolilli$^{2}$, Jun Thorsteinsdottir$^{2}$, Robert Forbrig$^{3}$, Nathalie L. Albert$^{4}$, Petar Yanchovski$^{1}$, Barbara Zollner$^{1}$, Raphael Bodensohn$^{1}$, Stefanie Corradini$^{1}$, Peter Bartenstein$^{4}$, Claas Belka$^{1,5}$, Jörg-Christian Tonn$^{2,5}$, Christian Schichor$^{2*}$, Maximilian Niyazi$^{1,5*}$.

1 Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany
2 Department of Neurosurgery, University Hospital, LMU Munich, Munich, Germany
3 Department of Neuroradiology, University Hospital, LMU Munich, Munich, Germany
4 Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany
5 German Cancer Consortium (DKTK), partner site Munich, Munich, Germany
Indrawati.Hadi@med.uni-muenchen.de
Annamaria.Biczok@med.uni-muenchen.de
Nicole.Terpolilli@med.uni-muenchen.de
Jun.Thorsteinsdottir@med.uni-muenchen.de
Robert.Forbrig@med.uni-muenchen.de
Nathalie.Albert@med.uni-muenchen.de
Petar.Yanchovks@med.uni-muenchen.de
Barbara.Zollner@ymail.com
Raphael.Bodensohn@med.uni-muenchen.de
Stefanie.Corrdatini@med.uni-muenchen.de
Peter.Bartenstein@med.uni-muenchen.de
Claus.Belka@med.uni-muenchen.de
Joerg.Christian.Tonn@med.uni-muenchen.de
Christian.Schichor@med.uni-muenchen.de
Maximilian.Niyazi@med.uni-muenchen.de

*I. Hadi and A. Biczok contributed equally as first, M. Niyazi and C. Schichor as last authors.

**Corresponding author**

Prof. Dr. med. Dipl. Phys. Maximilian Niyazi

Department of Radiation Oncology, University Hospital,

LMU Munich, Munich, Germany

Tel.: +4989-4400-73770 Fax: +4989-4400-76770
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°I CSM treated between 2003 and 2017 were included. Prior to FSRT, a 68Ga-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 were 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 9.2/10.8/4.3ccm for A/B/C, p=0.023). Median follow-up was 47/46/45 months and PFS at 5-years 55.7%, 100%, and 100% in A/B/C, respectively (p<0.001). Optic nerve compression was more common in A (91.7%) and B (84.0%) than C (16.7%), p<0.001. 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.

Keywords:

Meningioma, cavernous sinus, radiation therapy, neuro-oncology, stereotactic fractionated radiotherapy
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 absence of space-occupying effect.
Background

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/radiosurgery or radiation therapy/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). This specific subgroup of tumors originates from the cavernous sinus, or invades it from the anterior clinoid, inner sphenoid ridge. CSM are rare and represent only 1% of all meningiomas \(^3\).

Especially, because CSM develop close to vascular and nerve structures (e.g. internal carotid artery (ICA), the sympathetic plexus, and cranial nerves (CN) III, IV, and VI and the first two branches of the CN V), gross total resection (GTR) is nowadays not advisable due to the risk of severe morbidity (e.g. diplopia, 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 radiation therapy 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 radiation therapy 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 (e.g. neurofibromatosis type II), multiple lesions, atypical or anaplastic meningioma, or patients who were lost of follow up. These patients were excluded from the analysis. From the remaining 85 patients, 48 patients underwent surgery alone (group A), 25 patients were treated with MSR followed by 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 Fig.suppl 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 term 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 three 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 MR-imaging prior to FRST and pre-operative imaging. Total and intracranial volume was measured separately in all groups using the Oncentra® treatment planning system (OTP MasterPlan®, Elekta, Crawley, UK).

68Ga-DOTATATE PET/CT

PET/CT scans for radiation therapy treatment planning (Biograph 64; Siemens Healthcare, Erlangen, Germany) were acquired 60 minutes after intravenous injection of approximately 150 MBq 68Ga-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 min. 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 (e.g. 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 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 confirmed on a postoperative MRI after three months, initial space-occupying effects of CSM, compression of critical structures (e.g. 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 radiation therapy (RT) planning. The $^{68}$Ga-DOTATATE PET/CT and MRI were merged with 1 mm slice thickness native computed tomography (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).

Radiation therapy 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 six 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 were 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 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-squared 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\textsuperscript{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<0.05.

Statistical analyses were done with IBM SPSS Statistics, Version 25 (IBM, Armonk, New York, USA).
Results

Patients’ characteristics

We analyzed 85 patients with CSM, who were treated between 2003 and 2017 and fulfilled 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 gross tumor volumes 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 = 0.100. 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=0.023. 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=0.051. 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<0.001.

Patient characteristics are summarized in Table 1.

FSRT parameters

Patients in group 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 group A/B/C, respectively, local progression was reported in 18 patients (37.5%) of group A (according to the above mentioned RANO criteria). The initial resection status of these patients was subtotal resection (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 group B and C were not reached. The Kaplan-Meier analysis showed 5-year PFS estimates of 55.7%, 100.0% and 100.0 % for group A, B, and C respectively (Fig. 1). The 10-year PFS rates were 19.2% and 100.0% for group A and B, and not yet reached for group C. FSRT alone as well as in combination with surgery improved PFS significantly (p<0.001) compared to surgery alone.

Functional outcomes

Certain cranial nerve 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 group A, B, and C, respectively. Similarly, improvement of visual field restriction was also observed in 91%, 83%, and 100% for group A, B, and C, respectively.

Cognitive impairment in term 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: one patient developed cerebral infarction postoperatively with incomplete right-sided hemiparesis, one 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 FRST or combined modality, p=0.084), however, not reaching statistical significance. Apart from that, 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 are 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 gross tumor volume 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 3a and 3b.

Discussion

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

Management of CSM remains a challenge for modern neuro-oncologists. Although CSM are indolent and benign tumors, they grow slowly, but also unpredictable. CSM, which are confined only to the CS, without extracavernous extension could be diagnosed as incidental finding, or with 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. 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. 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\textsuperscript{10}. A more recent study showed a higher complete tumor resection rate of 41.5%\textsuperscript{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.

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\textsuperscript{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 an incomplete resection\textsuperscript{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\textsuperscript{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 subtotal resection.

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\textsuperscript{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 (subtotal resection and FSRT), and 100.0% after FSRT alone. In particular, accurate decompression of tumor components in close vicinity of relevant tissue at risk (e.g. the brainstem or optic pathways) facilitated maximum dose application during radiation therapy. 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 group 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 radiation therapy to optimize long-term neurological performance, corroborating results of other groups, pointing in a similar direction\textsuperscript{15}. We could not find a significant difference in total tumor volume, due to higher ratio of orbital involvement in patients treated with FRST alone.

Regarding radiation therapy, two methods are commonly utilized to treat CSM: either stereotactic radiosurgery (SRS), delivered with gammaknife/cyberknife or a conventional linear accelerator) or fractionated stereotactic RT (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\textsuperscript{14,16,17}. Various published SRS series treated CSM with a median tumor volume range from 4 up to 14 ccm\textsuperscript{13,14,18,19}. On the contrary, FSRT is recommended for larger lesions, tumors compressing the optic pathway, or tumors with irregular borders\textsuperscript{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\textsuperscript{23}. Furthermore, due to the complexity and shape of cavernous sinus meningioma, we also utilized \textsuperscript{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% to 99% after 3 years \(^{27-29}\), 92% to 100% after 5 years \(^{14,21,30,31}\), and 81% to 92.8% after 8 to 10 years \(^{32,33}\).

Regarding the neurological outcomes, 61- 82% of patients with certain cranial nerve 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% 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% patients. After FSRT alone, all patients who had cranial nerve 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% 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%. This heterogeneous results might be caused by the different criteria and definition, which were implemented to evaluate clinical response in each study. We did not observe any significant difference in terms of late onset cognitive impairments, pituitary insufficiency, and vascular adverse events between the three 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. In contrast to photon, proton therapy (PT) provides a characteristically unique dose deposition with a step dose gradient, known as Bragg-peak. This enables lower dose exposition to OARs, such as the optical tract, brain stem and hippocampi; these results have been derived from several comparative studies.

Hence, with its excellent effectiveness and functional outcomes, our results support the pivotal role of maximal safe resection followed by FSRT or FSRT alone in the treatment of cavernous sinus meningioma. These results are in line with other studies. The authors are aware of some limitation 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 trial 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 maximal safe resection 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.
References

1. Zhao L, Zhao W, Hou Y, et al. An Overview of Managements in Meningiomas. *Front Oncol.* 2020;10(August):1-12. doi:10.3389/fonc.2020.01523

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. doi:10.1016/j.clineuro.2016.01.006

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.* 2019;16(4):503-513. doi:10.1093/ons/opy120

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. doi:10.3171/2015.5.JNS15330

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. doi:10.1093/neuonc/noy137

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. doi:10.1016/S0090-3019(02)00995-3

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. doi:10.3171/2017.7.JNS17662

8. DeMonte F, Smith HK, Al-Mefty O. Outcome of aggressive removal of cavernous
sinus meningiomas. *J Neurosurg*. 1994;81(2):245-251.
doi:10.3171/jns.1994.81.2.0245

9. De Jesus 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):915-920. doi:10.1097/00006123-199611000-00005

10. Sindou M, Wydh E, Jouanneau E, Nebbal M, Lietaud T. Long-term follow-up of meningiomas of the cavernous sinus after surgical treatment alone. *J Neurosurg*. 2007;107(5):937-944. doi:10.3171/JNS-07/11/0937

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. doi:10.3171/2015.3.JNS142494

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. doi:10.1007/978-3-7091-9450-8_17

13. Marta GN, Correa SFM, Teixeira MJ. Meningioma: review of the literature with emphasis on the approach to radiotherapy. *Expert Rev Anticancer Ther*. 2011;11(11):1749-1758. doi:10.1586/era.11.162

14. Leroy HA, Tuleasca C, Reyns N, Levisier M. Radiosurgery and fractionated radiotherapy for cavernous sinus meningioma: a systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2018;160(12):2367-2378. doi:10.1007/s00701-018-3711-9

15. Walsh MT, Couldwell WT. Management options for cavernous sinus meningiomas. *J Neurooncol*. 2009;92(3 SPEC. ISS.):307-316. doi:10.1007/s11060-009-9824-5

16. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and
17. Correa SFM, Marta GN, Teixeira MJ. Neurosymptomatic carvenous sinus meningioma: A 15-years experience with fractionated stereotactic radiotherapy and radiosurgery. *Radiat Oncol*. 2014;9(1):1-9. doi:10.1186/1748-717X-9-27

18. Hung Y-C, Lee C-C, Guo W-Y, 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(01 June 2019):261-270. doi:10.1007/s11060-019-03090-6

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. doi:10.1227/01.neu.0000431471.64289.3d

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 [68Ga]-DOTATOC-PET. *Int J Radiat Oncol Biol Phys*. 2006;65(1):222-227. doi:10.1016/j.ijrobp.2005.12.006

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. doi:10.1016/j.ijrobp.2006.12.073

22. Kondziolka D, Levy EI, Niranjan A, Flickinger JC, Dade Lunsford D. Long-term outcomes after menigioma 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. doi:10.1016/S0360-3016(03)00587-X

24. Rachinger W, Stoecklein VM, Terpolilli NA, et al. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. *J Nucl Med.* 2015;56(3):347-353. doi:10.2967/jnumed.114.149120

25. Zollner B, Ganswindt U, Maihöfer C, et al. Recurrence pattern analysis after [68Ga]-DOTATATE-PET/CT -planned radiotherapy of high-grade meningiomas. *Radiat Oncol.* 2018;13(1):1-9. doi:10.1186/s13014-018-1056-4

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;0(0):1-7. doi:10.1093/neuros/nyaa333

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. doi:10.1016/j.surneu.2005.06.027

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. doi:10.1016/j.ijrobp.2008.09.012

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):1-9. doi:10.1186/s13014-019-
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. doi:10.1016/j.ijrobp.2009.08.006

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. doi:10.1016/j.radonc.2018.03.006

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. doi:10.1016/S0360-3016(98)00558-6

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):285-296. doi:10.1227/00006123-200102000-00006

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. doi:10.1016/j.adro.2019.07.009

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. *Strahlentherapie und Onkol*. 2006;182(11):635-640. doi:10.1007/s00066-006-1548-2
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 rasterscanning. *Radiat Oncol*. 2018;13(1):54. doi:10.1186/s13014-018-1002-5

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. doi:10.3171/2014.7.JNS131644

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. doi:10.1016/j.radonc.2019.08.019

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). doi:10.3390/cancers10110401

40. Poel R, Lobmaier AS, Andratschke N, et al. Dosimetric comparison of protons vs photons in re-irradiation of intracranial meningioma. *Br J Radiol*. 2019;92(1100). doi:10.1259/bjr.20190113
Fig. 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<0.001) compared to A.
Ethics approval and consent to participate
The institutional review board approved this analysis on 5th of July 2017 and all patients signed informed consent (UE nr. 17-334).

Consent for publication
Not applicable

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

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

Funding
Not applicable
Authors' contributions

IH, AMB, NT, JT, CS, MN  design of the work

IH, AMB, NT, JT, RF, PY, BZ  data acquisition, analysis

IH, AMB, NT, JT, RF, PY, BZ, RB, SC, CB, CS, MN, NA  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.

Acknowledgements

Not applicable
| Characteristics                              | A. Surgery only | B. Surgery + FSRT | C. FSRT only | p value |
|---------------------------------------------|-----------------|-------------------|--------------|---------|
|                                             | n=48            | n=25              | n=12         |         |
| Sex                                         |                 |                   |              |         |
| Male                                        | 11 (22.9%)      | 4 (16.0%)         | 6 (50.0%)    | 0.073   |
| Female                                      | 37 (77.1%)      | 21 (84.0%)        | 6 (50.0%)    |         |
| Median age, years                           | 54              | 60                | 65           | 0.061   |
| Range                                       | 32 - 79         | 39 - 78           | 50 - 74      |         |
| Median follow up, months                    | 47              | 46                | 45           | 0.712   |
| 95%-CI                                      | 15 - 79         | 39 - 53           | 25 - 65      |         |
| Median total volume of CSM on MRI, ccm      | 11.8            | 15.3              | 8.9          | 0.100   |
| 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          | 0.023   |
| Range                                       | 0.3 – 109.7     | 2.1 – 32.9        | (1.2 – 15.7) |         |
| Intracranial space-occupying effect of CSM  |                 |                   |              | 0.051   |
| Yes                                         | 26 (54.2%)      | 14 (56.0%)        | 2 (16.7%)    |         |
|                          | No                        | Yes                      | Compression of optic nerve | <0.001 |
|--------------------------|---------------------------|--------------------------|----------------------------|--------|
|                          | 22 (45.8%)                | 11 (44.0%)               | 44 (91.7%)                 |        |
|                          |                           |                          | 21 (84.0%)                |        |
|                          |                           |                          | 2 (16.7%)                 |        |
| Laterality of CSM        |                           |                          |                            | 0.138  |
| Right                    | 24 (50.0%)                | 10 (40%)                 | 24 (50.0%)                 |        |
| Left                     | 23 (47.9%)                | 13 (52%)                 | 21 (84.0%)                 |        |
| Bilateral                | 1 (2.1%)                  | 2 (8%)                   | 2 (16.7%)                 |        |
| Orbital infiltration     |                           |                          |                            | 0.066  |
| Yes                      | 33 (68.7%)                | 20 (80.0%)               | 33 (68.7%)                 |        |
| No                       | 15 (31.3%)                | 5 (20.0%)                | 15 (31.3%)                 |        |
| Infiltration of CS       |                           |                          |                            | 0.618  |
| based on radiographic grading |                       |                          |                            |        |
| Anterior third           | 9 (18.7%)                 | 2 (8.0%)                 | 2 (16.7%)                 |        |
| 2/3 of CS                | 10 (20.8%)                | 4 (16.0%)                | 10 (20.8%)                 |        |
| whole CS                 | 29 (60.4%)                | 19 (76.0%)               | 29 (60.4%)                 |        |
| Resection                |                           |                          |                            | <0.001 |
| Complete                 | 19 (39.6%)                | 0 (0%)                   | 0 (0%)                    |        |
| 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 – 52.2Gy             | 9 (36.0%)       | 1 (8.3%)       |
| 1.8 – 54.0Gy             | 16 (64.0%)      | 11 (91.7%)     |
| Median total dose        | 54.0Gy          | 54.0Gy         |

| 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 |

**Table 1** Patients’ characteristics
| 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      | 5 (71%)        | 2 (29%)  | 6      | 5 (83%)        | 1 (17%)  | 6      | 6 (100%)       | 0 (0%)   |           |           |
|                           | (15%)  |                |          | (24%)  |                | (17%)   | (50%)  |                  |          |           |           |
| Visual field restriction  |        |                |          |        |                |          |        |                |          |           |           |
|                           | 22     | 20 (91%)       | 2 (9%)   | 6      | 5 (83%)        | 1 (17%)  | 7      | 7 (100%)       | 0 (0%)   |           |           |
|                           | (46%)  |                |          | (24%)  |                | (17%)   | (58%)  |                  |          |           |           |
| Visual impairment         |        |                |          |        |                |          |        |                |          |           |           |
| right eye                 | 18     | 11 (61%)       | 7 (39%)  | 8      | 8 (100%)       | 0 (0%)   | 6      | 6 (100%)       | 0 (0%)   |           |           |
|                           | (38%)  |                |          | (32%)  |                | (0%)    | (50%)  |                  |          |           |           |
| Visual impairment         |        |                |          |        |                |          |        |                |          |           |           |
| left eye                  | 17     | 14 (82%)       | 3 (18%)  | 12     | 12 (100%)      | 0 (0%)   | 4      | 4 (100%)       | 0 (0%)   |           |           |
|                           | (35%)  |                |          | (48%)  |                | (0%)    | (33%)  |                  |          |           |           |
| Cognitive impairment      |        |                |          |        |                |          |        |                |          |           |           |
|                           | 3      | 3 (100%)       | 0 (0%)   | 0      | 0 (0%)         | 0 (0%)   | 0      | 0 (0%)         | 0 (0%)   |           |           |
|                           | (6%)   |                |          | (0%)   |                | (0%)    | (0%)   |                  |          |           |           |
| Hypopituitarism           |        |                |          |        |                |          |        |                |          |           |           |
|                           | 2      | 2 (100%)       | 0 (0%)   | 0      | 0 (0%)         | 3 (12%)  | 0      | 0 (0%)         | 1 (8%)   |           |           |
|                           | (4%)   |                |          | (0%)   |                | (12%)   | (0%)   |                  |          |           |           |
| Vascular adverse events   |        |                |          |        |                |          |        |                |          |           |           |
|                           | 0      | 0 (0%)         | 0 (0%)   | 0      | 0 (0%)         | 2 (8%)   | 0      | 0 (0%)         | 0 (0%)   |           |           |

Table 2 Functional status before and after treatment of CSM
### Parameters

| Parameters                        | Number of patients |
|-----------------------------------|--------------------|
| **n=18**                          |                    |
| **Treatment**                     |                    |
| Resection                         | 2 (11%)            |
| FSRT                              | 16 (89%)           |
| **FRST**                          |                    |
| 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

| 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%)  |

**Table 3** Management of secondary treatment after recurrence (a) and visual function before secondary treatment (b)
Figure 1

Progression-free survival

PFS [%]

Time [months]

- Surgery only (A)
- Surgery followed by FSRT (B)
- FSRT only (C)