

European Association of NeuroOncology Magazine

Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-
oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

Radiotherapy and Meningioma

Asklund T, Henriksson R

*European Association of
NeuroOncology Magazine 2013; 3 (3)
122-127*



Homepage:

[www.kup.at/
journals/eano/index.html](http://www.kup.at/journals/eano/index.html)

Online Database Featuring
Author, Key Word and
Full-Text Search



THE EUROPEAN ASSOCIATION OF
NEUROONCOLOGY

Member of the



Radiotherapy and Meningioma

Thomas Asklund, Roger Henriksson

Abstract: Although meningioma is the most common primary brain tumour no strict consensus exists on the exact role of radiotherapy due to the lack of controlled phase-III studies. In completely resected grade-I tumours, radiotherapy is usually deferred until possible recurrence. For grade-II–III tumours, the issue is more controversial and radiotherapy is occasionally

applied already in the primary setting. The development in radiotherapy, including fractionated stereotactic radiotherapy as well as radiosurgery and irradiation with protons and carbon ions, has given new possibilities to deliver irradiation with reduced effects on the unaffected brain. However, well-performed randomised studies are still warranted, evaluating both efficacy and as-

pects of short- and long-term quality of life for patients before the real value of radiotherapy can be determined. **Eur Assoc NeuroOncol Mag 2013; 3 (3): 122–7.**

Key words: meningioma, radiotherapy, radiosurgery, fractionated radiotherapy

■ Introduction

Meningioma, derived from arachnoidal cap cells in the spinal cord and brain, is the most common primary tumour of the central nervous system, accounting for approximately $\frac{1}{3}$ of all primary brain tumours. It is more common in older age and in females. In most cases (> 90 %), meningiomas are benign tumours [1–3]. Surgical resection still remains the treatment of choice when feasible, especially when radical extirpation seems reasonable. The reported 5-, 10-, and 15-year recurrence-free survival rates are around 90, 80, and 70 %, respectively [1–4]. Patients often suffer from life-long neurological or neurocognitive dysfunction due to the tumour location or due to deficits following surgery in the attempt to achieve neurosurgically complete removal of the tumour [5]. Occasionally, anatomical considerations or other medical problems may interfere with the curative intention of surgery. When meningiomas are not amenable to surgery, in the case of postoperative residual tumour, and in case of relapses radiotherapy is an option [4–6].

■ Classification of Meningiomas

An established and prognostically significant histological classification of meningioma was originally described by the WHO in 1993, with a significant subsequent revision in 2000 and further codification in 2007 [7, 8]. The majority of meningiomas are histologically classified as benign, or WHO grade I, having a more indolent course and a lower rate of local recurrence. The remaining entities are atypical meningiomas (WHO grade II), accounting for about 5–7 % of all meningiomas, and anaplastic meningiomas (WHO grade III) for about 1–3 %. The reported recurrence rates of grade-I, -II, and -III meningiomas are 7–25 %, 29–52 %, and 50–94 %, respectively [1–3, 8]. The employment of the most recent WHO grading system for meningiomas has significantly improved the correlation between histological grade and both progression-free survival (PFS) and overall survival [6–9].

■ Radiotherapy

The treatment approach for meningiomas depends on their intracranial location and on whether the meningioma is benign or malignant [1–3, 7, 8]. The patient's general health and preferences regarding potential treatment options and associated side effects are also of crucial importance in the treatment decision. Complete surgical resection is still the standard treatment when clinically and medically meaningful. If a meningioma is benign and in a part of the brain where neurosurgeons can safely completely remove it, surgery is likely to be the only treatment needed, followed by regular radiological and clinical follow-up. Radiotherapy is currently used in atypical, malignant, and recurrent meningioma or when safe surgical removal of the meningioma is not possible [1, 4, 6, 9]. However, the value of adjuvant irradiation in addition to primary radical surgery is still controversial [5, 10]. High doses of radiotherapy in few fractions or a single fraction (radiosurgery) have awakened more and more interest in the management of all types of meningiomas, especially in meningiomas that cannot be completely resected, which is the case for many skull base meningiomas.

Although the role of postoperative radiotherapy for patients with grade-II meningiomas who have undergone resection still remains unclear, some reports propose adjuvant radiotherapy. This is especially true when it comes to grade-III meningioma [11–13]. The controversial issue is mostly related to whether treatment should be limited to subtotally removed meningiomas. This lack of consensus could be associated with the inconsistency in the diagnostic criteria for the definition of grade-II meningiomas before the latest WHO definition [7, 8, 14], and enforced by access to new diagnostic tools, such as MRI, as well as improved surgery.

In a retrospective evaluation of 114 atypical meningiomas [13], it was suggested that radiotherapy should not be used after initial surgery for WHO grade-II meningiomas during which gross total resection has been achieved. For subtotally resected WHO grade-II meningiomas, the authors forwarded that factors, such as access to interval MR imaging, patient age, comorbidity, and irradiation-induced tissue reactions which might affect any future surgical interventions, should be considered before a decision is made to proceed with radiotherapy. The authors concluded that any postoperative, radiologically demonstrated tumour remnant should be

Received on April 20, 2013; accepted after revision on May 29, 2013; Pre-Publishing Online on July 17, 2013

From the Department of Radiation Sciences & Oncology, University Hospital, Umeå, and The Regional Cancer Center Stockholm Gotland, Karolinska University Hospital, Stockholm, Sweden

Correspondence to: Roger Henriksson, MD, PhD, Regionalt Cancercentrum Stockholm – Gotland, Box 6909, 10239 Stockholm, Sweden; e-mail: roger.henriksson@sl.se

treated with radiosurgery and that radiotherapy should be reserved for residual tumours deemed too large for radiosurgery and in which a second operation is inappropriate. On the other hand, another study prospectively evaluating 45 patients who underwent gross total resection for atypical meningioma (median follow-up of 44.1 months) showed a strong trend towards improved local control with postoperative radiotherapy. There was no recurrence in 12 of 13 patients (92 %) who received postoperative radiotherapy or in 19 of 32 patients (59 %) who did not undergo postoperative radiotherapy [12].

Even if limited access to data from well-controlled studies is taken into account, it may be proposed that there is support for the beneficial value of postoperative radiotherapy in the management of atypical meningioma, including lower recurrence rates of gross totally resected atypical meningiomas. However, the real value of radiotherapy in atypical meningioma must be compared in a randomised prospective setting, also to enable us to more precisely define the subset of patients who may benefit from the addition of adjuvant irradiation.

Combination of Radiotherapy

Combination of radiotherapy with medical therapies has so far not shown any beneficial effects at all and should therefore still be regarded as investigational.

Conventional Radiotherapy

Even if well-controlled randomised clinical trials are lacking, beneficial effects of postoperative conventional radiotherapy have occasionally been reported following subtotal surgical resection of benign meningiomas and at the time of recurrence [1, 4, 10]. Conventional external beam radiation up to a total dose of about 55 Gy seems to be an efficient and safe initial treatment of benign meningiomas with a reported 10-year control rate and PFS of 70–80 % in most published series. It equals favourably with tumour control rates reported after surgery alone, proposing that conventional fractionated irradiation may produce at least a temporary tumour growth arrest [1, 4, 10, 14].

The value of adjuvant irradiation in addition to radical primary surgery in non-benign meningioma is still controversial [10, 14]. No well-controlled randomised studies have so far been performed. In a recent retrospective, population-based evaluation of 657 patients with grade-II and -III meningiomas, of whom 244 received adjuvant radiotherapy, no survival benefit could be detected following external beam irradiation [10]. In addition, there was no survival advantage in an analysis of patients diagnosed after the WHO 2000 reclassification of meningiomas.

For grade-I meningiomas, the treatment volume proposed is defined by the contrast-enhancing volume including a safety margin of a few millimetres, while the target volume of grade-II–III meningiomas, in addition to the residual tumour, should encompass the resection cavity as well as a safety margin of 1–2 cm. While a total dose of 54–57 Gy can be recommended for benign low-grade meningiomas delivered in 25–33 fractions, lower doses of 50–52 Gy are reserved for large meningiomas involving the optic pathways. High-grade tu-

mours should receive 60–66 Gy with conventional fractionation to achieve long-term local control [15, 16].

Reirradiation for recurrent meningioma yields only modest tumour control rates, and patients with relapsed grade-II or -III tumours have a poor outcome [17].

Neurological deficits are usually present in up to 70 % of patients with skull base meningiomas as a consequence of tumour growth or previous surgery, and are mainly represented by deficits of cranial nerves II–VI [1, 5, 14, 18]. Improvement of neurological function is therefore a factor of great importance to consider when evaluating the outcome. Indeed, neurological improvement or stabilisation of up to 70 % has been reported in some studies after conventional radiotherapy [1, 4, 5]. Nonetheless, most of the published series do not show any clear figures for the functional outcome after conventional radiotherapy.

Neurocognitive dysfunction, including short-term memory deficit, is a well-known consequence of large-volume radiotherapy for brain tumours [14, 16, 18] and has been infrequently reported in irradiated patients with meningiomas. There is a significant risk of developing neurological deficits, such as optic neuropathy, brain necrosis, cognitive and memory deficits, and pituitary deficits with neuroendocrine disorders. However, the toxicity of conventionally delivered radiotherapy is reported to be relatively low, ranging from no risk up to a relative risk of 24 % [4]. Cerebral necrosis with locally associated clinical neurological deterioration is a severe and incurable complication, however, the risk is minimal when doses < 60 Gy and 3-dimensional dose planning systems are used. Patients with large meningiomas with a parasellar location are at risk of developing late hypopituitarism and must therefore be assessed lifelong after treatment.

Advances in Radiotherapy of Meningioma

Innovations during the last decades in radiation oncology include fractionated stereotactic radiotherapy (FSRT), intensity-modulated radiotherapy (IMRT), and high-dose single-dose stereotactic radiosurgery (SRS), permitting more accurate irradiation. Apparently, these techniques seem to give improved high local control rates and low morbidity for meningiomas and other benign skull base tumours, such as pituitary adenomas and craniopharyngiomas [6, 19–22].

Fractionated Conformal Stereotactic Radiotherapy (FCSRT)

Present knowledge in radiobiology and -therapy favours the use of fractionated irradiation due to the possibility of achieving improved local tumour control of meningiomas while minimizing damage to the brain by decreasing the volume of normal tissue irradiated at high doses. FCSRT seems to be a safe treatment modality with comparable tumour control obtained with other fractionated radiation techniques and radiosurgery (SRS) in the treatment of benign skull base meningiomas [4–6, 21]. A recent single-institution, prospective evaluation of quality of life in 44 patients during and after SRT (1.8 Gy up to 54 Gy) of meningiomas demonstrated a decrease in mean values of “physical component scale” (PCS)

and “mental component scale” (MCS) compared to a normal German population [23]. The QoL assessment after SRT revealed 3 phases: “depressive phase”, “recovery phase”, and “normalization phase”. Gender, age, and tumour-related symptoms did not affect QoL according to MCS and PCS. Local control rate was 98 % at 12 months. Treatment was well-tolerated and no severe side effects were observed during the study period.

The observed results obtained so far for conformal FSRT show a low frequency of side effects compared to conventional conformal radiotherapy. When evaluating current publications, it seems that FCSRT should be selected for patients suffering from large skull base meningiomas or those close to radiosensitive structures, such as the optic nerve. The main objective of FCSRT is to reduce long-term toxicity of radiotherapy and to increase the precision of treatment while maintaining or possibly increasing its efficacy.

Intensity-Modulated Radiotherapy

Intensity-modulated radiotherapy (IMRT) exemplifies a sophisticated form of 3-dimensional, conformal dose planning with a great potential in the management of large, complex, irregularly formed tumours adjacent to radiosensitively critical structures [20], such as meningiomas close to the optic chiasm and brain stem. In creating IMRT dose plans, computer optimization techniques are used to modulate intensities across the target volume and sensitive normal structures, starting from a pre-specified dose distribution. In large meningiomas close to the optic chiasm, better target coverage is achieved by IMRT than with conventional techniques, making it possible to spare more radiosensitive brain structures from higher radiation doses [24, 25]. The use of IMRT in the treatment of meningiomas seems to be promising, however, so far, limited data have been presented both regarding efficacy and long-term side effects. Much more efforts are needed to clarify if the potential reduction of toxicity using IMRT is clinically relevant in comparison with other techniques.

Volumetric-Modulated Arc Therapy

Volumetric-modulated arc therapy (VMAT) makes it possible to improve target volume coverage in comparison to conventional radiotherapy [26]. Another advantage offered by VMAT is the reduced treatment time compared to IMRT with conventional static fields. Fogliata et al [25] demonstrated that for benign tumours VMAT performed slightly better concerning PTV coverage than IMRT. However, VMAT was slightly inferior in sparing OAR and reducing integral doses to the healthy brain, especially at doses < 10 Gy. This could possibly have an impact in patients with an expected long survival, considering the risk for radiation-induced neurocognitive deficits and secondary malignancies.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) delivered as one single dose by Gamma Knife® or conventional linear accelerators has been extensively used in the treatment of various tumours. Single radiation doses between 12 and 18 Gy have demonstrated a high local control rate of meningioma [4, 22]. During the last years, radiation doses have been decreased in order to reduce long-term side effects while maintaining efficacy. Side

effects following radiosurgery are reported in 3–40 % of cases in the published studies, including transient or permanent complications (5.0 %). Even though radionecrosis of the brain and delayed cranial nerve deficits after radiosurgery are of concern, the rate of significant complications at doses of 12–15 Gy, as currently used in most centres, is < 6 %. The disease-specific survival rate has been reported around 97 % at 5 years and 94 % at 10 years. The 5- and 10-year local tumour control rate was 96 % and 89 %, respectively. The 1- and 5-year radiation-related complication rate was 6 % and 11 %, respectively [27].

Recently, a continuous real-time image-guided robotic radiosurgery system (Cyberknife®) for beam targeting and patient motion tracking has been employed for frameless radiosurgery in patients with skull base meningiomas [28]. This technique is believed to be safer than radiosurgery for large parasellar meningiomas, however, a large series with appropriate follow-up is clearly needed to confirm the proposed beneficial efficacy and safety profile, ie, the reduction of optic neuropathy.

Although well-controlled randomised trials are still lacking, it is clear that radiosurgery in doses of 12–15 Gy may represent a convenient and safe approach for patients with meningiomas with a tumour control rate at 10 years comparable to fractionated radiotherapy. Both radiosurgery and FCSRT are effective treatment options for benign skull base meningiomas, and the choice of stereotactic technique is mainly based on the features of tumours and the informed choice expressed by the patient. In our view, which is shared by most centres, radiosurgery should be used for tumours < 3 cm in diameter and a distance of at least 3–5 mm from the optic chiasm, whereas FCSRT is recommended for those tumours not amenable to radiosurgery. Patients with small-volume, non-resectable cranial-base or tentorial meningiomas had the best outcomes after single-fraction radiosurgery [27].

Proton Therapy

Proton therapy can accomplish improved target-dose conformity compared to other modalities, eg, 3D-CRT and IMRT [29]. The risk of delivering off-target doses, often in the low-dose range, to normal brain is significantly lower with protons compared to photons. The benefit is clearly evident when treating large volumes and in younger patients, thus probably avoiding long-term sequelae. Proton therapy can be delivered as a single dose or fractionated, using the same immobilization systems as for photon radiotherapy [29, 30].

The somatostatin receptor is often expressed by meningioma cells. The somatostatin-receptor ligand [68Ga]-DOTA-D-Phe1-Tyr3-Octreotide (DOTATOC) is therefore in use as a PET tracer for meningiomas and probably contributes to a more accurate target definition in the dose planning of meningiomas [31]. A recent prospective evaluation of early treatment efficacy and toxicity outcome in patients with meningioma-based target volume definition with MRI and DOTATOC-PET revealed very low rates of side effects, including headaches, nausea, and dizziness following proton irradiation (52.2–57.6 Gy). No severe treatment-related toxicity was observed. Local control for benign meningiomas

was 100 %. Actual local control after re-irradiation of high-risk meningiomas was 67 % at 12 months [32].

Proton radiotherapy alone or in combination with photons seems to be an effective alternative to other stereotactic techniques achieving a high local control rate and toxicity in the range of photon therapy. Based on the dosimetric gains of protons, including better conformality and reduction of the integral radiation dose to normal tissue, proton irradiation could be considered in patients with large and/or irregularly shaped meningiomas, limiting the long-term adverse effects of radiotherapy, especially in younger patients with an expected longer survival. However, well-controlled clinical trials assessing toxicity of different radiation techniques are needed to confirm the expected reduction in late adverse effects following proton irradiation.

Recently, carbon ion therapy has been evaluated in conjunction with photon irradiation or as a single-modality therapy for atypical meningioma or meningioma recurrence, respectively, with mild toxicity and with promising results. Prospective larger studies are warranted to verify these results [33].

■ Predictive Factors in Radiotherapy of Meningioma

Risk factors for meningioma recurrence are histological grade, large tumour size, incomplete surgical resection, age, papillary and haemangiopericytic morphology, brain infiltration, high proliferative rate, absence of progesterone receptors, deletions, and loss of heterozygosity [1, 3, 34–36].

Size and tumour site have been suggested as predictors of tumour control in the irradiation of meningioma. A 5-year control rate of around 93 % for 54 patients with skull base meningiomas < 5 centimetres in greatest dimension and 40 % for tumours > 5 centimetres has been reported [22, 37, 38]. Sphenoid ridge tumours seem to have a worse local control rate than other skull base meningiomas [39], and this finding was independent of the extent of surgery. Age and gender do not seem to provide any predictive value for benign meningiomas, however, younger age may be associated with better outcome in some series [1, 38, 39]. The reported local control and survival rates are similar for patients treated with radiotherapy as part of their primary treatment or at the time of recurrence in most series [1, 22, 39–41]. Obviously, only a prospective randomized trial can adequately determine whether long-term control is influenced by timing of radiotherapy (early versus delayed treatment after evidence of progression).

■ Radiation-Induced Meningioma

So far, we have discussed radiotherapy as a treatment option for meningioma. In this context, it is important not to neglect that radiation-induced meningiomas (RIM) are probably the most common radiation-induced tumours of the central nervous system [3, 42, 43]. This is of concern especially in the treatment of children with whole-brain radiotherapy. Approximately 20 % of survivors after childhood brain radiotherapy have been shown to develop RIM within 25 years. In

a large series of 426 patients with pituitary adenomas who received conventional radiotherapy at the Royal Marsden Hospital between 1962 and 1994, the risk of developing second brain tumours was 2.0 % at 10 years and 2.4 % at 20 years from the date of RT [44]. The relative risk for second brain tumours compared to the incidence in the normal population was 10.5 (95 %-CI: 4.3–16.7), being 7.0 for neuroepithelial and 24.3 for meningeal tumours.

■ Conclusive Remarks

One of the most striking findings when reviewing the literature evaluating the role of radiotherapy in meningioma is the obvious lack of well-performed randomised studies. It must also be emphasized that there is a lot of evidence pointing out that radiotherapy has a valuable role in the management of at least a subset of patients suffering from both benign and atypical meningioma. Local control following incomplete excision of a benign meningioma can be improved with conventional, fractionated, external beam radiotherapy with a reported 10-year progression-free survival in the range of 75–90 %. However, in the context of long-term survival, especially in WHO grade-I meningioma and in young patients, the recently described high incidence of neurological deficits, excess mortality in stroke, and the risk of secondary tumours must be further considered and evaluated [5, 42, 43]. In 89 long-term survivors (> 5 years), 67 % showed at least one neurological symptom and out of these 27 % were unable to perform normal daily activities [5]. In this study, tumour recurrence was higher than previously reported.

A major challenge is to define the population that will most likely benefit from radiotherapy while excluding the individuals who will experience only side effects. At present, no valuable predictive marker for therapeutic efficacy has been established. In this respect, it is of interest to highlight increased access to improved MRT for surveillance imaging as well as the promising value of molecular and metabolic imaging with PET in characterising features and borders of meningioma [45]. The development of radiosurgery and fractionated conformal stereotactic radiotherapy offers a more precise treatment compared with conventional radiotherapy techniques, and has the potential of reducing the risk of late-appearing side effects and low morbidity, affecting, eg, the optic nerve and causing impaired vision with decreased quality of life. In this context, it is also important to emphasize a comparative study of stereotactic radiosurgery, hypofractionated, and fractionated stereotactic radiotherapy in the treatment of skull base meningioma [6]. No significant difference in efficacy has been seen with a median follow-up of 32 months. Radiographic control was achieved in 91 %, 94 %, and 95 %, whereas clinical response was observed in 89 %, 100 %, and 91 % in the SRS, hFSRT, and FSRT groups, respectively. New promising modalities, such as proton therapy, might extend the possibility to treat even more complex tumours with irradiation in the vicinity of sensitive structures.

Exemplified by the patient case in the appendix, the beneficial value of radiotherapy must also be seen in malignant meningioma as a potentially long-term condition, in which there is now the opportunity of repeated interventions. In the very

end, the most important factor to consider is the increasing patient expectations for maintaining quality of life even with multiple interventions, in both the short term (minimizing the number of hospital admissions and side effects) and the long term (cognitive concerns). The literature implies that radiotherapy continues to have value in the management of meningioma.

Nevertheless, due to the lack of well-controlled studies more robust data are needed in order to optimally evaluate the long-term efficacy and toxicity of all types of radiotherapy. Because of the slow-growing potential of meningiomas, the potential superiority of individual techniques needs to be confirmed in prospective and methodologically rigorous studies with 10–20 years follow-up.

Conflict of Interest

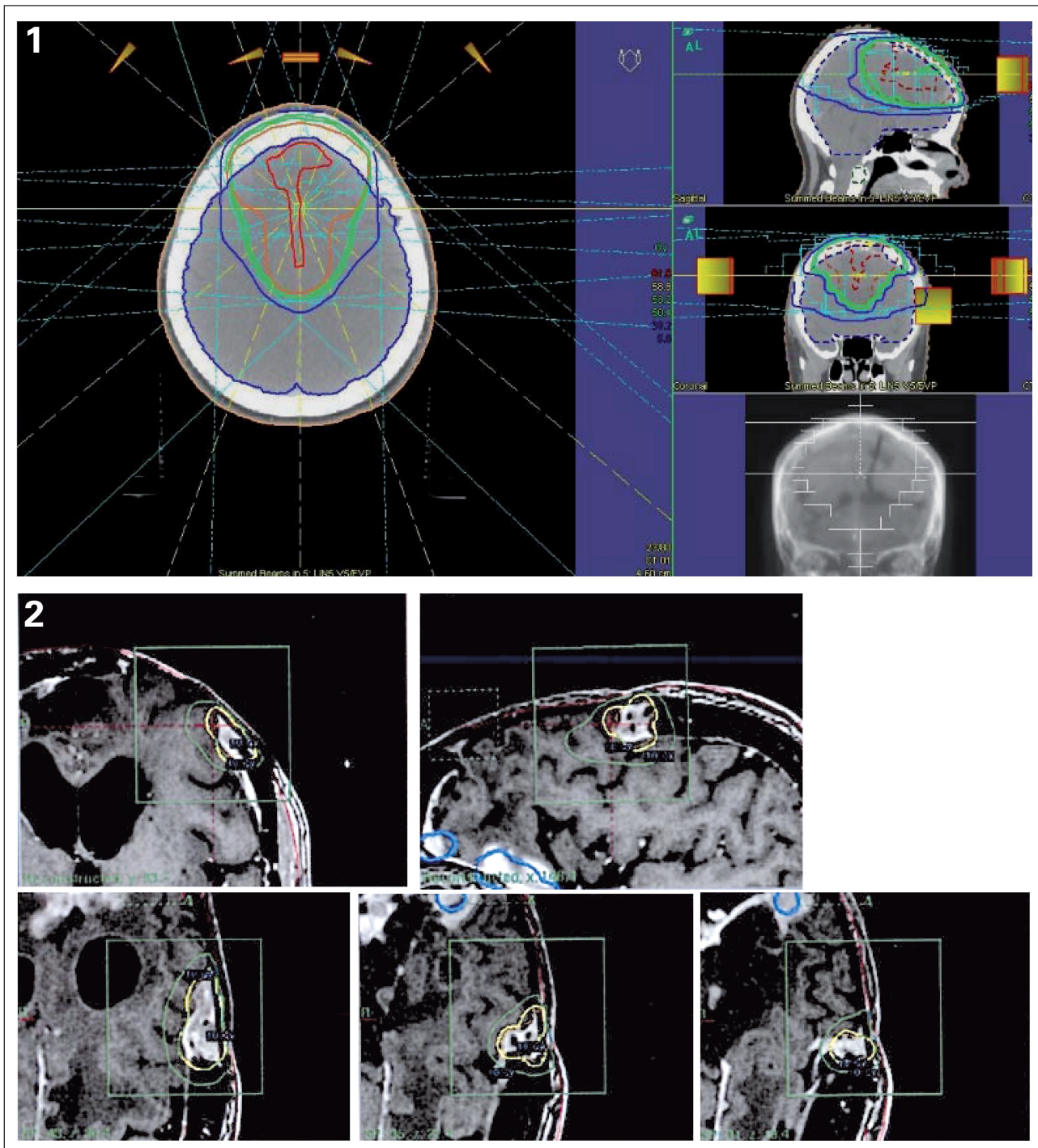
The authors have no conflict of interest regarding the subject discussed in this article. RH is a member of the international steering committee for the AVAglio study (Roche).

References

- Marosi C, Hassler M, Rössler K, et al. Meningioma. *Crit Rev Oncol Hematol* 2008; 67: 153–71.
- Kallio M, Sankila R, Hakulinen T, et al. Factors affecting operative and excess long-term mortality in 935 patients with intracranial meningioma. *Neurosurgery* 1992; 31: 2–12.
- Bondy M, Ligon BL. Epidemiology and etiology of intracranial meningiomas: A review. *J Neurooncol* 1996; 29: 197–205.
- Minniti G, Amichetti M, Enrici RM. Radiotherapy and radiosurgery for benign skull base meningiomas. *Radiat Oncol* 2009; 4: 42.
- van Alkemade H, de Leau M, Dieleman EM, et al. Impaired survival and long-term neurological problems in benign meningioma. *Neuro Oncol* 2012; 14: 658–66.
- Han J, Girvignan MR, Chen JC, et al. A comparative study of stereotactic radiosurgery, hypofractionated, and fractionated stereotactic radiotherapy in the treatment of skull base meningioma. *Am J Clin Oncol* 2012 [Epub ahead of print].
- Kleihues P, Cavenee VK (eds). World Health Organization classification of tumours: pathology and genetics: tumours of the nervous system. 2nd ed. IARC Press, Lyon, 2000.
- Perry A, Louis DN, Scheithauer BW, et al. Meningiomas. In: Louis DN, Ohgaki H, Wiestler OD, et al (eds). WHO Classification of Tumours of the Central Nervous System. IARC Press, Lyon, 2007; 164–72.
- Ko KW, Nam DH, Kong DS, et al. Relationship between malignant subtypes of meningioma and clinical outcome. *J Clin Neurosci* 2007; 14: 747–53.
- Stessin AM, Schwartz A, Judanin G, et al. Does adjuvant external-beam radiotherapy improve outcomes for nonbenign meningiomas? A Surveillance, Epidemiology, and End Results (SEER)-based analysis. *J Neurosurg* 2012; 117: 669–75.
- Maier H, Ofner D, Hittmair A, et al. Classic, atypical, and anaplastic meningioma: three histopathological subtypes of clinical relevance. *J Neurosurg* 1992; 77: 616–23.
- Komotar RJ, Iorgulescu JB, Raper DM, et al. The role of radiotherapy following gross-total resection of atypical meningiomas. *J Neurosurg* 2012; 117: 679–86.
- Mair R, Morris K, Scott I, et al. Radiotherapy for atypical meningiomas. *J Neurosurg* 2011; 115: 811–9.
- Imon M, Boström J, Koch P, et al. Inter-institutional variance of postoperative radiotherapy and follow up for meningiomas in Germany: impact of changes of the WHO classification. *J Neurol Neurosurg Psychiatry* 2006; 77: 767–73.
- Debus J, Wuendrich M, Pirzkall A, et al. High efficacy of fractionated stereotactic radiotherapy of large base-of-skull meningiomas: Long-term results. *J Clin Oncol* 2001; 19: 3547–53.
- Engenhart-Cabillie R, Farhoud A, Sure U, et al. Clinicopathologic features of aggressive meningioma emphasizing the role of radiotherapy in treatment. *Strahlenther Onkol* 2006; 182: 641–6.
- Wojcieszynski AP, Ohri N, Andrews DW, et al. Reirradiation of recurrent meningioma. *Clin Neurosci* 2012; 19: 1261–4.
- Crossen JR, Garwood D, Glatstein E, et al. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. *J Clin Oncol* 1994; 12: 627–42.
- Minniti G, Traish D, Ashley S, et al. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. *Clin Endocrinol* 2006; 64: 542–8.
- Milker-Zabel S, Zabel-du Bois A, Huber P, et al. 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: 858–63.
- Minniti G, Saran F, Traish D, et al. Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas. *Radiother Oncol* 2007; 82: 90–5.
- Kondziolka D, Mathieu D, Lunsford LD, et al. Radiosurgery as definitive management of intracranial meningiomas. *Neurosurgery* 2008; 62: 53–8.
- Henzel M, Fokas E, Sitter H, et al. Quality of life after stereotactic radiotherapy for meningioma: a prospective non-randomized study. *J Neurooncol* 2013; 113: 135–41.
- Maclean J, Fersht N, Bremner F. Meningioma causing visual impairment: outcomes and toxicity after intensity modulated radiation therapy. *Int J Radiation Oncol Biol Phys* 2013; 85: 179–86.
- Fogliata A, Clivio A, Nicolini G, et al. Intensity modulation with photons for benign intracranial tumours: a planning comparison of volumetric single arc, helical arc and fixed gantry techniques. *Radiother Oncol* 2008; 89: 254–62.
- Teoh M, Clark CH, Wood K, et al. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. *Br J Radiol* 2011; 84: 967–96.
- Pollock BE, Stafford SL, Link MJ, et al. Single-fraction radiosurgery of benign intracranial meningiomas. *Neurosurgery* 2012; 71: 604–12.
- Colombo F, Casentini L, Cavedon C, et al. Cyberknife radiosurgery for benign meningiomas: short-term results in 199 patients. *Neurosurgery* 2009; 64: A7–A13.
- Weber DC, Lomax AJ, Rutz HP, et al.; Swiss Proton Users Group. Spot-scanning proton radiation therapy for recurrent, residual or untreated intracranial meningiomas. *Radiother Oncol* 2004; 71: 251–8.
- Noël G, Bollet MA, Calugaru V, et al. Functional outcome of patients with benign meningioma treated by 3D conformal irradiation with a combination of photons and protons. *Int J Radiat Oncol Biol Phys* 2005; 62: 1412–22.
- Gehler B, Paulsen F, Oksüz MO, et al. [68Ga]-DOTATOC-PET/CT for meningioma IMRT treatment planning. *Radiat Oncol* 2009; 4: 56.
- Combs SE, Welzel T, Habermehl D, et al. Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and (68)Ga-DOTATOC-PET. *Acta Oncol* 2013; 52: 514–20.
- Rieken S, Habermehl D, Haberer E. Proton and carbon ion radiotherapy for primary brain tumors delivered with active raster scanning at the Heidelberg Ion Therapy Center (HIT): early treatment results and study concepts. *Radiat Oncol* 2012; 7: 41.
- Perry A, Stafford SL, Scheithauer BW, et al. Meningioma grading: an analysis of histologic parameters. *Am J Surg Pathol* 1997; 21: 1455–65.
- Jaaskelainen J, Haltia M, Servo A. Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. *Surg Neurol* 1986; 25: 233–42.
- Torp SH, Lindboe CF, Grønberg BH, et al. Prognostic significance of Ki-67/MIB-1 proliferation index in meningiomas. *Clin Neuro-pathol* 2005; 24: 170–4.
- DiBiase SJ, Kwok Y, Yovino S, et al. Factors predicting local tumor control after gamma knife stereotactic radiosurgery for benign intracranial meningiomas. *Int J Radiat Oncol Biol Phys* 2004; 60: 1515–9.
- Maire JP, Caudry M, Guérin J, et al. Fractionated radiation therapy in the treatment of intracranial meningiomas: local control, functional efficacy, and tolerance in 91 patients. *Int J Radiat Oncol Biol Phys* 1995; 33: 315–21.
- Nutting C, Brada M, Brazil L, et al. Radiotherapy in the treatment of benign meningioma of the skull base. *J Neurosurg* 1999; 90: 823–7.
- Vendrey V, Maire JP, Darrouzet V, et al. Fractionated radiotherapy of intracranial meningiomas: 15 years' experience at the Bordeaux University Hospital Center. *Cancer Radiother* 1999; 3: 311–7.
- Mendenhall WM, Morris CG, Amdur RJ, et al. Radiotherapy alone or after subtotal resection for benign skull base meningiomas. *Cancer* 2003; 98: 1473–82.
- Harrison MJ, Wolfe DE, Lau TS, et al. Radiation-induced meningiomas: experience at the Mount Sinai Hospital and review of the literature. *J Neurosurg* 1991; 75: 564–74.
- Banerjee J, Paakko E, Harila M, et al. Radiation-induced meningiomas: a shadow in the success story of childhood leukemia. *Neuro Oncol* 2009; 11: 543–9.
- Minniti G, Traish D, Ashley S, et al. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. *J Clin Endocrinol Metab* 2005; 90: 800–4.
- Cornelius JF, Langen KJ, Stoffels G, et al. Positron emission tomography imaging of meningioma in clinical practice: review of literature and future directions. *Neurosurgery* 2012; 70: 1033–41.

Appendix: Case Report

The following case report from our department can serve as an example of how a multidisciplinary and multitargeted approach may be of benefit for patients with malignant meningiomas: a 56-year-old woman was operated for a grade-III meningothelial meningioma in 2006 and reoperated in July 2007 after recurrence. This was followed by radiotherapy to a total of 56 Gy with 2-Gy daily fractions (Figure 1) concomitant with temozolomide 100 mg daily. The disease recurred 24 months after the second operation, and in September 2009 the third operation was made. However, in January 2010, the disease progressed exhibiting multiple tumour manifestations. It therefore seemed appropriate to reconsider systemic treatment. Bevacizumab was initiated in March 2010. MRT evaluation in May showed stable disease according to the McDonald criteria. Because of strong immunohistochemical overexpression of EGFR erlotinib was added in June 2010.



Figures 1 and 2 depict the dose plan of 3-dimensional conformal radiotherapy and a dose plan of stereotactic radiosurgery (Gammaknife®), respectively, delivered to the patient described in the case report. In **Figure 2**, the upper row represents, from left to right, a coronal and a sagittal section, while the lower row shows selected transaxial sections of the MR-based dose plan.

However, in September 2010 an MRT follow-up showed a new 9-mm contrast-enhanced nodule, while remaining tumour manifestations were considered stable. Thus tumour progression was evident after 6 months of bevacizumab with subsequent addition of erlotinib. Stereotactic radiosurgery (Gammaknife®) was performed in November 2010, repeated in February 2012, and finally in September 2012, at a time

when a total of 15 meningiomas have been treated with radiosurgery (Figure 2). In October, temozolomide was reintroduced in a more dose-intensive schedule of 75 mg/m²/day in 21 day cycles every 28th day. Interestingly, MRT in March 2013 showed stable disease compared to MRT 6 months before. At present (March 2013), 6 years after diagnosis the patient has a Karnofsky Performance Status of 70.