Fractionated Stereotactic Radiation Therapy in the Management of Benign Cavernous Sinus Meningiomas

Long-Term Experience and Review of the Literature

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Purpose: To analyze own long-term results with fractionated stereotactic radiotherapy (FSRT) in patients with benign meningiomas of the cavernous sinus and to review the literature on these rare lesions.
Patients and Methods: 57 patients were treated with FSRT for benign meningiomas of the cavernous sinus between 01/1990 and 12/2003 at the authors' institution. Histology was WHO grade I in 28/57 lesions, and undetermined in 29/57 lesions. 29 patients received radiotherapy as primary treatment, ten following surgery, and 18 patients were irradiated for recurrent disease. Median target volume was 35.2 cm^3. Median total dose was 57.6 Gy with 1.8 Gy per fraction. 51/57 patients showed clinical symptoms before radiotherapy like reduced vision (n = 19), diplopia (n = 25), or trigeminal hyp-/dysesthesia (n = 17).
Results: Median follow-up period was 6.5 years. 50/57 patients were followed for > 36 months. Overall local tumor control was 100%. 39/57 patients had stable disease based on CT/MRI, while 18/57 had a partial remission of tumor volume. Overall survival for patients with WHO grade I meningiomas was 95.5% after 5 and 10 years. Two patients died 2.8 and 4.1 years after radiotherapy due to cardiac failure. In 11/57 patients, preexisting neurologic deficits improved. There was one patient with recurrent hyperlacrimation of one eye on the side of the irradiated meningioma. Three patients complained about subjective visual deterioration after FSRT without any objective findings in an ophthalmologic examination. No late toxicity RTOG $\geq$ °III was seen.
Conclusion: These data demonstrate that FSRT is an effective and safe treatment modality for local control of benign cavernous sinus meningiomas with a minimal risk of significant late toxicity.

Key Words: Fractionated stereotactic radiotherapy (FSRT) · Cavernous sinus meningioma · Local control · Long-term experience · Review of the literature

Strahlenther Onkol 2006;182:635–40
DOI 10.1007/s00066-006-1548-2

Fraktionierte stereotaktische Strahlentherapie in der Behandlung gutartiger Sinus-cavernosus-Meningeome. Langzeiterfahrungen und Literaturüberblick

Ziel: Darstellung der Langzeitergebnisse nach fraktionierter stereotaktischer Strahlentherapie (FSRT) von benignen Sinus-cavernosus-Meningeomen und Literaturübersicht dieser seltenen Befunde.
Patienten und Methodik: Zwischen 01/1990 und 12/2003 wurden 57 Patienten mittels FSRT an einem benignen Sinus-cavernosus-Meningeom in der Abteilung der Autoren behandelt. Histopathologisch entsprachen 28/57 Befunde WHO-Grad I, und 29/57 Befunde waren ausschließlich bildmorphologisch eindeutig als Meningeom diagnostiziert worden. 29 Patienten wurden primär, zehn postoperativ und 18 in einer Rezidivsituation bestrahlt. Die mediane Zielvolumengröße betrug 35,2 cm^3. Die mediane applizierte Gesamtdosis betrug 57,6 Gy bei einer wöchentlichen Fraktionierung von 5 × 1,8 Gy. Initial zeigten 51/57 Patienten neurologische Symptome, wie Sehverschlechterung (n = 19), Doppelbilder (n = 25) oder Trigeminushyp-/-dysästhesie (n = 17).
Ergebnisse: Die lokale Tumorkontrollrate betrug 100% nach einer medianen Nachbeobachtungszeit von 6,5 Jahren. Bei 50/57 Patienten war der Nachbeobachtungszeitraum > 36 Monate. 39 Meningeome zeigten eine Größenkonstanz im CT/MRT, 18 Befunde eine Größenreduktion. Das Gesamtüberleben betrug 95,5% nach 5 und 10 Jahren. Zwei Patienten verstarben 2,8 und 4,1 Jahre nach Strahlentherapie an kardialer Ursache. Bei 11/57 Patienten zeigte sich nach Strahlentherapie eine deutliche Besserung der vorbestehenden neurologischen Symptomatik. Ein Patient entwickelte im Verlauf rezidivierendes Augentränen auf der Seite des bestrahlten Meningeoms. Drei Patienten berichteten über rezidivierende subjektive Sehverschlechterung ohne ophthalmologisches Korrelat. Es traten keine Spättoxizitäten RTOG $\geq$ °III auf.

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Received: November 14, 2005; accepted: July 11, 2006

Schlussfolgerung: Die FSRT ist sicher anwendbar und erreicht gute lokale Tumorkontrollraten bei geringem Risiko für radiogene Spätkomplikationen.

Schlüsselwörter: Fraktionierte stereotaktische Strahlentherapie · Sinus-cavernosus-Meningeome · Lokale Kontrolle · Langzeiterfahrungen · Literaturüberblick

Introduction

Meningiomas are the most common nonglial primary brain tumors, accounting for approximately 14–20% [34, 36]. With 10–15% of all meningiomas, cavernous sinus meningiomas are relatively rare lesions. Nevertheless, meningiomas, pituitary adenomas and schwannomas are the most benign tumors close to the cavernous sinus [15, 22, 41]. The treatment of cavernous sinus meningiomas is a challenge for neurosurgeons due to adjacent neurovascular structures, like the venous plexus, internal carotid artery and trigeminal/oculomotor nerves. Negligible risks of perioperative morbidity and mortality exist. Total resectability rates range from 20% to 82% [9, 31].

Postoperative radiotherapy after subtotal resection has the potential to prolong the time to recurrence and prevents tumor regrowth [9, 10]. In order to reduce radiation-induced side effects and to increase local control, sophisticated treatment planning like stereotactic radiotherapy and intensity-modulated radiotherapy is recommended [1, 14, 16, 25, 42, 43]. For lesions within the cavernous sinus, as well as for brain metastases, stereotactic radiosurgery has been reported as a therapeutic modality with promising results [5, 13, 20]. Cavernous sinus meningiomas often present irregular morphology that requires highly conformal dose distributions to optimize the treatment while reducing exposures to surrounding radiosensitive structures, like trigeminal and oculomotor nerve, as well as optic pathway and diencephalic-hypophyseal system. Such precision may be obtained with fractionated stereotactic radiotherapy (FSRT).

In this article, we report our long-term experience with FSRT in the treatment of benign cavernous sinus meningiomas with respect to local control, radiation-induced side effects, and overall survival.

Patients and Methods

Patient Characteristics

FSRT has been applied in over 500 patients with intracranial meningioma at the University of Heidelberg, Germany. Among these were 57 patients with benign cavernous sinus meningioma. This study is based on this rare subgroup treated between January 1990 and December 2003. Institutional approval was obtained for the conduct of this study by our institutional review board. 28 patients had a histologically proven diagnosis of meningioma of World Health Organization (WHO) grade I. In 29/57 patients, the clinical and radiologic characteristics of the tumor were consistent with the clinical diagnosis of meningioma although no biopsy was obtained.

23 patients received radiotherapy as primary treatment, six patients after biopsy only, and ten patients after subtotal resection. 18 patients were irradiated for recurrent disease.

Treatment Planning

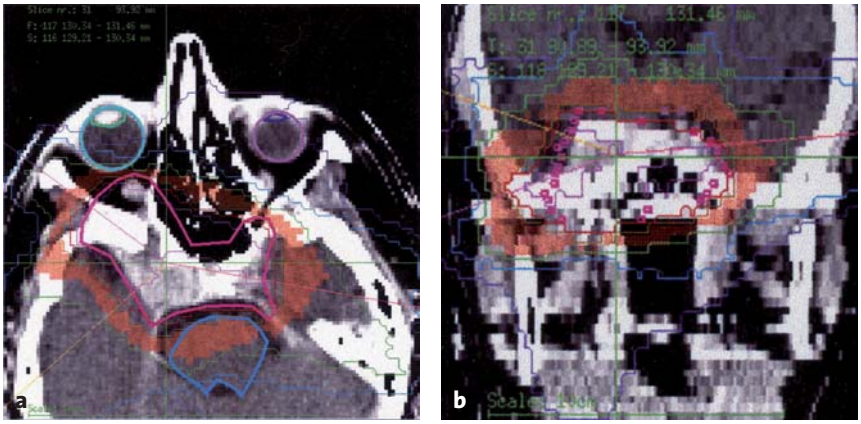
The patients were immobilized in an individual head-mask fixation system made of scotch-Cast™. The head mask assures an overall accuracy of 1–2 mm [27]. Treatment planning was based on CT and MRI of the head under stereotactic guidance [7]. The patient-specific mask may be attached to the CT/MRI couch for planning or to the treatment couch. A noninvasive stereotactic frame could be attached to the mask during CT/MRI or before irradiation to mask the isocenter. Treatment planning was performed on a three-dimensional CT data cube generated from continuous 3-mm CT scans. MRIs were obtained in treatment position and stereotactically fused to the CT. For treatment planning, the three-dimensional planning system Voxelplan/dkfz (available as Virtuoso, Leibinger Co, Freiburg, Germany) was used [6, 17, 37]. The planning target volume (PTV) included the macroscopic tumor visible on MRI with a safety margin of 1–2 mm to the brain tissue, 3 mm to adjacent osseous structures, and 5 mm along the dura. After stereotactic image fusion, PTV and organs at risk were delineated on each slice of the data cube. A median of four noncoplanar isocentric fields were irregularly shaped by a multileaf collimator (leaf width: 5 mm at isocenter) [7]. The PTV was covered by the 90% isodose. FSRT was delivered with a 6/15-MV linear accelerator (Siemens AG, Erlangen, Germany). The target dose was prescribed to the isocenter, where we delivered a median total dose of 57.6 Gy (range, 52.2–61.4 Gy), with a median daily fraction of 1.8 Gy. Figure 1 shows an exemplary treatment plan with corresponding dose-volume histogram.

Follow-up and Toxicity

Follow-up included radiologic (CT/MRI), clinical and neurologic examinations at 6 weeks, 3 months, and 6 months after radiotherapy, and then once a year. Ophthalmologic examination was performed 6 months following FSRT and at 1-year intervals thereafter. Side effects were documented according to the Common Toxicity Criteria (CTC) and the guidelines of the Radiation Therapy Oncology Group (RTOG).

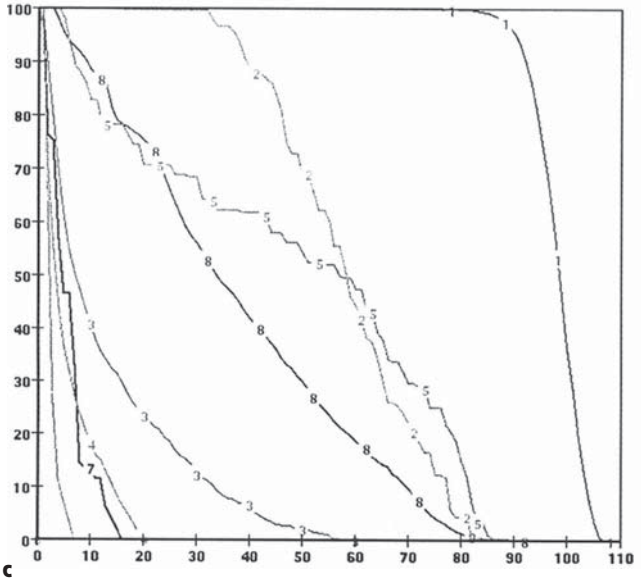
Results

Median follow-up was 6.5 years. All patients were followed for > 12 months, 50/57 patients for > 36 months. The PTV was



Figures 1a to 1c. Exemplary treatment plan. a) Transverse view, b) coronal view. Isodose lines are 107%, 90%, 80–70% (color wash), 50%, 30%, and 10%, respectively. c) Dose-volume histogram (1: target; 2: right optic nerve; 3: left optic nerve; 5: brainstem; 8: chiasm).

Abbildungen 1a bis 1c. Exemplarischer Bestrahlungsplan. a) Axiale Dosisverteilung und b) koronale Dosisverteilung. Abgebildet sind jeweils die 107%-, 90%-, 80- bis 70%- (orange unterlegter Bereich), 50%-, 30%- und 10%-Isodosen. c) Dosis-Volumen-Histogramm (1: Zielvolumen, 2: rechter Sehnerv, 3: linker Sehnerv, 5: Hirnstamm, 8: Chiasma).



defined as described above. Median PTV was 35.2 cm^3 (range, 1.0–386.8 cm^3) and > 30 cm^3 in 31 patients.

Radiologic Response

Stable disease based on CT or MRI was seen in 39/57 patients, while 18/57 patients had a reduction of tumor volume of > 50% during follow-up. Figure 2 shows the MRI of a WHO grade I meningioma with a partial remission 3.5 years after FSRT. No correlation between irradiated tumor volume and tumor volume reduction was seen.

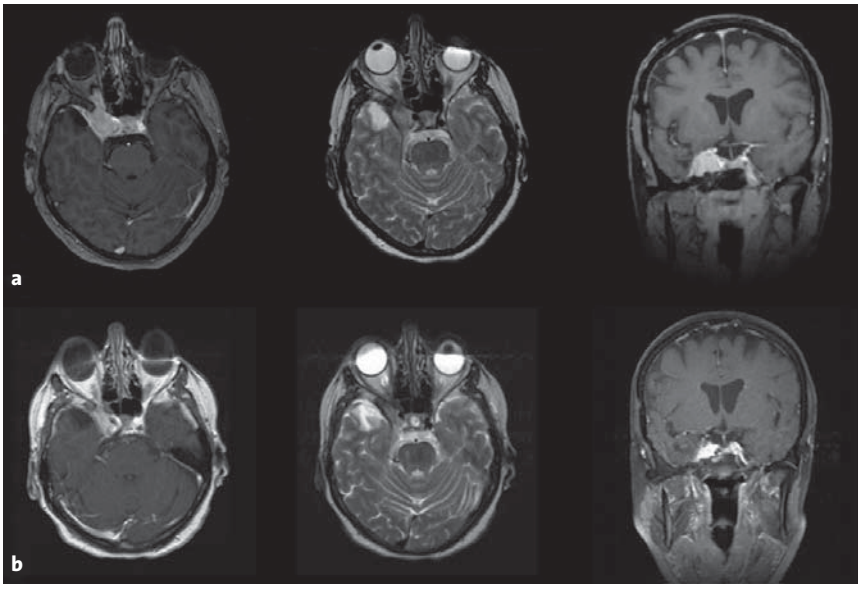
Clinical Response

51/57 patients showed clinical symptoms before radiotherapy like diplopia (43.9%), reduced vision (33.3%), loss of visual fields (17.5%), trigeminal dysesthesia (29.8%), or exophthalmos (5.3%). Most patients (57.9%) had more than one clinical symptom before radiotherapy.

In 11/57 patients, preexisting neurologic deficits improved. One patient showed no further diplopia, another patient an improvement in preexisting exophthalmos. Three patients had an improvement in trigeminal dysesthesia, and four patients an improvement in preexisting headache symptoms.

Survival and Toxicity

Two patients died 2.8 and 4.1 years after FSRT due to cardiac failure. Survival calculated according to the Kaplan-Mei-



Figures 2a and 2b. a) Initial MRI for treatment planning of the same patient as shown in Figure 1. b) Radiologic response in MRI 3.5 years after FSRT.

Abbildungen 2a und 2b. a) Initiales MRT des Patienten aus Abbildung 1 zur Bestrahlungsplanung. b) Radiologisches Ansprechen im MRT 3,5 Jahre nach FSRT.

er method was 95.5% at 5 and 10 years. Recurrence-free survival was 100% at 5 and 10 years.

Acute toxicity was mild and consisted of hair loss as well as mild skin irritation (skin erythema CTC grade I). There was one patient with recurrent hyperlacrimation of one eye on the side of irradiated cavernous sinus meningioma. Three patients complained about subjective visual deterioration after FRST without any objective findings. No patient developed hypothalamic-pituitary dysfunction, or intracranial malignancies after FSRT. No clinically significant toxicity to normal-tissue structures was observed.

Discussion

We have shown that FSRT is safe and feasible in the treatment of benign cavernous sinus meningiomas with low risk of significant late toxicity. The indications for FSRT included residual tumors after subtotal resection, recurrent disease, and cases of inoperability due to the proximity to critical structures or comorbid conditions of the patients.

The preferred treatment of meningiomas is complete resection with their dural base. However, complete resection is often not possible without causing cranial nerve deficits as well as a high mortality rate due to vascular complications like bleeding. In modern microsurgical series, the mortality rates range from 0% to 7% and significant cranial nerve deficits were seen in 8–26% [9, 31].

Radiologic and Clinical Response after Fractionated Radiotherapy and Radiosurgery

The results from studies using radiosurgery and fractionated radiotherapy in the treatment of cavernous sinus meningiomas are presented in Tables 1 and 2. Maguire et al. [26] reported of 28 patients with cavernous sinus meningiomas treated with fractionated conformal radiotherapy. Local tumor progression was seen in 3/28 patients after a median follow-up of 41 months. In the study of Debus et al. [8], partial response was documented in 14% after FSRT, defined as at least 50% reduction in tumor volume. After conventional treatment of meningiomas, a radiologic shrinkage was reported in 29%, but no criteria for determining an imaging response were provided [13]. Comparing the imaging response after FSRT and radiosurgery, the result rate after FSRT appears to be inferior to that reported after radiosurgery [4, 30, 37, 38]. After gamma-knife treatment of large series of cavernous sinus meningiomas, imaging responses were reported in 34% and 63% [24, 30]. However, in none of these reports the imaging criteria for response after radiosurgery were enumerated. Only in one analysis, a quantitative measurement of tumor response after linac-based radiosurgery was provided [40]. These authors reported a tumor reduction of at least 20% in 60% of patients. Similar to fractionated approaches, the imaging response of meningiomas after radiosurgery is related to the follow-up duration. Nicolato et al. [30] stated that complete disappearance or volume reduction after radiosurgery was noted in 79.5% of patients followed > 30 months compared with 47.5% of patients followed ≤ 30 months, without providing criteria of reduction. A volume dependence of imaging response is also discussed, but a complete resolution of cranial nerve deficit was not documented [38]. Patients treated with radiosurgery usually have smaller tumor volumes than those treated with fractionated radiotherapy. A greater imaging response rate of meningiomas after radiosurgery compared with FSRT is seen due to a selection of smaller volumes. An overall response rate of 37% was reported after radiosurgery in 24 patients with an ir-

Table 1. Radiosurgery of benign cavernous sinus meningiomas.
Tabelle 1. Einzeitbestrahlung gutartiger Sinus-cavernosus-Meningeome.

Study	Patients (n)	Target volume (cm^3)	Median dose (Gy)	Follow-up (years)	Local control (%)	Permanent deficits (%)
Chang & Adler 1997 [3]	24	6.8	17.7	3.8	100	0
Chang et al. 1998 [4]	55	7.3	–	4.0	98	7
Pendl et al. 1998 [32]	43	15.4	13.2	3.25	100	0
Roche et al. 2000 [35]	80	5.8	15	2.5	93	3
Shin et al. 2001 [39]	40	4.3	18	3.5	86.4	2.5
Lee et al. 2002 [24]	79	6.5	15	4.9	96	10
Nicolato et al. 2002 [30]	122	8.3	14.6	4.1	97.5	1
Spiegelmann et al. 2002 [40]	42	8.4	14	3.0	97.5	7.1
Iwai et al. 2003 [18]	42	14.7	11	4.1	90.5	0
Kuo et al. 2004 [22]	139	3.4	15	3.5	97.8	2.2

Table 2. Fractionated radiation therapy of benign cavernous sinus meningiomas.
Tabelle 2. Fraktionierte Strahlentherapie gutartiger Sinus-cavernosus-Meningeome.

Study	Patients (n)	Target volume (cm^3)	Median dose (Gy)	Follow-up (years)	Local control (%)	Permanent deficits (%)
Alheit et al. 1999 [2]	24	21.7	50—55	1.1	100.0	4.2
Maguire et al. 1999 [26]	28	–	53.1	3.4	92	7.1
Debus et al. 2001 [8]	189	52.5	56.8	2.9	98.3	1.6
Jalali et al. 2002 [19]	41	57.2	50—55	1.8	100	9.8
Selch et al. 2004 [38]	45	14.5	56	3.0	100	–
Pollock et al. 2005 [33]	49	10.2	15.9	4.8	100	4.1
Present study	57	35.2	57.6	6.5	100	–

radiated volume from 0.45 to 22.45 cm^3 [3]. In a subgroup of patients with a tumor volume > 12 cm^3, no response was seen. In the recently published study of Milker-Zabel et al. [28], 317 patients with intracranial meningiomas and a median target volume of 33.6 cm^3 underwent FSRT. These authors reported a recurrence rate of 15.5% in patients with a tumor volume > 60 cm^3 versus 4.3% in patients with a tumor volume ≤ 60 cm^3 ($p < 0.001$). In contrast to our present analysis, no correlation between irradiated tumor volume and reduction of tumor volume after radiotherapy was seen. One cause may be the smaller number of patients in the present study.

Normalization of oculomotor nerve dysfunction was reported in 8/54 patients by Roche et al. [35]. Complete resolution of various neuropathies was noted in 8/19 patients by Chang & Adler [3]. Clinical improvement has been reported as long as 36 months after radiosurgery. No predictors of clinical response could be identified [33]. In radiosurgery experience, improved cranial nerve function was more likely after treatment of patients with deficits present for > 1 year and those treated for primary meningiomas [30, 40]. In our analysis, 19.3% of the patients showed improvement in preexisting neurologic deficits, like reduction of diplopia, exophthalmos, trigeminal dysesthesia, and headache symptoms after a median follow-up of 6.5 years.

Survival and Toxicity

In the present study, overall survival was 95.5% at 5 and 10 years. Two patients died 2.8 and 4.1 years after radiotherapy due to cardiac failure. In the literature, the overall survival rate at 5 and 10 years after radiotherapy was 100% and 93.7%, respectively [12]. Progression-free survival was 100% after 10 years in our series. In the literature, progression-free survival rates of 96% at 5 years after radiosurgery [30], and of 92.8% at 10 years after fractionated radiotherapy [12, 26] are reported.

In the present study, only three patients complained about subjective visual deterioration after FRST without any objective findings. The influence of ionizing radiation on the development of posterior capsule opacification in vitro was recently published [11]. In the literature, radiation-induced morbidity rates of 3.6–5.5% are reported, consisting of edema, loss of vision, worsening hemiparesis, mental status changes, and trigeminal nerve problems [15]. The risk of intratumoral bleeding after radiosurgery is reported to be 1.3–2.7% [21, 23]. After neurosurgery of cavernous sinus meningiomas, side effects manifested primarily as delayed cranial neuropathies (third, fourth, and sixth cranial nerve). It is widely accepted that cranial motor nerves in the cavernous sinus seem to tolerate radiation well.

In the series of Roche et al. [35], only a single sixth cranial nerve deficit deteriorated after radiosurgery, whereas 43% of ophthalmopareses improved or recovered. Lee et al. [24] reported no evidence of deterioration of the oculomotor nerves after radiosurgery. Trigeminal nerve dysfunction was observed in 5/176 patients. In four of these patients, the deficits were permanent, and three of five experienced preexisting trigeminal dysfunction before radiosurgery. Morita et al. [29] reported on 9/88 radiation-induced permanent trigeminal neuropathies 2–7 months after gamma-knife radiosurgery. In our analysis, one patient showed an improvement in preexisting trigeminal dysesthesia after FSRT. In accordance with our data, no hypothalamic-pituitary dysfunction or intracranial malignancies after FSRT were seen in the analysis of Selch et al. [38].

Conclusion

Our data demonstrate that FSRT is an effective and safe treatment modality for local control of larger benign meningiomas of the cavernous sinus with low risk of significant late toxicity, especially cranial nerve deficits.

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