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Editorial

Dear EANO members, dear colleagues,

following my last editorial several issues have come up and we had an extraordinary board meeting in Vienna on September 9 to decide on some important issues.

Firstly, a final draft of the updated society bylaws (after almost 20 years) has been finalized with the approval of a lawyer and a tax consultant, thus, in November, all EANO members will be asked for approval by an extraordinary assembly on the website.

The editorial board of Neuro-Oncology will be restructured from January 2014: Michael Weller is leaving the position of EANO executive editor and the board has decided to nominate Riccardo Soffietti as the new executive editor. Soon after, the nomination of associate editors and editorial board members will follow. Moreover, SNO is launching Neuro-Oncology Practice, a new printed journal with a clinical focus and EANO will be part of this initiative. In this regard, we appointed Wolfgang Grisold as co-editor and Martin Taphoorn (expert on quality-of-life issues) as associate editor to assist Susan Chang (San Francisco), who will act as editor-in-chief.

We will maintain our EANO Magazine, which is quite successful, and we are discussing with SNO and ASNO the transformation of EANO Magazine into the World Federation of Neuro-Oncology Magazine.

The relationships with other scientific societies are increasing: we have now educational events in conjunction with the World Federation of Neurology and the Canadian Group for Neuro-Oncology, and others are being discussed.

We will support, also financially, the participation of a young EANO member in a Cochrane Neuro-Oncology review.

By the end of the year guidelines on malignant gliomas and primary CNS lymphomas will be ready for publication both in a major scientific journal and on our website.

Last but not least, the preparation of the programme for the EANO meeting in Torino from October 9–12, 2014, is ongoing: it will be finalized by the end of November and available on the website. In the meantime, the online submission of abstracts for scientific presentations (proffered papers and posters) has been opened.

In conclusion, we are a growing society with an increasing number of initiatives and new members also from non-European countries: ultimately, this reflects the high level reached by European neuro-oncologists in terms of making science and caring of patients.

Best regards

Riccardo Soffietti
EANO President 2012–2014
Editorial to Special Issue

Dear reader,

EANO Magazine is turning into the fourth year of its existence and serves the purpose of an educational tool, designed to distribute interdisciplinary and multiprofessional knowledge among the neuro-oncologic community based on the open access format. The main content is review articles devoted to all aspects of brain tumours and also brain metastases. We also appreciate the informative content of individual cases and we are glad to also have columns on nurses and health-related groups as well as patient issues, among others.

The download numbers of articles are as high as 1000–2000 downloads and even 6600 for a review article on chemotherapy-induced toxic neuropathies.

Time has come to provide a platform for special topics and we are trying to invite and engage knowledgeable colleagues worldwide to supply us with contributions. We have currently planned 2 special topics within our magazine, which will include articles that go beyond the usual knowledge attached to specific diseases addressed. The present issue 3/2013 focuses on aspects of meningiomas (Figure 1), which account for about 1/3 of intracranial tumours, and can present with various different aspects, such as incidental finding, recurrence, malignancy, and topographical distribution, as well as aspects of treatment, which can be surgical, radiotherapy and last but not least we have many unresolved issues in drug therapy.

The next special issue will cover aspects of nerve infiltration by malignant tumours. This can occur within the skull, not infrequently when the nerve passes through the skull and in the tissues and cavities around the skull, most notably in the next region (Figures 2, 3). Infiltration is not a homogeneous process and can result from compression, nerve metastasis, or infiltration. Nerve infiltration can also lead to a retrograde spread of the tumour tissue, which has been described not only in tumours of the ENT region but also of the face. The issue of affection of autonomous nerves has become a prognostic factor in some intestinal tumours, spread of tumour tissue into the brachial sacral plexus is a matter of daily clinical practice, and accumulation of knowledge may serve the purpose of improving diagnosis, treatment, and prognosis.

We hope that such special issues will teach us additional aspects of diseases, treatments, and conditions in neuro-oncology, and we will gladly accept suggestions for special topics for our upcoming issues, which will appear quarterly from 2014. Please do not hesitate to make suggestions on special topics, give us a short outline what makes the topic so special, and also suggest experts in the field.

Riccardo Soffietti, MD
EANO President (2012–2014)

Wolfgang Grisold, MD
Managing Editor
Epidemiology of Meningioma
Adelheid Wöhrer

Abstract: Meningiomas are among the most common intracranial tumours, their incidence rising with increasing age. The majority of meningiomas show a benign clinical behaviour, which might in part explain the former lack of systematic registration with only imprecise estimates of incidence and survival. With the introduction of specialized brain tumour registries, detailed epidemiological information has become available. Herein, besides demographic disease characteristics, the latest findings on aetiological risk factors are reviewed. Eur Assoc NeuroOncol Mag 2013; 3 (3): 95–6.

Key words: meningioma, epidemiology, risk factors, aetiology

Background and Incidence
Meningiomas account for approximately 1/3 of primary intracranial tumours in adults [1], with an age-adjusted incidence rate of approximately 7 per 100,000 person-years [1, 2]. While in Scandinavia the incidence seemingly increased between 1968 and 1997 from 2.6 to 4.5/100,000 in women and from 1.4 to 1.9/100,000 in men [3], no such increase was observed in Italy or the United Kingdom, where the disease rate has remained stable for decades [4, 5]. Small meningiomas are often asymptomatic and, thus, constitute frequent incidental autopsy findings (in 1.4 % of a Swedish autopsy-based cohort) [6].

Histological Subtypes and Prognostic Considerations
Meningiomas exhibit a wide range of morphologic appearances. According to the WHO classification, up to 15 histopathological variants are distinguished [7]. Of the various histological subtypes meningothelial, fibrous, and transitional meningiomas (all WHO grade I) constitute the most common variants [7]. Whereas the majority of meningioma subtypes (> 80 %) show a benign clinical behaviour (WHO grade I), those variants which fall into the WHO grade-II and -III categories (atypical and anaplastic meningiomas) are associated with a higher likelihood of tumour recurrence and a more aggressive disease course. Five-year overall survival rates of 55 % have been reported for malignant meningioma [8]. In contrast, a recent study in the United States found 3-year overall survival rates of > 85 % for non-malignant intracranial meningiomas [9].

Age and Gender Distribution
The majority of meningiomas occur in middle-aged and elderly individuals, the incidence rising with increasing age [1]. In contrast, meningiomas are extremely rare in children [10]. However, childhood examples tend to include more aggressive meningioma subtypes with 5-year overall survival rates of 83.9 % [10]. Whereas benign meningiomas show a strong predilection for women (ie, twice as common in females as compared with males) [2], malignant meningiomas tend to occur more frequently in males [2, 11].

Tumour Site
Meningiomas usually occur in an intracranial, intraspinal, or orbital location, the cerebral convexity being the most common site [11]. Still, rare meningiomas have been observed in almost all organs [7]. Moreover, atypical and anaplastic variants have the potential to produce systemic metastases most often to the lung [12–16]. In addition, tumour-to-tumour metastasis (of a systemic cancer to meningioma) has been reported [17, 18]. In fact, meningiomas are the most common “recipients” among intracranial tumours. However, the exact mechanisms of this rare phenomenon are not yet fully understood [17, 18].

Aetiology
Meningiomas are well-known to be induced by low-, moderate-, and high-dose radiation, most commonly administered for childhood malignancies, with median times to tumour occurrence of 35, 26, and 19–24 years, respectively [19]. Younger patients often exhibit a longer latency period [20]. In fact, meningiomas are the most common form of radiation-induced neoplasms reported [21]. Compared with their sporadic counterparts, radiation-induced meningiomas are often aggressive or malignant, generally occur in younger age groups, are likely to be multiple, and associated with higher recurrence rates [22]. In contrast to ionizing radiation, the association of meningioma risk with non-ionizing low-frequency electromagnetic fields from mobile and cordless phone use is less consistent. A recent meta-analysis of the Hardell group and IARC Interphone studies did not yield an increased hazard ratio for meningioma [23].

The predominance of women among meningioma patients suggests an aetiopathological role for sex hormones. However, so far, little evidence has been found for reproductive and menstrual factors such as age at menarche, age at menopause, or parity [24]. Still, at first operation, 88 % of meningiomas exhibit progesterone, 40 % oestrogen, and 39 % androgen receptors [25]. However, the higher incidence of meningiomas in women cannot be explained by differences of sex hormone expression [25].
Genetic Susceptibility

Meningiomas usually occur in a sporadic setting. However, if they occur at multiple sites, they are mostly (> 90%) associated with familial tumour syndromes [7]. They are common in neurofibromatosis type 2 (NF2) families with 50–75% of affected individuals developing a meningioma during their lifetime [26]. Outside the setting of NF2, a number of families have been reported to be at increased risk. Meanwhile, several additional genes have been implicated in those multiple meningiomas, such as mutation of the SMARCB1 gene [27, 28] or loss-of-function mutations in SUFU [29]. Most recently, an association of loss-of-function mutations in the SMARCE1 gene with multiple spinal meningiomas of clear-celled phenotype has been described [30].

Summary and Conclusion

Meningiomas account for approximately 1/2 of all intracranial tumours, their incidence rising with increasing age. The majority of tumours are of benign behaviour, whereas atypical and anaplastic variants are associated with a higher likelihood of disease recurrence. Benign meningiomas are twice as common in females as compared with males, although the aetiological role of sex hormones is not yet fully understood. Ionizing radiation constitutes an established risk factor. The vast majority of meningiomas occur sporadically, whereas multiple meningiomas are most often associated with familial tumour syndromes such as NF2.

Conflict of Interest

None.

References:

Incidental Meningiomas
Florence Lefranc

Abstract: Background: The growing use of magnetic resonance and computed tomography imaging has facilitated the diagnosis of brain tumours even before the presence of clinical signs. A significant proportion of incidental lesions identified will be meningiomas, at a point for consideration that > 40 % of the diagnosed meningiomas are not associated with clinical signs.

The natural history of incidental, asymptomatic, intracranial meningiomas is to be better understood for the development of the treatment strategy: what is the tumour growth rate? How many asymptomatic tumours do eventually become symptomatic?

Method: We performed a literature review trying to answer the questions.

Results: In case of incidental meningioma, the elements to consider are its location, size, and radiological aspect, the patient’s age and the risk of complications from eventual surgery, any unknown symptoms, multiplicity of lesions, the possibility of malignancy, and other pathological conditions that mimic meningiomas. Radiological characteristics associated with low tumoral growth rate are the presence of calcifications and hypointense regions on T2-weighted MR images.

On the radiological aspect, it seems that > 60 % of asymptomatic meningiomas will not grow in size. However, some of them grow rapidly and some meningiomas even of small size will be treated with regard to their location or due to the risk that they might produce neurological deficits.

Conclusion: We are in favour of careful follow-up and neurosurgical consultation for all patients with an incidental meningioma. Eur Assoc NeuroOncol Mag 2013; 3 (3): 97–9.

Key words: incidental meningiomas, natural history, radiological findings, treatment

Incidence of Asymptomatic Meningiomas

The use of magnetic resonance imaging (MRI) for justified indications such as unusual headaches, epileptic seizures, or a neurological deficit has facilitated the diagnosis of meningiomas. Such imaging during medical checkups nonetheless helps detect a significant proportion of meningiomas incidentally in asymptomatic patients [1, 2]. In times prior to the development of medical imaging, the incidence of meningioma among the general population was 2.3/100,000 inhabitants [2]. An epidemiological study conducted in Germany between 1961 and 1986 found an annual incidence of meningioma of 1.85/100,000 people [3]. Approximately 50 % of the meningiomas in this study were discovered during autopsy, explained by the fact that these lesions are typically slow-growing tumours that remain asymptomatic for a long time [3]. The rate of meningiomas diagnosed during autopsy series is 3 % for patients aged > 60 with a tendency to find larger-sized meningiomas the older the patient is [4]. In another study conducted at the Mayo Clinic, the incidence of meningiomas discovered during autopsy was 5.9/100,000 people [5].

Since the advent of the cerebral CT scan and MRI, the number of diagnosed cases of asymptomatic meningioma has sharply increased. In a recent, prospective, population-based study in the Netherlands involving 2000 people ≥ 45 years of age, the prevalence of benign brain tumours was 1.6 %, with meningiomas being the most common (0.9 %) [6]. These meningiomas ranged from 5–60 mm in diameter and their prevalence was 1.1 % in women and 0.7 % in men. In the study by Kuratsu et al [7], of 504 patients with meningiomas admitted in 27 hospitals in the Kumamoto region of Japan between 1989 and 1996, 196 were asymptomatic, ie, 39 %, of whom 117 were < 70, and 79 > 70. In reviewing the rates per year, the authors noted an increase in the rate of discovery of asymptomatic meningiomas from 34.6 % between 1989 and 1992 to 44 % between 1993 and 1996 [7]. These data were confirmed in 2006 by the Yano group [8]. Of 1434 patients with meningiomas admitted between 1989 and 2003, 603 were asymptomatic, equalling 42 % of the population studied [8].

We used the PubMed database to review the different published series concerning asymptomatic meningiomas and their natural history.

Natural History of Asymptomatic Meningiomas

The first studies to investigate the radiological development of asymptomatic meningiomas are based essentially on the diameter of the tumour or on the measurements of 2 different axes estimating its volume [8–13]. These studies analyse growth in 2 dimensions. New software has in time been introduced in medical imaging devices and can calculate the volume of a lesion with greater precision. These studies report volumetric growth of the meningioma in 3 dimensions [7, 14–18]. Zeidman et al [17] showed that the average volumetric growth in a limited series of 21 patients was significantly higher than that in 2-D, suggesting that as meningioma can grow in different directions, the volumetric measurement yields more information and is more efficient for monitoring tumoural growth. This observation was recently confirmed by Chang’s group [18] on a series of 31 patients.

According to studies, imaging monitoring shows a growth of asymptomatic meningiomas in a variable percentage of 24–44 % of patients [7–13, 15, 19]. The reported series often concern limited groups of patients and the duration of monitoring in particular is variable. In case of imaging development, neu-
Incidental Meningiomas

The critical size of a meningioma in connection with the appearance of symptoms is not elucidated [21] because the latter depends on many factors that include in particular: (1) size at the time of initial diagnosis [8, 12, 13, 15, 20], (2) the location of the lesion [22, 23], (3) the presence of a consecutive oedema of the brain [19], and (4) the possibility of venous invasion and secondary infarction.

Radiological and Clinical Signs Associated with the Growth Rate of Asymptomatic Meningiomas

The radiological characteristics identified as being associated with slow tumoural growth are: (1) the presence of calcification in the meningioma [7, 8, 12, 13, 16, 19] and (2) the hypointense character thereof in the MRI’s T2 sequences [7, 8, 12, 16, 19]. Clinical characteristics associated with slower growth of the meningioma are more advanced age and small size of the meningioma at the time of diagnosis [12, 13, 15, 16, 19].

What Should Be Done When an Incidental Meningioma Is Discovered?

It appears that the majority of patients diagnosed with an asymptomatic meningioma can be at first closely monitored radiologically and clinically [8, 15]. This is particularly true for small-sized meningiomas, especially in older patients in whom meningioma growth is slower [16] and surgery is associated with a higher morbidity [7, 8]. However, patients with a rapidly or significantly growing meningioma or patients who become symptomatic should be referred for treatment.

To determine the therapeutic strategy or monitoring of an asymptomatic meningioma, it is necessary to take into consideration the characteristics of the meningioma, its location, size, radiological characteristics (calcification, hypointense in sequence T2 of the MRI), the presence of a perilesional oedema, the possibility of malignity or another histological type, and the characteristics of the patient (age, general state of health, case history, and life expectancy) [24]. The patient’s history of prescriptions is important because spontaneous regressions have been reported when the patient stops taking cyproterone acetate [25–27]. It is also necessary to verify that the patient is really asymptomatic by means of a clinical neurological examination conducted in accordance with the location of the lesion, such as a neuro-ophthalmological as well as a neuropsychological examination.

The opinion of a neurosurgeon is desirable at the time when an asymptomatic meningioma is detected [24].

Some meningiomas will, irrespective of their size, have to be treated depending on their location and risk of provoking neurological disorders. It appears in fact that nearly 50% of meningiomas discovered incidentally are treated either by surgery or, most often, by radiosurgery from the outset or by a multidisciplinary approach (surgery followed by radiosurgery) [7].

This situation may be encountered when an asymptomatic patient presents straightforwardly with a large, non-calcified meningioma surrounded by an oedema. Treatment should take into consideration the patient’s age, life expectancy, anaesthesiological risks, and the higher probability of growth for a non-calcified meningioma. A multidisciplinary approach is essential in such a situation. Even though the morbidity rate is lower in patients with an asymptomatic meningioma than in those with a symptomatic lesion the results show that an asymptomatic meningioma is not without risk, especially in patients > 70. A meningioma residue may very well remain in place to avoid excessive surgical risks. Monitoring is indicated or additional treatment by radiosurgery is envisaged for such a residue.

Another situation is the diagnosis of a limited-size meningioma of the cranial base, compatible with radiosurgery or a minimum distance from the optic nerve. In such a case, radiosurgical treatment may be discussed from the outset.

When a strategy for the monitoring of asymptomatic meningioma is decided on by the neurosurgeon, initial clinical and imaging examinations are extremely important because even though the majority of meningiomas are benign tumours, there is a small proportion of aggressive lesions that require rapid and multidisciplinary treatment. MRI examination is advised within 3–4 months after diagnosis [1]. One fourth of meningiomas that show signs of growth might belong to the atypical or malignant grade [28]. In such situations, it is very important to have arguments to gauge the nature of the non-
operated tumour. To that end, spectro-MRI sequences that detect the metabolites dissolved in the tissues in a non-invasive manner can prove very useful [29, 30].

**Conclusion**

Imaging monitoring of asymptomatic meningiomas shows growth in a variable percentage of patients [7–13, 15, 19]. Nevertheless, in case of imaging development, neurological signs appear in < 50%.

A meningioma’s growth rate is an important factor in determining whether a lesion should be treated. The use of volumetric analysis could prove a useful tool for neurosurgeons [17, 18].

It seems advisable to obtain a neurosurgeon’s opinion for an incidental meningioma. The treatment of asymptomatic meningiomas remains controversial and should be defined individually for each patient by considering the characteristics of the meningioma and of the patient. Some recommendations can be made on the basis of the data of our review.

Conservative treatment should be recommended for asymptomatic patients > 70 with a small calcified meningioma. Conversely, surgical treatment could be opted for more easily in patients < 60 with a large convexity lesion. These patients actually have a lower surgical risk but a greater risk for meningioma growth and longer monitoring. Surgery is also recommended when the patient becomes symptomatic or the meningioma grows, is surrounded by oedema, has a mass effect on the brain, or shows signs of malignity.

**Conflict of Interest**

None.

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**References:**


## Prognostic Factors in Meningioma

### Ulrich Roelcke

**Abstract:** Age, WHO grade, and extent of resection represent strong prognostic factors in meningiomas. The majority of further clinical factors and laboratory findings reflects disease according to the WHO grade. Therefore, research should focus on heterogeneity of prognostic factors within a given WHO grade. This may allow to identify also factors predictive for response to systemic therapy, and to promote the design of studies which stratify according to these factors.

**Key words:** meningioma, prognosis, WHO grade, hormone receptors, angiogenesis, VEGF receptor, osteopontin

### Introduction

The term “prognostic” relates to the behaviour of a tumour with regard to the spontaneous course as well as to the course after medical intervention. In contrast, the term “predictive” indicates the chance to respond to a given therapy. In meningiomas, the term “prognostic” is differently used across the literature and includes risk for incidence, risk for tumour development as well as risk for meningioma progression and recurrence. In the following, the term “risk factor” is used with regard to meningioma aetiology. „Prognostic“ denotes factors which may determine the clinical course once a meningioma is diagnosed. “Predictive factors” particularly with regard to systemic therapy have not been evaluated in meningiomas.

### Risk Factors

Genetic alterations, status of sex hormones, and ionizing radiation represent well-established risk factors in meningiomas. These tumours can be part of hereditary syndromes such as neurofibromatosis type 2 (NF2), Li-Fraumeni, Turcot, Gardner, von Hippel-Lindau, Cowden, Gorlin, and multiple endocrine neoplasia type 1 [1]. In neurofibromatosis type 2, there are probably several genes involved in the development of meningioma, ie, a significant risk was observed also in the absence of alterations on the NF2 gene [2]. The association between hormones and meningiomas is evident by the increased incidence of these tumours in women (female:male ratio up to 3:1), the presence of female hormone receptors on meningiomas, meningioma growth during pregnancy, and regression of meningioma after cessation of oestrogen agonist therapy [3–5]. In addition, also long-term use of oral contraceptives and post-menopausal hormonal replacement therapy increases the risk of developing meningioma [3]. Ionizing radiation induced meningiomas as a long-term complication of prophylactic cranial irradiation for leukaemia in childhood [6]. Whether radiographs of the mouth [7] or the use of mobile phones [8] represent risk factors is still a matter of debate.

### Prognostic Factors

Prognostic factors can be grouped into clinical factors at first presentation, extent of resection, and laboratory markers obtained from tissue. Most studies present data on prognostic factors which show significant correlation with the WHO tumour grade.

#### Clinical Factors and Extent of Resection

Tumour recurrence and progression depend on characteristics of the individual tumour presentation as well as on treatment modalities. Histology predicts mortality and recurrence: relapse rates in WHO grade I (benign) / II (atypical) / III (malignant) of 7 / 40 / 80 % have been reported, and median survival in these studies was > 10 / 11.5 / 2.7 years, respectively [9, 10]. Of note, even in the absence of the cellular criteria of WHO grade II also brain invasion qualifies for WHO grade II because recurrence and mortality rates are similar to atypical meningiomas [11]. Also meningiomas which present with bone invasion show poorer outcome compared to non-invading tumours [12]. Apart from WHO grade, age and extent of resection [13] represent strong prognostic factors as well. The extent of resection is graded according to the original description of Simpson (grades 1–5). Grade I denotes macroscopic gross total resection with excision of dura, sinus, and bone, whereas grade 5 denotes biopsy only [14]. On multivariate analysis, age < 40 years, male gender, less than gross-total resection, and a high mitotic index are independently associated with shorter progression-free survival [15]. However, although many patients with completely resected grade-I meningiomas can be considered as cured, late recurrences are observed even after 20 years [16]. As surgical options are determined by tumour location this factor has to be considered as well. While gross-total resection can be achieved in many tumours of the convexity, patients with skull-base tumours involving the petroclival region, cavernous sinus, or orbit are post-operatively left with a residual tumour of varying size. On the other hand, a follow-up study on incidental non-operated meningiomas showed that 26 % of skull-base tumours grow with a relative growth rate of 6.8 % per year, whereas 95 % of non-skull base tumours grow faster with a relative growth rate of 13.8 % per year during a median observation time of 49 months [17]. In line with this observation, Kane et al reported on a series of 378 operated meningiomas (82 % WHO grade I; 56 % skull base, 44 % non-skull base tumours) where patients with non-skull base lesions were significantly more likely to have atypical or malignant meningiomas on uni- and multivariate analysis [18]. The authors discussed that

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From the Department of Neurology – Brain Tumor Center, Cantonal Hospital, Aarau, and the University of Basel, School of Medicine, Basel, Switzerland

**Correspondence to:** Ulrich Roelcke, MD, Department of Neurology – Brain Tumor Center, Cantonal Hospital, Tellstrasse 15, 5001 Aarau, Switzerland; e-mail: roelcke@ksa.ch
this difference may reflect the distinct embryologic origin of skull base and non-skull base dura, which may imply different genetic alterations and, therefore, a different biological behaviour [19–21].

Laboratory Markers
The proliferation markers Ki-67 and MIB labelling index correlate with the WHO tumour grade, and therefore – not surprisingly – with prognosis [22]. Within a specified WHO grade the correlation between Ki-67, the status of the tumour suppressor gene, p53, and prognosis is maintained (WHO grade I [23]). Also the expression of sex hormone receptors correlates with the tumour grade and impacts prognosis. Progestosterone receptors are more frequent in benign meningiomas and correspond to a median recurrence rate of 5 %. Meningiomas which express oestrogen receptors, or tumours lacking sex hormone receptors, belong more frequently to WHO grades II and III and are associated with recurrence rates of up to 30 % [24]. Furthermore, telomerase activity, which indicates immortal cells characterized by clonal expansion and growth potential, was found in 95 % of atypical and malignant meningiomas [25]. The frequency of telomerase positivity is much lower in benign meningiomas [25, 26]. Of note, telomerase-positive benign meningiomas may show early recurrence even following gross-total resection [25].

The identification of prognostic factors which show a substantial range of expression within a distinct subgroup of meningioma (eg, WHO grade) and which relate to targets where treatment is available may allow to allocate patients to distinct molecular subgroups with regard to therapy. It has been established that meningiomas of all grades exhibit vascular endothelial growth factor (VEGF) to a variable degree [27, 28]. VEGF receptor mRNA expression varies within benign meningiomas. One study demonstrated that 6/8 benign meningiomas which occurred within a median of 3.9 years express VEGF receptor mRNA, whereas non-recurrent tumours did not [29]. Also, the balance between pro-angiogenic (VEGF) and anti-angiogenic (seminoparin 3A [SEMA3A]) factors corresponds to the prognosis of meningiomas. Barresi et al reported that low scores (ie, a VEGF:SEMA3A expression ratio < 3.0) are associated with longer progression-free survival [30]. Furthermore, the expression of the integrin-binding osteopontin protein, which is involved in angiogenesis, cell proliferation, and migration, impacts prognosis. In a series of 32 operated patients with WHO grade-I meningiomas, 28 % recurrences were observed during a mean follow-up of 34 months. In patients with “early” recurrences, the osteopontin staining score was approximately 6 times higher compared to non-recurring tumours [31]. Similar findings were reported for atypical meningiomas [32]. These studies accentuate the importance to assess the biological variability within distinct prognostic groups (WHO grade). Results may prompt prospective trials which evaluate eg antiangiogenic strategies in osteopontin-positive meningioma.

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Conflict of Interest
The authors state that no conflict of interest exists.

References:

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Prognostic Factors in Meningioma
Genomic Characterization of Meningiomas

Peleg M Horowitz1,4, Rameen Beroukhim3,4, Ian F Dunn1,4, Priscilla K Brastianos3–5

Abstract: Meningiomas are common tumours arising from the arachnoidal cap cells of the leptomeninges that can cause significant morbidity by compressing and potentially invading the adjacent brain, vasculature, and cranial nerves. Those tumours arising from the skull base and tumours with more aggressive histopathologic features (World Health Organization grades II and III) are particularly challenging to treat, frequently recurring even after optimal surgical resection and growing despite radiation treatments. Currently, no effective chemotherapeutic options are available for recurrent and aggressive meningiomas. Until recently, the only genetic driver of meningiomas to be identified was bi-allelic loss of the tumour suppressor gene NF2 on chromosome 22, encoding the protein Merlin. However, several recent efforts have uncovered new driver mutations, particularly in the approximately 40–60 % of tumours that are wild-type for NF2. Such mutations, including those in signalling molecule genes such as AKT1 and SMO, epigenetic modifier genes such as KDM5C and SMARCB1, and additional genes whose function remains unclear, such as TRAF7 and KLF4, predominate in grade-I tumours of the skull base. Patients with these difficult-to-treat tumours may therefore benefit from specific targeted medical therapies based on the mutations present in their individual tumours. Higher-grade tumours are characterized by increased genomic instability, particularly elevated numbers of chromosomal and arm-level losses, though few specific genes involved in their pathogenesis have been identified apart from NF2. Here, we review these recent advances in our understanding of meningiomagenesis through genetic profiling and the potential clinical applications of these findings. Eur Assoc NeuroOncol Mag 2013; 3 (3): 102–4.

Key words: meningiomas, genomics, AKT1, SMO

Introduction

Meningiomas are the most common primary central nervous system tumour, constituting approximately 1/3 of all primary intracranial tumours [1, 2]. While most meningiomas (80 %) are grade I and do not invade the brain tissue, their growth within the intracranial space often leads to serious and potentially lethal consequences. A significant number of these lesions are located at the skull base, a region that increases both the morbidity of treatment and risk of recurrence after surgery. Overall, 5-year recurrence rates are as high as 18 % for grade-I tumours, leading to significantly reduced long-term survival [3]. Higher-grade meningiomas (grades II and III) are marked by brain invasion, increased mitoses, necrosis, higher nuclear-to-cytoplasmic ratios, or histologic appearance resembling carcinoma, sarcoma, or melanoma [4]. These more aggressive lesions have a worse prognosis, with grade-II and -III recurrence rates as high as 40 % and 80 %, and 5-year overall survival rates of 76 % and 32 %, respectively [2, 5, 6].

While there are case reports and case series of meningiomas progressing from grade I to higher grade [7, 8], the grade-II and -III meningiomas more often are diagnosed on initial resection.

Treatment options for meningiomas of all grades are limited. The primary treatment modality in almost all cases is surgical resection, with recurrence rates primarily related to histologic grade and extent of resection [4, 9]. Radiation is often used as an adjunct to surgery in cases of recurrence or growth of residual tumours, with variable response rates [10, 11]. However, the medical treatment of meningiomas is severely limited, with no effective chemotherapeutic options when surgery and radiation fail to provide durable disease control [12]. Systemic agents that have been investigated in this setting with limited success include hydroxyurea [13], bevacizumab [14], imatinib [15], irinotecan [16], mifepristone [17], and erlotinib [18].

A limited understanding of the causes of these tumours has hampered development of novel medical treatments; however, our understanding of meningiomagenesis has been advanced recently by genomic studies of these tumours that have uncovered a number of genes that may both drive tumour development and offer unique windows for chemotherapeutic interventions.

NF2 Syndrome and Gene

The first identification of a genetic cause for meningiomas, nearly 30 years ago, was the discovery of the gene underlying the neurofibromatosis type-2 syndrome on chromosome 22 [19, 20]. The NF2 gene, a tumour suppressor encoding the protein Merlin (also known as Schwannomin), is inactivated by a combination of mutation and deletion in neurofibromatosis-associated meningiomas as well as between 30–70 % of non-syndromic (sporadic) meningiomas [21, 22]. A 2-hit mechanism is commonly seen in these tumours, where a nonsense, splice-site, or frame-shift mutation results in a non-functional product from one allele, while the second allele is knocked out by hemizygous loss, usually by loss of part or all of chromosome 22 [23]. Recently, a radiation-induced meningioma was shown to have a copy-neutral rearrangement (by intrachromosomal inversion), a novel mechanism for disruption of the NF2 gene [24]. Loss of the NF2 gene has also been linked to both neurofibromatosis-associated and sporadic schwannomas [25].

In addition to association with neurofibromatosis and the NF2 gene, predisposition to development of meningiomas has been reported in several other familial syndromes. These in-
include syndromes associated with alterations or defects in the NF1, PTCH, CREBBP, VHL, PTEN, and CDKN2A genes [26].

The mechanisms by which Merlin acts as a tumour suppressor are not fully understood. Merlin belongs to the larger 4.1 protein family that interacts with multiple cell surface proteins [27]. Mounting evidence suggests that Merlin is involved in regulation of contact-dependent inhibition of cellular proliferation through a complex network involving cell surface proteins and several intracellular signalling pathways such as the Hippo, Notch, and Patched pathways [28]. There is also evidence that inactivation of Merlin leads to downstream activation of mTOR in meningioma cell lines [29, 30]. Interestingly, allelic losses and decreased expression of DAL1, another member of the 4.1 protein family, have been described in meningioma to varying degrees [23, 31].

While NF2 loss is likely sufficient to drive formation of grade-I meningiomas, other genes may be involved in meningiomagenesis and in progression to higher grades [32]. Grade-II and -III meningiomas tend to harbour greater levels of genomic disruption, especially chromosomal losses [33]. Loss of the tumour suppressor CDKN2A/B has been linked to aggressive histology both in human tumours and in mouse models [7, 32], and frame-shift mutation of CDKN2C has also been shown in an NF2-mutant grade-II meningioma [24].

Unfortunately, development of medical therapies targeting NF2 loss in meningiomas has not been successful to date. Furthermore, approximately half of sporadic meningiomas of all grades lack discernible lesions in the NF2 gene [21, 22], leading researchers to re-examine the genetic landscape of sporadic meningiomas in the hopes of discovering additional genes that contribute to meningiomagenesis and may be more amenable to targeted therapeutics.

**Mutations in NF2-Wild-Type Grade-I Meningiomas**

Several recent studies profiling the genomic alterations in meningiomas have identified a handful of novel genes as potential drivers of meningiomas, primarily of non-NF2 mutant meningiomas [24, 34, 35]. These genes include AKT1, SMO, TRAF7, and KLF4. Combined, mutations in these genes account for approximately 40% of grade-I meningiomas, and are almost always mutually exclusive with NF2 loss. Mutations in these genes are found primarily in grade-I meningiomas of the skull base, a region that increases risks of surgical resection and radiation therapies. These mutations also correlate with histological subtype: while NF2 mutations confer a fibrosarcoma histology, AKT1 and SMO mutations were present in tumours of meningothelial and transitional histology, and combined TRAF7 and KLF4 mutations were found almost exclusively in the rarer secretory subtype.

Identical mutations in the proto-oncogene AKT1 (E17K substitution) have been found in 27% of non-NF2 mutant grade-I meningiomas, primarily those of the skull base [24, 34]. This mutation is a known oncogenic alteration frequently encountered in breast, thyroid, lung, and endometrial cancers [36–38]. The alteration in charge causes constitutively active AKT, leading to activation of downstream mTOR signalling. Meningiomas with the AKT1 E17K mutation show gene expression patterns distinct from NF2 mutant tumours [34] and show immunohistochemical evidence of downstream pathway activation of the mTOR pathway [24]. Interestingly, a novel mutation of MTOR (D1279V) also caused similar downstream activation in an AKT1 wild-type tumour [24]. Targets of the PI3K/AKT/mTOR pathway are already in clinical use in other cancer types [39].

Mutations in the hedgehog signalling member SMO were found in 9% of non-NF2 mutant grade-I meningiomas, which were mostly located in the anterior midline skull base [24, 34]. Two different mutations in SMO, L412F and W535L, had similar effects on gene expression [34] and downstream pathway activation as measured by GAB1 immunostaining [24]. These mutations have been previously characterized in other tumours such as basal cell carcinoma [40] and desmoplastic medulloblastoma [41]; hedgehog pathway inhibitors are already in use clinically for these tumours [42].

The pro-apoptotic E3 ubiquitin ligase TRAF7 was mutated in 12–25% of all meningiomas profiled [19, 29] and frequently co-existed with mutations in AKT1 or KLH4, a transcription factor associated with induction of pluripotency in other cell types. Interestingly, the combination of TRAF7/KLH4 mutations was characteristic of all secretory meningiomas profiled [35]. While the mechanisms by which KLH4 and TRAF7 lead to meningioma development are unclear, it is clear from gene expression analyses that distinct differences are observed between these tumours and those driven by NF2 loss [34]. It also remains to be seen whether these mutations, like those in AKT1 and SMO, are amenable to generation of targeted medical therapeutics.

**Mutations in Epigenetic Modifiers**

Mutations in genes categorized as epigenetic modifiers (genes that directly or indirectly modify chromatin structure leading to differential expression of many genes) were identified in 8% of meningiomas in one recent study [24]. Among these were the histone demethylases KDM5C and KDM6A, as well as the SWI/SNF complex member SMARCB1. The SMARCB1 gene is located 6 Mb from NF2 on chromosome 22, and a “4-hit” model of biallelic inactivation of both genes has been described in familial schwannomas [43]. Interestingly, mutations in SMARCB1 appear to cluster within a small region of the C-terminus, suggesting a gain or alteration of function in these tumours [24, 44]. Germline mutation in the related gene SMARCE1 has also been implicated in familial spinal meningioma [45]. While mutations in epigenetic modifiers are clearly implicated and may be causative in a minority of meningiomas, the mechanisms by which they act remain unknown.

**Genomic Rearrangements**

While most grade-I meningiomas have non-aneuploid genomes or harbour only loss of chromosome 22, a small proportion of these benign tumours show more complex genomic

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rare rearrangements that can affect numerous genes. For example, whole-genome sequencing of a radiation-induced meningioma identified a copy-neutral inversion on chromosome 22 leading to truncation of the NF2 gene in the first intron and fusion with nearby gene TCF-20; this represents a novel mechanism of NF2 disruption, one which would not be detectable with standard exome sequencing or array-based copy number analyses [24]. Another tumour in the same cohort analysed harbourd chromothripsis, a simultaneous rearrangement of one or more chromosomes estimated to occur in 2–3% of aggressive malignancies [46], affecting a large portion of chromosome 1. This rearrangement disrupted the putative tumour suppressor NEGR1, which was also disrupted by rearrangement in a second meningioma [24]. While interchromosomal rearrangements are sufficient to drive several hematologic malignancies and solid tumours, it has yet to be demonstrated whether such alterations are drivers or passengers in meningioma formation.

Conclusions

Recent advances in genetic analysis of tumours through whole-genome and whole-exome sequencing have facilitated the discovery of several new candidate drivers of meningiogenesis, particularly in those tumours that harbour no discernible defects in the tumour suppressor NF2. Several of these recurrent mutations, specifically those in AKT1 and SMO, are promising as treatment targets as there are already drugs in development or use targeting these mutations in other tumour types.

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Conflict of Interest

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References:

Recurrence and Progression in Meningiomas: The Clonal Cytogenetic Evolution of a Benign Human Tumour

Ralf Ketter, Joachim Oertel, Stefan Linsler, Steffi Urbschat

Abstract: Meningiomas are mostly benign tumours that originate from the coverings of brain and spinal cord. Only a minority of cases show progression to an anaplastic tumour (WHO grades II and III). Multiple and familial cases are rare and mostly associated with (hereditary) neurofibromatosis 2 (NF2). Meningiomas show an unexpectedly high recurrence rate. Also, completely removed low-grade tumours can recur. On a cytogenetic level, meningiomas are the best-studied tumours in humans. The majority of high-grade but only a minority of low-grade meningiomas show loss of merlin, a cytoskeleton-cytosplasm-linker protein. Merlin is the product of the NF2 gene located on chromosome 22. A second tumour suppressor gene on chromosome 22 on 22q12.3 is the gene for the tissue inhibitor of metalloproteinase 3 (TIMP3), which appears to be involved in meningioma progression and a high-grade meningioma phenotype. In contrast to other solid tumours, progression of meningiomas is correlated with increasing hypodiploidy, showing characteristic clonal evolution that mostly include chromosomes 14, 18, and 19 and, more rarely, 6 and 10. Structural aberrations are rare, except for the loss of the short arm of one chromosome 1, which appears to define the first step for anaplastic growth. A bio-statistical approach has been proposed, using an oncogenetic tree model that estimates the most likely cytogenetic pathways of meningioma patients in terms of accumulation of chromosome changes in tumour cells. The genetic progression score (GPS) estimates the genetic status of a tumour as progression in the corresponding tumour cells along this model. High GPS values are highly correlated with early recurrence of meningiomas (p < 10^-4). This correlation holds true even when patients are stratified by WHO grade. Tumour location also has an impact on genetic progression. Clinical relevance of the GPS is demonstrated with respect to origin, WHO grade, and recurrence of the tumour. As a quantitative measure, the GPS allows a more precise assessment of the progression of meningiomas than categorical cytogenetic markers based on single chromosomal aberrations. Comparative histochromical and molecular cytogenetic studies point to the alkaline phosphatase gene (ALPL, liver-bone-kidney type) located on 1p36.1–p34 as a candidate tumour suppressor gene. Eur Assoc NeuroOncol Mag 2013; 3 (3): 105–11.

Key words: meningioma, recurrence, deletion of 1p, chromsomes, genetic progression

Introduction

Meningiomas are derived from the arachnoidal cap cells of the leptomeninges, the soft coverings of the brain and spinal cord. Although their matrix tissue constitutes < 5 % of the intracranial and intraspinal masses, meningiomas are estimated to constitute between 13 % and 26 % of the primary tumours within the CNS. Most meningiomas are sporadic, slowly growing benign tumours and correspond histologically to WHO grade I. However, certain histological subtypes and also a minority of common-type meningiomas show a more aggressive biological behaviour and are associated with an increased risk of recurrence and an unfavourable prognosis. Corresponding to their localization, meningiomas of the spinal cord tend to be significantly more benign than those of the brain basis, which, in turn, are more benign than meningiomas of the brain convexity [1, 2]. The current WHO classification of brain tumours [1] distinguishes 3 grades of meningiomas: the common type (WHO grade I), the atypical or intermediate type (WHO grade II), and the anaplastic (WHO grade III) meningioma.

For appropriate treatment of tumour patients, prediction of time until death or time to progression after initial treatment is an important task. Due to many clinical, topographical, radiological, and surgical factors, histology is not solely decisive for prognosis [3], although mitotic activity, cellular pleomorphism with prominent nucleoli and micronecrosis, and focally raised cell density have been discussed as indicators of a poorer prognosis [4]. A major challenge is the identification of genetic prognostic markers that better reflect tumour biology.

Multiple occurrences are rare events, observed in only about 2 % of cases. Frequently, multiple meningiomas occur in patients with neurofibromatosis 2 (NF2), an autosomally dominant tumour syndrome, in combination with vestibular schwannomas and ependymomas. A polyclonal origin must be supposed in these cases.

In non-NF2 cases, molecular genetic studies demonstrate a common clonal origin of multiple or recurrent meningiomas [5, 6]. The development of familial (multiple) meningiomas within the same or different generations has so far been reported in < 20 families. Pathologic and genetic data on these families first suggested a biologically variant type of NF2 with the development of meningiomas only but no schwannomas. Molecular studies on a few cases indeed excluded the involvement of the NF2 gene although a chromosome 22 was missing. Alternatively, homozygous inactivation of a different tumour suppressor gene on the same chromosome was proposed [7].

The meningioma is one of the cytogenetically best-studied solid tumours. The characteristic and most frequent chromosomal aberration in meningiomas is monosomy 22 [8], which, however, seems not to be relevant for prognosis as an isolated anomaly. The progression from common-type to atypical and anaplastic meningioma is characterized by 2 different cytogenetic events: Firstly, further loss of up to 6 other chromosomes, with a mostly typical pattern of clonal evolution, and, secondly, partial or complete loss of the short arm of one chromosome 1 [3, 9–15].

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The identification of pathogenetic pathways in human tumours is one of the main challenges in molecular oncology. For many tumour types, genetic events defined by somatic chromosome alterations or gene mutations, respectively, are known to accumulate over time in the course of the disease. Based on these findings, genetic changes associated with chromosome instability are believed to play an important role in both tumourigenesis and tumour progression in meningiomas. There is a vast amount of literature on linking single genetic alterations to survival [16], but only few efforts have been made to construct more complex and comprehensive models. Zang [15] described a first model of clonal evolution in meningiomas based on conventional cytogenetic studies. Data of the cytogenetic findings of 394 meningiomas led to an empirical model of meningioma progression.

Cytogenetic analyses show that numerical and structural chromosome changes with pronounced hypodiploidy, or rarely hyperdiploidy [17], and especially deletion of the short arm of a chromosome 1, are accompanied by more aggressive biological characteristics [3, 9–15, 18].

By using a mathematical model for estimating the most likely cytogenetic pathways in meningiomas, a model for tumour recurrence could be established. In this model, each tumour is represented by the genetic events that have occurred in the tumour. The most important difference of the mathematical model compared to the “hand-crafted” model [15] is that it allows an objective assignment of the estimated time to recurrence for a single tumour based on its genetic status.

Incidence, Materials, and Statistics

Patient Population
We performed a retrospective study on 661 patients (482 women and 179 men) with meningiomas operated on at the Department of Neurosurgery, Saarland University, between January 1973 and April 2005. Average age of the overall patient population was 57.3 years (SD ± 12.8 years). Average age of the female patients was 57.6 years (SD ± 12.3 years), average age of the male patients was 56.7 years (SD ± 14.1 years).

Clinical Variables
The clinical variables investigated comprise patient gender and age, tumour location and histology, and the completeness of tumour extirpation.

Location
We formed 9 groups depending on meningioma location: (1) convexity, (2) parasagittal region, (3) tuberculum sellae, (4) olfactory groove, (5) sphenoid wing ridge, (6) posterior cranial fossa, (7) tentorium, (8) ventricular, and (9) spinal channel. The classification was carried out on the basis of the preoperative CT and NMR.

Tumour Extirpation
Complete surgical extirpation of the tumour was defined as Simpson grades I and II corresponding to a macroscopically complete tumour resection with bipolar coagulation of the dura insertion.

Tumour Histology
The 661 cases investigated comprised 465 common-type (WHO grade I), 156 intermediate-type (WHO atypical meningioma, grade II), and 14 anaplastic meningiomas (WHO grade III). Meningioma grade was assessed by a combined histological and morphometric approach on routinely HE and Ki-67/Feulgen-stained, formalin-fixed, paraffin-embedded tissue sections [12].

Cell Culture and Cytogenetic Preparation
Cell cultures from 661 meningioma biopsies and chromosome preparations with GTC banding were carried out according to standard procedures. Many tumours were characterized by multiple patterns of cytogenetic aberrations. In total, 1068 clonal patterns were observed in the 661 tumours.

Histochemical Detection of ALPL
The histochemical findings shown in Figure 1 were performed on frozen sections as described by Niedermayer et al [3].

Follow-up
Patients were investigated in the neurosurgical outpatient department of the Saarland University, either within the framework of routine follow-up or because of the appearance of neurological symptoms. Recurrence was evaluated as new evidence of a tumour in CT or NMR after previous complete extirpation (Simpson grades I and II). The Simpson grade II was established on the basis of the operation report and the postoperative CT or NMR investigation. Average follow-up time was 40.3 months (41.5 months for female patients and 37.2 months for male patients).

Statistical Analyses
Oncogenetic Tree Models
Mixtures of oncogenetic trees were used to describe the ordered accumulation of genetic aberrations during tumour progression. In a single oncogenetic tree, vertices represent genetic events, and edges between vertices represent transitions between the events. Each edge is associated with the probability that the successor event will occur, given the predecessor event has already occurred. In the model, genetic events are assumed to be non-reversible, thus the disease process can be fully described by the accumulation of genetic aberrations. In the mixture model, more than one tree component is estimated [18].

Genetic Progression Score
In oncogenetic tree models, consecutive genetic aberrations are associated with corresponding conditional transition probabilities. These probabilities can be converted to average waiting times by assuming Poisson processes for the occurrence of aberrations (see Rahnenführer et al [19] for details). Formally, waiting time associated to an edge of the tree with corresponding conditional probability p is given by (1–p)/p multiplied with a scaling factor that is typically set to 1. The genetic progression score (GPS) of a tumour then is defined as the average waiting time of its pattern of genetic aberrations, given the underlying tree mixture model. Tumours with few aberrations that appear early in the model receive low GPS values; tumours with many late aberrations in the model are associated with high GPS values. For 221 out of the 661 pa-
patients, more than one cytogenetic pattern was detected. In these cases, the GPS of the tumour was defined as the highest GPS of all clones found in the tumour.

### Clinical Factors of Meningioma Prognosis

Grading of meningiomas has always been controversial. Obviously, the biological behaviour of meningiomas cannot be accounted for by histological parameters alone [14, 15]. In 1979, Zülch stated that it is not the histological grading which is most crucial for the rate of recurrence of meningiomas, but primarily the completeness of extirpation [20]. There is agreement in the literature that radical surgical extirpation is correlated with a good prognosis [21, 22].

It is well known that females are affected far more frequently by meningiomas than males [20, 21]. This observation was confirmed in our previous study [12, 14, 15] with a ratio of 2.67:1. In particular, in the 49 spinal tumours investigated, the female sex was overrepresented (87%). This sex ratio was shifted when the tumours were broken down by karyotype. In the GPS group 2 (GPS ≥ 6.39), ie, in tumours with a pronounced aberration of the karyotype with deletion 1p, we found a sex distribution of 1.81:1.

### Cytogenetic Aspects of Meningiomas

#### Localization of Meningiomas

Frequency and behaviour of meningiomas at different intracranial locations were first discussed in 1922 [23]. A correlation between tumour localization and malignancy has repeatedly been observed. Meningiomas of the spinal cord tend to be significantly more often benign than those of the brain basis, which, in turn, are more often benign than meningiomas of the brain convexity [1, 2]. In 1980, it was shown that tumours located at the base of the skull typically contain cells with 46 chromosomes, whereas meningiomas located at the convexity show significant numbers of chromosomal aberrations [15]. In spinal tumours, almost exclusively a 22-monosomic karyotype was detected. It was already striking at that time that meningiomas which recurred showed significantly more chromosomal aberrations and a preference of the convexity. These findings are also in line with the results of a large series of meningioma patients (n > 9000 cases), where benign meningiomas were more frequently located at the skull than malignant meningiomas (p < 0.02) (Figure 2) [2].

#### Cytogenetic Findings and Histomorphology

Among histopathologically prognostic parameters, mitotic activity is the most important one. As the cut-offs of mitotic...
activity (MI) are defined for each grade by the WHO classification of brain tumours and because MI can be applied as the sole grading criterion, the reliable and reproducible assessment of MI is crucial for appropriate risk stratification. In 2007, we classified 661 meningiomas according to their genetic progression scores (GPS values) [18]. We found a high correlation between cytogenetic findings and histomorphology: higher genetic progression scores correlated highly significantly with higher histological grades (p < 10^{-10}, Fisher’s exact test). This result is important since in the literature no clear correlation between histological grading and the rate of recurrence in meningiomas has been reported [9, 24, 25]. In our study, no clear distinction between the histological grades I and II with respect to tumour recurrence could be shown, either (Figure 1). However, WHO grade-III meningiomas show a statistically significant correlation with earlier tumour recurrence.

Expression of the Alkaline Phosphatase ALPL in Meningiomas

More than 4 decades ago, Osske and Jänisch [26] reported differences in the expression of ALPL in meningiomas. However, no clear correlation with tumour grade or subtype was found. It could be shown that there is a strong homogeneous expression of this enzyme in low-grade meningiomas, with increasing patchwork-like patterns of expression loss in anaplastic meningiomas [15]. ALPL is located on the short arm of chromosome 1 (1p34–1, p36.1). In a more detailed study using interphase FISH on frozen sections of native meningioma cells [3, 27], the authors were able to show a complete correlation between losses in 1p and reductions in the amount and activity of alkaline phosphatase (Figure 1). As the activity of alkaline phosphatase can easily be detected histochemically and is highly correlated with the presence of 1p, this prognostically relevant parameter is also available to non-cytogeneticists. The data speak in favour of a tumour suppressor gene function of ALPL; however, the mechanism of inactivation of the second allele is not yet explained.

Oncogenetic Tree Models

The basis for the oncogenetic tree mixture models are single oncogenetic trees as introduced by Desper et al [28] that can be used to estimate the most likely pathogenetic routes in tumours from observed subsets of genetic events. These models are of high explanatory power, but often only for a portion of the analyzed tumour samples. A subset of genetic events is only represented by this tree model if for any event in this subset all precursor events in the tree also belong to the subset. All other subsets of events are assigned likelihood zero. Von Heydebreck et al [29] propose to include additional hidden events in the tree and to model genetic events as leaves in the tree. This method trades feasibility of maximum-likelihood estimation of oncogenetic trees with reduced interpretability due to the introduction of hidden events.

We introduced mixture models of the single oncogenetic trees as used in Desper et al [28]. In these mixture models, one tree component is restricted to have a star-like topology, representing independence between genetic events. Owing to the starlike component, every combination of genetic events is represented in the model. The oncogenetic tree mixture models combine interpretability of the trees of Desper et al [28] with an appropriate probabilistic framework.

Relevance of Gender for Genetic Progression Models

Breaking down the oncogenetic tree by gender, there is a reversal concerning chromosomes 14 and 1p– in the male population. For males, monosomy 14 is estimated to be an earlier event followed by the deletion of the short arm of one chromosome 1. Monosomy 14 has been found to be associated with aggressive behaviour of meningiomas [14, 24, 25, 30, 31]. However, in the literature the loss of chromosome 14 has never been correlated with gender. It is well known that females predominate over males with a ratio of 2.67:1 when it comes to the overall incidence of meningiomas.

It could be shown that the deletion of the short arm of one chromosome 1 has to be regarded as a more valid cytogenetic parameter than monosomy 14 for the prediction of tumour recurrence, particularly because all anaplastic meningiomas in our series displayed a deletion of chromosome 1p (Figure 3).
The Genetic Progression Score of Meningioma

Predictive Value of Genetic Progression Scores for Tumour Recurrence

We introduce the GPS of a tumour as the estimated average waiting time of its observed genetic pattern in the timed oncogenetic tree. Using Cox regression analysis, we demonstrate that for meningiomas the GPS has prognostic value with respect to clinical outcome and recurrence (Figure 4). Previously, it was shown that the information gain due to GPS holds true also for tumour samples from 2 other cancer types with notably different genetic backgrounds, namely glioblastoma and prostate cancer [19].

Strong correlations were found between histological measurements and the GPS. Interestingly, histological grades I and II alone were not informative with respect to recurrence of meningioma. Figure 4 shows the clinical relevance of the calculated GPS classification broken down to the WHO classification. This demonstrates that the genetic aberrations, especially the deletion of 1p, are independent markers for the clinical courses of meningiomas. Thus, the GPS classification allows a prognostically significant distinction between low-risk and high-risk meningiomas at the time of primary surgery. It can be expected that a combination of both histopathological and cytogenetical description of meningiomas could result in improved prognostic accuracy [3, 12, 32].

Accordingly, the deletion of the short arm of one chromosome 1 is an independent prognostic factor which correlates significantly with a raised risk of recurrence. Due to the limited follow-up period we have to expect that the recurrence rate may further increase over time.

Our results are in agreement with former cytogenetic investigations which indicated that the deletion of the distal part of the short arm of a chromosome 1 (1p–) is associated with progression in meningiomas [3, 10–14, 27, 33]. After initial speculation on the role of 1p deletion for tumour recurrence [10], the importance of this aberration beside monosomy 22, 14, and 10 for the development of atypical and anaplastic meningiomas [13] and for progression from typical to atypical meningioma [15] has been pointed out.

Further Parameters Involved in Meningioma Progression, Infiltration, and Recurrence

A very peculiar phenomenon in meningioma is invasion into the neighbouring anatomical structures, such as brain tissue and skull bone. Extracellular matrix (ECM) degradation by several proteolytic enzyme systems is a critical step in tumour infiltration. Matrix metalloproteases (MMP) are involved in the degradation of ECM components such as collagen and proteoglycans in normal embryogenesis and remodelling as well as in many disease processes such as tumour development, invasion, and progression. Okuducu et al [34] found an association between transcription factor Ets-1, the main regulator of several MMPs, and MMP-2 and -9 expression indicating a possible role for Ets-1 in MMP regulation in meningiomas. They found that increased Ets-1 expression was associated with high WHO grades in meningiomas, offering a possible additional diagnostic and prognostic tool for the evaluation of meningiomas [34].

The increasing frequency of chromosome aberrations in higher-grade meningiomas might be the result of loss of apoptotic control. Surprisingly, data on TP53 are relatively scarce and inconsistent. With common SSCP techniques, mutations have rarely been detected. However, histochemically there appears to be a significant accumulation of (inactive) p53 protein in higher-grade and recurrent meningiomas [35].
A further gene located on chromosome 22 is the gene for the tissue inhibitor of metalloproteinase 3 (TIMP3) on 22q12.3. In 2010, Barski et al. [36] examined a series of 50 meningiomas, including 27 benign meningiomas (World Health Organization [WHO] grade I), 11 atypical meningiomas (WHO grade II) and 12 anaplastic meningiomas (WHO grade III). They found hypermethylation of TIMP3 in 67% of anaplastic meningiomas, but only 22% of atypical and 17% of benign meningiomas. Therefore, TIMP3 inactivation by methylation seems to be involved in meningioma progression as well, at least it is associated with a more aggressive, high-grade meningioma phenotype [36].

Especially the deletion of chromosome 1p was ascertained to be an early and crucial event in the progression in meningiomas. In order to verify the information gain due to GPS, it is of particular interest to demonstrate improved performance over established histopathological parameters. By fitting multivariate Cox regression models we also found that for meningiomas the GPS is prognostic also after adjustment for age. The GPS can thus be used to further identify subgroups. We define low-risk patients as those with histological WHO grade-I tumours that belong to GPS group 0 or 1, and high-risk patients as those who harbour tumours that are grade II or III and/or belong to GPS group 2. High-risk patients should undergo an intensified regimen of postoperative surveillance including NMR follow-up every 6 months and glucose PET studies to assess the biological activity of early recurrent tumour growth. Consequently, a multimodal approach to meningioma grading is most promising for identifying meningiomas with an increased tendency to recur and for planning their follow-ups.

Conflict of Interest

None.

Figure 4. Kaplan-Meier survival curves for time to recurrence of meningioma patients; patients are split into 3 subgroups according to grouping based on the genetic progression score (green line: GPS ≤ 1.81, blue line: 1.81 < GPS ≤ 6.39, red line: 6.39 < GPS). In the first 3 plots, only subsets of patients according to WHO grade are considered. Reprinted with permission from [Ketter R, Urbschat S, Henn W, Feiden W, Beenewinkel N, Lengauer T, Steudel WI, Zang KD, Rahnenführer J. Application of oncogenetic trees mixtures as a biostatistical model of the clonal cytogenetic evolution of meningiomas. Int J Cancer 2007; 121 (7): 1473–80]. © 2007 Wiley-Liss, Inc.
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Current Surgical Strategies in the Treatment of Intracranial Meningiomas

Matthias Millesi, Magnus Küß, Georg Widhalm, Engelbert Knosp

Abstract: Meningiomas account for approximately 35% of all primary intracranial CNS tumours and the mean age at the time of diagnosis is 63 years. Currently, the best-evaluated risk factor in association with meningiomas is exposure to ionizing radiation. Depending on their location, meningiomas can present with a wide variety of symptoms and in several locations; they can reach a reasonable size before becoming symptomatic due to their slow growth. On the other hand, in specific regions, early presentation is also possible due to compression of neurovascular structures. Ever since the publication by Harvey Cushing, surgical removal has been the treatment of choice and the risk of recurrence depends strongly on the degree of resection. In the past decades, due to higher morbidity rates with removing skull base meningiomas due to the close proximity to vital neurovascular structures, radiosurgery has become a viable option in specific locations for treating residual tumour tissue or as stand-alone therapy in case of cavernous-sinus meningiomas. Nevertheless, surgical resection remains the main treatment modality for most intracranial meningiomas. Eur Assoc NeuroOncol Mag 2013; 3(3): 112–7.

Key words: meningioma, complete resection, skull base surgery, radiosurgery

Introduction

Epidemiology/Aetiology

Being the most common primary brain tumour, meningiomas account for approximately 35% of all CNS tumours. In most cases, meningiomas are primarily diagnosed in the elderly population. Mean age at the time of diagnosis is 63 years and the overall incidence for meningiomas is 7.10 per 100,000. Among the patients developing a meningioma, there is a marked female preponderance with a female : male ratio of 1.7–2:1. In meningiomas located along the spinal cord, the female preponderance is even stronger approaching 90% of all cases [1–4].

In autopsy studies, the prevalence of meningiomas is as high as 2.3–2.8% [1–5]. Arachnoid cap cells are assumed to be the cells of origin as they compose a single fibroblast-like cell layer that can show thickened epitheloid nests of several layers with increasing age [5].

Due to their slow growth in general, nearly ¾ of meningiomas are asymptomatic and are found incidentally on neuroradiologic imaging for other reasons. Symptoms that can occur are mostly due to the space-occupying effect and depend on the specific location of the tumour. Other general symptoms that can occur are headache, visual impairment, and seizures [2, 3].

Currently, the best-evaluated risk factor is exposure to radiation. Low-dose exposition to radiation in nuclear bomb survivors or following treatment for tinea capitis as well as high-dose radiotherapy for brain tumours or haematooncologic diseases has been associated with meningioma formation besides other diseases in various follow-up studies [6–8].

Because of the fact that women show a higher incidence than men, hormonal factors as elements influencing the development of meningiomas have been studied and expression of progesterone, oestrogen, and androgen receptors has been identified in a number of tumours. The functional status of these receptors remains to be studied and meningioma is far from being dependent on hormonal stimulation [4, 9].

Hereditary susceptibility has been discussed as a major risk factor. Genetic mutations associated with meningioma development are neurofibromatosis type 2 (NF2), Li-Fraumeni syndrome, Cowden syndrome, and Gorlin syndrome. With NF2, there is a penetrance of almost 100% at the age of 60 years. Especially spinal meningiomas are frequent findings in patients with NF2. On the other hand, most cases of NF2 are spontaneous mutations without a family history. On the contrary, neurofibromatosis type 1 does not show a higher incidence of meningiomas [5, 10].

Pathology/Biological Behaviour

Currently, meningiomas are classified into 3 groups according to the WHO (World Health Organization) classification of 2007. Benign lesions account for approximately 80–92% of all meningiomas [2]. In 2007, brain invasion was implemented into the current classification as a feature of WHO grade-II and -III tumours. Therefore, the number of atypical meningiomas classified as WHO grade-II has risen. Currently, the proportion of atypical and anaplastic meningiomas is approximately 20–25% with 5–20% accounting for WHO grade-II tumours and 1–5% accounting for WHO grade-III meningiomas [4, 5, 11, 12].

Besides brain invasion, further characteristics of WHO grade-II tumours are chordoid and clear-cell histological subtypes as well as frequent mitoses (≥4 per high-power field) or 3 as aspects of the following: hypercellularity, prominent nucleoli, small cells, and foci of spontaneous necrosis. For WHO grade-III anaplastic meningiomas, histological characteristics are excessive mitoses (≥20 per high-power field) or frank anaplasia and differentiation resembling sarcoma, carcinoma, or meningioma. Furthermore, histological subtypes of papillary or rhabdoid meningiomas are classified as grade III [13].
Various signalling pathways have been studied concerning the growth pattern of meningiomas, disruption of the arachnoid layer, as well as the great variability of peritumoural brain oedema formation. Vascular endothelial growth factor (VEGF) is probably the best-studied angiogenic factor in association with biological behaviour and clinical outcome of meningiomas.

Other investigated factors upstream or downstream of the angiogenic pathway associated with VEGF are hypoxia-induced factor 1α (HIF-1α), carboanhydrase (CA-IX), and glucose transporter 1 (Glut-1). In a recent analysis, higher-grade meningiomas have shown a correlation with a significant higher expression of CA-IX, VEGF, and HIF-1α [11, 12, 14].

### Location

Meningiomas growing on the convexity form the biggest group followed by tumours growing along the falx and parasagittal meningiomas. Up to 25% of all intracranial meningiomas show involvement of structures of the skull base. Of those, lesions in the anterior cranial fossa form the biggest group. Spinal meningiomas account for approximately 12% of all meningiomas and form the largest group of spinal intradural tumours [15–18].

### Treatment

The primary treatment of meningiomas is surgery and little has changed since the publication of the monograph by Harvey Cushing and Louise Eisenhardt in 1938 except for meningiomas arising in the central skull base [19]. In 1957, Donald Simpson published a hallmark paper on the significance of complete surgical resection for the rate of recurrence. He gradually classified surgical outcome and could demonstrate a gradual increase of recurrences in tumours that have not been completely resected. Regarding skull base meningiomas, Simpson stated that reaching macroscopically complete removal is hardly possible [20]. Due to refined techniques in surgery, this is not true in all locations [21, 22].

Ever since, macroscopically complete tumour resection with excision of altered dura and bony structures should be the goal of surgical treatment if achievable without significant morbidity [23–26].

In a study by Hasseleid et al, the importance of complete removal was shown again regarding recurrence rates of patients undergoing Simpson grade-I versus -II resections in convexity meningiomas [23].

In recent years, a number of other studies have also re-evaluated the outcome of more aggressive surgical strategies [24, 25]. In 2010, Sughrue et al showed that recurrence rates for Simpson grade-I resections did not differ significantly compared to Simpson grade-II, -III, or -IV resections. Nevertheless, they found a gradual decrease in 5-year progression-free survival (PFS) from 95% in Simpson grade-I to 85% in Simpson grade-II, 88% and 81% in Simpson grade-III and Simpson grade-IV removal, respectively [24].

Radiotherapy or stereotactic radiosurgery (SRS) has proven its value in treating residual tumour tissue. In anaplastic tumours following subtotal resection (STR) or partial resection (PR), broad agreement about the need for radiotherapy exists. The necessity of radiotherapy following resection of an atypical meningioma is still a matter of discussion and a consensus has not been found yet [13, 27]. In recent studies investigating these results, a trend towards a decreased rate of recurrence in patients receiving postoperative radiotherapy was noted. However, sample sizes were too small to detect statistical significance [27–29].

Depending on their location, various treatment strategies have been developed over the last decades.

### Convexity Meningiomas

In convexity meningiomas, the primary form of treatment remains complete surgical resection since it is the easiest location to achieve Simpson grade-I resection with acceptable morbidity. New neurological deficits occurred in only 3 patients postoperatively in a study performed by Morokoff et al including 163 convexity meningiomas [23–25, 30, 31]. Although Morokoff et al included only patients undergoing Simpson grade-I resection, the rate of recurrence was as high as 4.3% [31]. Various additional factors besides extent of resection and histological grade have been investigated to be responsible for tumour recurrence. In 1986, Borovich et al showed the existence of satellite lesions up to 3 cm in distance from the primary tumour at the time of initial treatment. To achieve gross total resection (GTR), they postulated a modified Simpson grade-“O” resection with excision of adjacent dura up to 4 cm if feasible [18, 32]. Besides these satellite lesions, the focus of interest was also directed towards the importance of a cleavage plane to completely resect meningiomas. A study performed by Alvernia et al showed a higher rate of recurrence in tumours that showed a subpial cleavage plane as a sign for pial vascular supply and brain-invasive growth pattern compared to meningiomas with an extrapial cleavage plane. A further modification of the Simpson classification was contemplated with respect to small tumour remnants due to cortical invasion or invasion of cortical blood vessels [33].

### Parasagittal and Falcine Meningiomas

Difficulties in resecting parasagittal and falcine meningiomas occur with involvement of the superior sagittal sinus (SSS) and large bridging veins. Due to the deep localization within the interhemispheric fissure, achieving GTR is a surgical challenge. In case of parasagittal meningiomas with a stenotic or an obstructed sinus, complete surgical resection with excision of the excluded sinus is possible in the frontal region, but not always possible in central and parietal localizations. With the advent of stereotactic radiosurgery (SRS), treatment strategies for parasagittal meningiomas with a patent sinus have changed. For large tumours involving a patent sinus, GTR is attempted. If a residual tumour is present adhering to large bridging veins or the sinus, conservative treatment with serial magnetic resonance (MR) imaging can be performed in case of benign tumours. Postoperative SRS can be performed in small tumours involving a patent sinus and residual tumours that show progression on MR imaging, and tumour control rates as high as 89% can be achieved [34–36].
Current Surgical Strategies in the Treatment of Intracranial Meningiomas

Our policy for meningiomas invading the SSS is to resect the tumour together with the SSS anterior to the coronal suture. In case of a meningioma behind the coronal suture, the tumour is resected to the lateral wall of the sinus leaving all bridging veins intact. No efforts are made to incise or remove tumour from within the SSS. Resection and reconstruction of the sinus have been advocated but result in an unacceptably high risk of complications [35, 37]. In those cases with residual tumour within the SSS or its walls, radiosurgery is a given option.

Skull Base Meningiomas
As mentioned, up to 25 % of all tumours involve structures of the skull base, where complete removal is hardly possible without significant morbidity due to the close relationship to cranial nerves or large vessels supplying or draining blood from the brain [20, 26, 38–40].

Various treatment strategies exist for different regions of the skull base. For tumours arising in an accessible localization, surgical resection remains the modality of choice.

Olfactory Groove Meningiomas
In case of olfactory groove meningiomas, complete surgical resection can be achieved with modest morbidity. At the time of presentation, these tumours can already have reached an imposing size and mental changes represent the most common symptoms. A typical combination in olfactory groove meningiomas is the Foster-Kennedy syndrome consisting of anosmia, ipsilateral optic atrophy, and contralateral papilloedema. In a series of 82 olfactory groove meningiomas by Nakamura et al, complete resection (Simpson grades I and II) was achieved in 92 % using a unilateral frontolateral or bifrontal approach [41]. The preferred approach at our institution is pterional because of a lesser surgical trauma compared to a bilateral approach as well as early identification of the optic nerve and internal carotid artery.

Tuberculum Sellae Meningiomas
In contrast to olfactory groove meningiomas, due to early compression of the optic nerve or the chiasm, tuberculum sellae meningiomas are usually smaller at the time of diagnosis and visual impairment (Figure 1) is the typical first symptom. The combination of primary optic atrophy and bilateral hemianopsia occurring in cases of tuberculum sellae meningiomas has been termed chiasmal syndrome. Due to the close relationship to neurovascular structures, their surgical resection can be challenging. Nevertheless, gross total removal and improvement of visual function should be the aim of surgical resection. Nakamura et al published a series of 72 tuberculum sellae meningiomas resected via a transcranial approach and

Figure 1. Tuberculum sellae meningioma found due to blurred vision operated via a right-sided subfrontal approach.
GTR (Simpson grades I and II) was achieved in 66 patients (91.7%). Visual impairment was present in all of these cases. Postoperative visual examination was performed in 56 of these patients. Improvement of visual function was noted in 38 of 56 patients (67.9%) while in 11 patients (19.6%) visual function remained stable. Deterioration of visual impairment was found in 7 patients (12.5%).

As an alternative to transcranial resection of tuberculum sellae meningiomas, an endoscopic transsphenoidal approach can be a suitable alternative in selected cases without lateral extensions [42–44].

Sphenoid Wing Meningiomas

According to their location on the lesser wing of the sphenoid bone, sphenoid wing meningiomas are subclassified into lateral, middle, and medial meningiomas. Besides headaches, symptoms vary according to their location. In a series of 59 patients by Sughrue et al, seizures were the most common symptoms in lateral and middle sphenoid wing meningiomas, whereas visual impairment was the most common symptom for medial sphenoid wing meningiomas. Regarding surgical outcome, a trend towards a lower rate of GTR for medial meningiomas was shown but differences were not statistically significant. Nevertheless, for lateral and middle sphenoid wing meningiomas, complete surgical resection remains the treatment of choice.

Due to the close relation and involvement of the cavernous sinus as well as encasement of the internal carotid artery, subtotal resection with postoperative SRS can be a viable option for treatment of selected cases of medial sphenoid meningiomas [45].

Meningiomas of the Cavernous Sinus

In the past, large efforts have been made in surgical resection of meningiomas involving the cavernous sinus. Sekhar et al stated in a report about the surgical treatment of intracavernous neoplasms that meningiomas are probably most difficult to remove. In his series of 42 patients, neurological outcome of cranial nerves (CN) was stated as follows: loss of olfaction occurred in 3 patients due to the chosen subfrontal surgical approach. Dramatic loss of vision occurred in one patient and the loss of corneal sensation due to invasion of the ophthalmic nerve (V1) was found in 4 patients. Furthermore, permanent paralysis of the abducens nerve was found in 4 cases [46].

In a series by DeMonte et al, results of surgical resection of 41 cases of benign meningiomas were published. Complete removal was achieved via an orbito-zygomatic approach in 31 patients (76%). In 3 cases, cerebral ischaemia occurred postoperatively due to injury of small perforating vessels or the middle cerebral artery. Furthermore, episodes of transient diabetes insipidus and non-fatal pulmonary embolism occurred in another 3 patients. A cerebrospinal fluid (CSF) leak was reported in another 2 cases [22].

In a series of 29 meningiomas of the cavernous sinus at our institution, deterioration of preoperative oculomotor paralysis did occur in 14% of patients. Improvement of oculomotor function was noted in 43%. Deterioration of trochlear nerve function was seen in 4 patients. Impairment of the abducens nerve was noted in 55% of patients preoperatively and improvement was noted in half of them. The other half remained unchanged. Additionally, a new abducens nerve deficit was found in one patient who had good abducens nerve function preoperatively [38].

Due to these higher morbidity rates and with further technological development, stereotactic radiosurgery has become the treatment of choice for cavernous sinus meningiomas. In 2000, Roche et al presented a series of 80 patients undergoing SRS and a tumour control rate of 92.7% could be achieved [39, 40].

Current treatment standards for cavernous sinus meningiomas consist of primary SRS or radiotherapy (Figure 2) in case of close proximity to the optic nerves and reported tumour control rates in the current literature reach up to 96% [40, 47].
Petroclival Meningiomas

Due to its location in the posterior fossa and close proximity to cranial nerves and other vital neurovascular structures, treatment of petroclival meningiomas can be challenging and the best treatment strategy is still a matter of discussion. A higher risk of developing new cranial nerve deficits, either transient or permanent, has to be seen alongside the potentially curative aspect of surgical resection. Early intraoperative visualization of neurovascular structures is regarded as a major requirement to preserve neurological function, therefore extensive approaches have been developed. However, complete surgical removal also highly depends on the existence of a dissection plane. In cases without such a dissection plane or with infiltration of neurovascular structures or the brainstem, subtotal removal can be reasonable. For small asymptomatic tumours, SRS can represent a viable option given the lack of an exact histological diagnosis [47–49].

Foramen Magnum Meningiomas

In case of a meningioma arising at the foramen magnum, surgical resection remains the primary treatment modality. Borba et al published a series of 15 tumours arising at the foramen magnum – in 2 cases complications occurred related to surgery. One patient suffered from transient XII cranial nerve (CN) palsy and a cerebrospinal fluid (CSF) leak and one patient showed transient worsening of a motor deficit with improvement after 6 months. Especially ventral or ventrolateral tumours can pose surgical challenges and as for petroclival meningiomas, various surgical approaches have been developed to optimize operative exposure in order to protect vital neurovascular structures. Talacchi et al recently presented their results in 64 cases of ventral and ventrolateral foramen magnum meningiomas. A dorsolateral surgical approach was chosen in each patient and GTR could be achieved in 52 patients (81 %). Pre-existing cerebellar deficits and long-tract signs improved in 74 and 77 %, respectively, preoperative cranial nerve deficits showed improvement in 27 %. On the other hand, new cranial nerve deficits were noted in 23 patients (CN IX–XII) with difficulties with swallowing being the most common symptom. All of these cases were managed conservatively with prevention of aspiration being of utmost importance. After one month, swallowing improved sufficiently in 71 % [50–52].

Conclusion

Surgical resection is the primary treatment modality for intracranial meningiomas with gross total resection being the goal of surgery in case of convexity meningiomas or parasagittal or falciine meningiomas. Meningiomas involving the SSS or the transverse or sigmoid sinus should be resected to the greatest extent possible but utmost care has to be taken not to compromise venous drainage.

In case of meningiomas arising at specific locations at the skull base surgical excision can be challenging and the best treatment strategies are the topic of ongoing development in skull base surgery. In certain skull base meningiomas, Simpson grade-I resection is hard to achieve with an acceptable morbidity due to close relations to major blood vessels and cranial nerves.

With the advent of radiosurgery, new treatment options have become available for those lesions in close relation to vital neurovascular structures. Figure 3 shows different treatment approaches in skull base meningiomas. Radiosurgery became the treatment of choice in cases of meningiomas arising within or invading the cavernous sinus due to high morbidity during surgical exposure. In case of petroclival meningiomas, there is an ongoing discussion whether radiosurgery is a viable option in small, asymptomatic meningiomas. Tumours arising in other locations of the skull base are usually amenable to surgical resection.

A major drawback of radiosurgery as a stand-alone therapy is the lack of histopathological diagnosis as well the lack of a precise grading.

At our institution, symptomatic tumours, meningiomas > 3 cm in diameter, as well as documented growth of a lesion are indications for surgical excision. Furthermore, the existence of a peritumoural brain oedema (PTBE) as an expression of the disruption of the arachnoid layer are indications for surgery.

Smaller, asymptomatic lesions without the occurrence of PTBE and highly calcified tumours may be followed conservatively.

Conflict of Interest

The authors declare there is no conflict of interest.

References:


Spinal Meningiomas: A Comprehensive Overview and Own Experience

Gedeon Perneczky, Michel Loyoddin, Horst Schappelwein, Camillo Sherif

Abstract: Among intradural extramedullary tumours, neurinomas followed by meningiomas are the most common histological entities. Spinal meningiomas constitute only for 7.5–12.7 % of all meningiomas. More than 2/3 of all spinal meningiomas are located in the thoracic spine. 86–95 % of the tumours are found purely intradurally. Risk factors are ionizing radiation, genetic predisposition, and female gender.

Introduction

Approximately 2/3 of all intraspinal neoplasms are intradural extramedullary tumours. Among those, neurinomas followed by meningiomas are the most common histologic entities [1]. Spinal meningiomas occur less frequently than intracranial meningiomas. They constitute only for 7.5–12.7 % of all meningiomas [2].

Comparable to intracranial meningiomas their incidence is 2–3 times higher in women than in men. These lesions are a typical disease of the middle or older age [3, 4].

The purpose of this article is an update of this disease based on a literature review and our own experience. Additionally, we present our most recent own consecutive case series collected between 2010 and 2012.

Localization

More than 2/3 of all spinal meningiomas are located in the thoracic spine (67–84 %), followed by 14–27 % in the cervical spine and 2–14 % in the lumbar spine. Typically, they are found purely intradurally in 86–95 %. Only 5–14 % have an additional extradural part [3–7]. On rare occasions, spinal meningiomas occur completely extradurally (3–9 %) [4, 7]. In the latter, in 2 locations they are predominantly dumbbell tumours causing an enlargement of the intervertebral foramen.

Risk Factors

Most publications focus on risk factors for the development of meningiomas in general [8]. Only a few papers refer directly to spinal meningiomas.

Ionizing Radiation

Hiroshima and Nagasaki survivors showed an elevated risk of developing intracranial meningiomas. Their risk depended on their vicinity to the epicentre of the nuclear explosion [9–11]. Several US studies reported a significant correlation between X-ray dosage prior to the 20th year of life with the risk of meningioma development [12–14]. Also acute lymphoblastic leukaemia (ALL) patients showed an elevated risk of meningioma development after a latency of decades [15–20]. The latter lesions are more frequently multifocal, atypical, or malignant [21, 22]. It is unclear whether this risk is caused by irradiation of the whole neuroaxis alone or whether additional factors such as chemotherapy are causative.

Genetics

Changes or complete or partial loss of chromosome 22 may play a role in the development of meningiomas. Other changes in the gene loci are also associated with carcinogenesis and could play a role in the development of spinal meningiomas [23]. Contradictorily, Ketter et al. documented a series of 23 spinal meningiomas, all of which showed a regular set of chromosomes or a monosomy 22 [24]. Additionally, neurofibromatosis type 2 with mutation of chromosome 22Q12 is an autosomally recessive, hereditary disease with elevated risk of developing meningiomas or schwannomas [25]. In a very recent publication, changes in the gene SMARCE1 could be identified in relation to an increased incidence of familial spinal meningiomas [26].

Gender

Women have a 2–3 times higher incidence of meningioma development. Additionally, the gender-related risk is slightly
higher in women who take contraceptives or receive hormone replacement therapy [27–29]. The coincidence of breast carcinoma and meningiomas has been observed for many years [30]. It may be due to a joint risk profile (age, genetics, environmental factors in interaction) [31, 32].

Symptoms
At the beginning of the disease, mostly sensation disorders, a discrete spasticity of extremities, and gait disturbance are observed. Due to the slow growth tendency of these tumours, their symptoms remain often untypical for a long period of time. Because of the higher patient age (> 50 a) the altered gait pattern is often misinterpreted as ordinary joint pain. Due to these non-characteristic clues the correct diagnosis is often significantly delayed, especially in the most frequent location of the thoracic spine. Diagnosis remains unclear until the typical vesical and rectal disorders and progressive paraparesis emerge. With the help of magnetic resonance imaging spinal meningiomas are diagnosed earlier than several years ago.

Management

Diagnosis and Operative Planning
The methods of choice are magnetic resonance imaging (MRI) scans, including T1- and T2-weighted images, with and without contrast agent (Figure 1). They show spheric contrast-enhancing tumours with their intradural and extra-medullar localization [33]. The tumour matrix is in a lateral position in most of spinal meningiomas, more often dorsolateral than ventrolateral. Extensive growth and infiltration of the pia are significantly less frequently observed than in intracranial meningiomas. It is sometimes difficult to differentiate meningiomas from neurinomas in the rare cases when meningiomas grow intra- and extradurally (dumbbell tumours). Distinct calcifications, which can only be recognized in computed tomography (CT), suggest a meningioma. Larger cystic areas rather indicate a neurinoma.

Cystic changes are very rare in spinal meningiomas in contrast to calcifications. The latter may influence the surgical approach especially in ventrally positioned tumours. For this reason, we believe that it makes sense to perform a CT scan in ventrally positioned tumours to estimate the extent of calcifications prior to surgery. In central calcified tumours that are completely covered by the spinal cord total removal via a dorsal or dorsolateral approach is very difficult and may only be carried out at an elevated neurological risk.

Surgical Technique
We prefer the dorsal approach except for a few cases, sometimes laterally extended by partial resection of the vertebral joint or the head of rib in the area of the thoracic spine [2, 5, 33]. The rare ventral approach is discussed in the literature as an alternative mainly for purely ventral tumour locations completely covered by the spinal cord. The intention is to minimize manipulations at the spinal cord. The advantage of the ventral approach is a lower neurological risk for the spinal cord and better chance of radical removal in ventral tumours. The disadvantages are complications caused by the larger approach with vertebral body resection and the need for stabilization.

The application of intraoperative ultrasound [34] improves the precise localization and helps avoid unnecessarily large approaches with multi-level laminectomy. Depending on the longitudinal extension of the tumour we try to remove the vertebral arch only at one level. In many cases, surgery can be performed via an extended interlaminar approach with partial preservation of the vertebral arches. In younger patients, the vertebral arch should be preferably restored by laminoplasty, especially in the lumbar and cervical spine. The dura is opened paramedially vertically depending on the lateralization of the tumour. In ventrally positioned tumours, the incision can be enlarged laterally by way of a dural flap. Resection of the denticulate ligaments allows for a better view, especially of ventral tumours. Opening the dura directly at the tumour site instead of choosing the common median incision leaves the spinal cord mostly covered by the dura during surgery. This reduces the risk of spinal cord impingement in the slit-like area of the dural opening. Comparable to intracranial meningiomas, spinal tumour de-
Spinal Meningiomas

Intraoperative Neuromonitoring

The use of intraoperative neurophysiological monitoring (IOM) is based on the observation that the function of neurological structures usually changes by a measurable value before it completely fails [35].

In contrast to laboratory tests, IOM is carried out in a “hostile environment” with permanent electric smog which may impair monitoring.

In the area of the spine, somatosensory evoked potentials (SEP) – monitoring ascending pathways, dorsal column somatosensory system, and motor-evoked potential (MEP) – monitoring descending pathways and the corticospinal motor system – are applied and used in our monitoring setting.

In general, tibial and median SEP are applied depending on the location of the pathology. Mostly surface values are derived but also subcortical components may be extrapolated.

The use of SEPs alone for the monitoring of motor function is inadequate. For MEP, electrical transcranial stimulations are applied and EMGs are derived from the extremities [36–39].

IOM requires close cooperation of all groups involved in spinal tumour surgery [40]. Also anaesthesia has to be adapted to IOM, as temperature and blood pressure may influence the measured potentials. Additionally, “lost” electrodes may cause erroneously positive monitoring results and can therefore influence the surgical strategy and prolong operation time considerably.

Our Recent Case Series

Between 1/2010 and 12/2012, 80 patients were operated on spinal tumours with remarkable female prevalence (2.5:1) at our department.

The number of neurinomas (36%) was nearly equivalent to meningiomas (34%), followed by metastases (14%) and other entities (16%) like ependymoma, cavernoma, and compressive arachnoid cysts.

Postoperative Outcome

The great majority of patients have excellent postoperative outcomes (26/27 in our series). More than 90% show clinical improvement with ameliorated gait pattern or even restart walking without assistance [2–5, 7, 33]. Possible reasons for rare clinical deterioration are manipulations of the spinal cord, considerably sudden extension, or ischemia due to a vascular lesion. A vascular disorder may occur mainly in meningiomas at the thoracolumbar region in proximity to the arteria radicularis magna. In such cases, it makes sense to refrain from radical resection and leave small tumour parts adhering to the artery untouched. Rare complications requiring revision surgery include epidural haematomas (2–5%) and cerebral spinal fluid fistulas (<1%). In our series, we had no case of epidural haematoma or fistula, but 2 cases of tumour recurrence.

Tumour Recurrence

The recurrence rate in spinal meningiomas is significantly lower than in intracranial meningiomas. As expected, total removal at first surgery is the key factor to avoid tumour recurrence. En plaque meningiomas, which often cannot be radically removed, show a significantly higher relapse rate. This is also the case in tumours with ventral matrix or in cases with severe calcifications of the tumour. Due to higher rates of subtotal tumour removal close to the arteria radicularis magna the recurrence rate in this location is also higher.

Concerning the treatment of tumour recurrence, reoperation is the first-line treatment option. The role of radiotherapy is still controversially discussed [3, 7, 33]. However, it is a possible treatment option in recurring tumours. During the years to come its significance will grow due to the development of new radiotherapeutic alternatives such as the proton beam radiation.

So far, we indicate radiotherapy only after recurrent surgery or in very old patients with an increased surgical risk profile. In cases of subtotal tumour removal, we closely follow the patients with special focus on further tumour growth (“wait and see”).

Discussion

Comparable to intracranial meningiomas, we find histological subtypes such as meningotheliomatous, hypoplastic, transitional, and psammomatous tumours.
The first 2 types are predominant in spinal meningiomas. Interestingly, the histological type does not seem to influence prognosis. Compared to intracranial meningiomas spinal tumours less frequently belong to WHO grades II and III [1–7]. Nevertheless, spinal meningioma represents an entity of its own.

Surgery is always the therapy of choice in spinal meningiomas. In the vast majority of patients, the operation results in significant improvement of the preoperative neurological deficits [2, 4–6, 33].

In rare tumours exclusively located ventrally or in close proximity to the artery radicularis magna, the risk of complete removal has to be evaluated against the preservation of function on a case-by-case basis. In these patients, age plays an important role for the decision.

Concerning our surgical philosophy we prefer dorsal approaches whenever possible. Also, ventral tumours normally displace the spinal cord and thus create enough space for surgical manipulation using the dorsal or dorsolateral approach. In very rare cases of ventral tumours located exactly in the midline, the spinal cord may cover the tumour bilaterally. Only in these cases a ventral approach with vertebral body resection is necessary.

Conclusions

During the last 3 decades the prognosis of spinal meningiomas has improved for the following 3 reasons:

- Significantly earlier diagnosis because of magnetic resonance imaging and, consequently, better neurological status at the time of surgery.
- Reduction of surgical trauma and improvement of functional outcomes due to improved localization with the help of intraoperative ultrasound and the use of CUSA dissection and intraoperative neuromonitoring techniques.
- Avoidance of secondary defects (instabilities and postoperative deformities after years) with the help of lamino-plasty when applying the dorsal approach and improved stabilizing techniques including spinal body replacement when applying the ventral approach.

Conflict of Interest

No author has a conflict of interest related to this paper.

References:


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 aspects 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 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 (radiotherapy) 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
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 tumours 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 para- sellar meningiomas, however, a large series with appropriate follow-up is clearly needed to confirm the proposed beneficial efficacy and safety profile, i.e., the reduction of optic neuropa thy.

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 proton 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 meningiomas.

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).

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## 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.
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.

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.
Drug Therapy for Recurrent, Progressive, Atypical, and Malignant Meningiomas

Christine Marosi

Abstract: So far, no breakthrough for systemic therapy of recurrent meningiomas has been achieved. Despite a multitude of optional drugs there is so far no standard of care. On the other hand, although the disease is rare, each neuro-oncological centre is faced with some patients with unmet treatment needs. Future attempts of drug therapy in meningiomas should be planned for the distinct subgroups of these heterogeneous tumours. Cohort studies should be able to answer the question of whether meningiomas occur more rarely or do not become symptomatic in individuals under treatment with statins, glitazones, or calcium channel blockers. If found effective, such drugs would be suitable as first-line treatment in patients with grade-I recurrent meningiomas, as well as for those indications most probably long treatment periods appear necessary. For patients whose tumours recur with such drugs, oral mTor antagonists such as everolimus or targeted therapies could potentially represent further treatment options which should be evaluated in multicentre phase-II studies, whereas cytotoxic drugs with severe side effects such as trabectedin could perhaps be investigated for recurrent malignant meningiomas after all other options have been exhausted.

Key words: meningioma, statin, tyrosine kinase inhibitor

Introduction

Only a minority of patients with meningioma are referred to neuro-oncologists for therapy. Nevertheless, this task is challenging as there is currently no established therapy for patients with recurrent, progressive, or malignant meningiomas.

Meningiomas are the most frequent primary brain tumours but their incidence might still be underestimated [1] as the VITA study, a cohort study on healthy elderly people, showed a twice-as-high incidence of indolent meningiomas in asymptomatic women aged 75 years [2], corresponding to a calculated prevalence of 2800/100,000 clinically silent meningiomas in 75-year-old women. The incidence of meningiomas increases with age, with a peak incidence in the sixth decade [3, 4]. A large series on > 1600 patients with meningiomas who underwent surgery in a single centre showed that non-skull-based location and age > 65 years were independent risk factors for higher-grade meningiomas with ORs of 1.779 and 1.5, respectively [5].

The main part of meningiomas can be curatively resected. Modern microneurosurgery has developed with the challenge of refining the techniques of resection of “difficult” meningiomas. However, some meningiomas cannot be resected due to their involvement of vital structures; some WHO grade-I meningiomas recur after surgery, as do atypical and malignant meningiomas. Most of them respond to radiation, either fractionated radiotherapy or radiosurgery.

Still, some meningiomas exhaust all local therapies and patients require systemic treatment. Those patients have usually undergone several neurosurgical procedures and repeated courses of radiotherapy and/or radiosurgery when they are presented to the neuro-oncologist, usually because of ongoing progression of a far advanced disease. Most of these patients are heavily symptomatic from their meningiomas, presenting with pain, neurological deficits, and meningioma-related seizures. These patients may already receive treatment for their seizures as well as against pain and often against depression.

During the last years, basic research has elucidated the pathways associated with the proliferation and recurrence of meningiomas [6–16], providing better understanding of the pathophysiology of meningiomas and suggesting potential therapeutic targets. In this review, data accumulated on systemic treatment of meningiomas will be briefly reviewed and the potential development of systemic therapies reflected.

Genetic Background

Meningiomas were one of the first solid tumours in which a characteristic genetic aberration, a deletion from the long-arm chromosome 22, was found [17]. This aberration leads to loss of the tumour suppressor gene coding for the neurofibromatosis 2 tumour suppressor gene product (Merlin) which has been found in up to 40–60 % of sporadic meningiomas. Merlin is a negative regulator of the mTor complex 1 and positive regulator of mTor complex 2, resulting in cell proliferation [18–20]. These findings imply that antagonising mTor could be a successful therapeutic strategy in meningiomas depending on mTor deregulation. In fact, at the 2012 meeting of the European Society of Medical Oncology (ESMO) 2 groups presented in vivo models where mTor inhibition by everolimus or by everolimus plus octreotide showed an inhibitory effect on mouse meningiomas [21, 22]. Currently, one clinical trial with everolimus in recurrent or progressive meningiomas is listed at www.clinicaltrials.gov.

Treatment

There is no established or approved systemic treatment for patients with recurrent, progressive, atypical, or malignant meningiomas that has shown efficacy in a randomized controlled trial. Nevertheless, 3 systemic treatments – hydroxyurea, interferon-α, and somatostatine analogues – are listed for the treatment of recurrent meningioma by the Central

Most of the published experience relies on small (often retrospective and monocentric) series or case reports. Interpretation of these small studies is difficult, as they often include very heterogeneous patient samples as well patients with recurrent WHO grade-I meningiomas as well as with atypical and malignant meningiomas which have indeed a different prognosis, furthermore patients who are at different stages of their illness trajectory, either newly diagnosed atypical or anaplastic meningiomas or after failure of one or multiple radiation therapies, which also has to be considered before interpreting outcomes of a given intervention. The compilation of all those different meningioma patient categories has to be seen in the context of the rarity of the disease and of the lack of interest of potential sponsors for trials for meningioma patients.

Recurrent, progressive, atypical, or malignant meningiomas are orphan diseases – only a joint effort of an international study group would succeed in recruiting patients for a pivotal study to test a promising hypothesis. Even the treatments recommended by the NCCN guidelines rely on a low evidence level.

Unlike gliomas, meningioma vessels do not have a blood-brain barrier and circulating drugs penetrate into the meningiomas. However, potentially increased intratumoural pressure in the meningioma could be high enough to preclude the penetration of drugs from the blood stream eg in meningiomas, causing large rims of vasogenic oedema.

Another factor to be considered before initiating and evaluating drug therapies for these patients is that most of them present with complex medications involving enzyme-inducing antiepileptic drugs, non-steroidal antirheumatic drugs against pain, and drugs that might modify intestinal resorption of other drugs such as proton pump inhibitors. So the bioavailability of any study drug might be heavily affected by the often extensive co-medication of this patient subgroup.

Appreciation of the systemic therapeutic options of systemic therapy in meningiomas has been reviewed in re-evaluated repeatedly in the last years [24–29] and in the current issue by Simó et al [30].

It would be of no benefit to repeat that hormonal treatment with mifepristone has been found ineffective [31] or that only in vitro experiments showing effectivity of the drug in cell lines of atypical and malignant meningiomas [58].

Targeted Therapies

Over the last years, basic science has shown that meningiomas express potential drug targets on their cell membranes [9, 59–64]. Due to the lack of efficacy of treatment strategies against recurrent, progressive, atypical, and malignant meningiomas, targeted therapies interfering with potential targets identified in progressive meningiomas were investigated as soon as they became available. Formal prospective studies are rare; the present state appears more like a hypothesis-finding phase hopefully preceding a phase with intense study activity.

Imatinib

It has been known for a long time that meningiomas express platelet-derived growth factor beta (PDGF-β) and that meningioma proliferation is stimulated by autocrine growth stimulation loops [59, 65–67]. Therefore, it was obvious to try treatment of recurrent meningiomas with molecules targeting the PDGF-Rα and the first available was imatinib.

The first data on 23 heavily pre-treated patients (13 benign, 5 atypical, and 5 malignant meningiomas) were disappointing with a progression-free survival (PFS) of only 2 months [68]. Reardon et al [56] treated 21 patients with hydroxyurea and imatinib, PFS6 was 61 %. Our own experience on 9 patients is favourable [69] but we observed a severe, fortunately reversible episode of hepatic toxicity in one patient [56, 68].

Gefitinib and Erlotinib

As the epidermal growth factor is often over-expressed, 25 patients with recurrent meningiomas (8 meningiomas WHO grade I, 9 atypical and 8 malignant meningiomas) were treated using either gefitinib (500 mg/day) or erlotinib (150 mg/day). For benign tumours, PFS6 was 25 % and PFS12 13 %. For atypical and malignant meningiomas, PFS6 was 29 % and PFS12 18 %. 32 % of patients maintained stable disease. Nevertheless, the authors considered treatment with epithelial growth factor antagonists as ineffective [70].

Bevacizumab

Recurrent meningiomas show increasing microvascular density and VEGF expression, suggesting a potential role of
neoangiogenesis in the proliferation of meningiomas [71–74]. Drugs targeting VEGF-R have been used in recurrent meningiomas, mainly in case studies [72, 75]. Based on our own experience, bevacizumab induces rapid clinical improvement in patients with significant peritumoural oedema. In a retrospective trial on 14 patients, PFS6 was observed in 86 %, but also one cerebral haemorrhage and one gastrointestinal perforation [76].

Multikinase Inhibitors
Several other inhibitors of PDGF are undergoing evaluation, including sunitinib, MLN518, dasatinib, AMN 107, pazopanib, sorafenib, CP673451, and CHIR 265; sunitinib and pazopanib also inhibit VEGFR 1, 2, and 3 as well as c-Kit, while sorafenib and CHIR 265 inhibit VEGFR, c-Kit, and Raf. These drugs may be more effective than imatinib as monotherapy against meningiomas but also present a higher risk for side effects [77].

Other Drugs
There are drugs approved for other clinical conditions showing efficacy against meningioma cell lines or primary cell cultures of meningiomas in vitro which have so far not been followed by in vivo testing or clinical trials [78].

Calcium Channel Antagonists
Calcium channel antagonists such as nifedipine, diltiazem, and verapamil can block calcium-mediated growth signals to PDGF-R and other growth factors expressed by meningiomas. It could be shown that meningiomas in patients treated with calcium channel blockers were generally smaller and less vascularised than those found in other patients [79].

AKBA
Park et al [80, 81] report that resin of the incense tree, acetyl-11-keto-beta-boswellic acid (AKBA), has been identified as an orally available inhibitor of topo-isomerase I and II and of lipooxygenase. AKBA showed potent cytotoxic activity on primo cell cultures of 11 meningiomas in the concentration of 2–8 μM/I.

Statins and Glitazones
A different approach was tested by Gehring et al on 2 cell lines of malignant melanoma and 2 cell lines from benign meningiomas [82–85]. They investigated the antiproliferative and even cytotoxic effects of drugs used to control hyperlipidaemia and non-insulin-dependent diabetes mellitus, alone and in combination.

Statins inhibit the rate-limiting step of hepatic cholesterol synthesis, thus indispensable for dividing normal or tumour cells. Moreover, statins are known to regulate Ras and Rho, inhibiting the activation of the mitogen-activated protein kinase pathway (MAPK).

Glitazones (thiazolidinediones) are drugs used for decreasing insulin resistance in diabetes mellitus type 2, but they have also been shown to induce cell cycle arrest, differentiation, and/or apoptosis in tumour cells in vitro by induction of reactive oxygen species (ROS).

Gehring et al [82] used both drugs alone and in combination and were able to demonstrate a synergistic proapoptotic effect of simvastatin with proglitazone in meningioma cell lines and will try their promising hypothesis in an orthotopic mouse model. It would be appealing to test such hypotheses in case control studies on patients with meningiomas whose medication is recorded. If meningioma recurrence is less frequent in patients with statins and/or glitazones and calcium antagonists which the patients received to treat diabetes and/or hypertension, prospective trials to prevent meningioma recurrence with these well-known and well-tolerated drugs should be planned. A multinational platform such as EANO could potentially endorse such a project.

Summary
To date, no breakthrough for systemic therapy of recurrent meningiomas has been achieved. The multitude of optional drugs shows that none of them so far could become a standard of care. On the other hand, although the disease is rare, each neuro-oncological centre has some patients with unmet treatment needs.

Future attempts of drug therapy in meningiomas should be planned for the distinct subgroups of these heterogeneous tumours. Cohort studies should be able to answer the question of whether meningiomas occur more rarely or do not become symptomatic in individuals under treatment with statins, glitazones, or calcium channel blockers. If found effective, such drugs would be suitable as first-line treatment in patients with grade-I recurrent meningiomas, as for these indications most probably long treatment periods appear necessary. For patients whose tumours recur with such drugs, oral mTor antagonists such as everolimus or targeted therapies could potentially represent further treatment options which should be evaluated in multicentre phase-II studies, whereas cytotoxic drugs with severe side effects such as trabectedin could perhaps be investigated for recurrent malignant meningiomas after all other options have been exhausted.

Conflict of Interest
None.

References:


Systemic Treatment of Recurrent Meningioma

Marta Simó1,2, Cristina Izquierdo1, Jordi Bruna1

Abstract: Meningioma is the most frequently diagnosed primary brain tumour. Although only a subset of meningioma patients suffer recurrence after standard therapy, these patients require further rescue treatment. Owing to the fact that meningioma over-expresses a great number of potential therapeutic targets, some systemic therapies have been evaluated in recurrent meningioma patients. Cytostatic agents, including combined chemotherapeutic regimens, hydroxyurea and temozolomide, are generally ineffective. Immunotherapy and hormonal therapy with somatostatin analogues have been suggested as potential therapeutic agents, even though studies have presented contradictory results. Recently, several studies using targeted therapies, such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor (VEGF) inhibitors, showed early promising results. However, additional long-term results are still under evaluation. Furthermore, the combination of various medical therapies, such as hydroxyurea and a PDGFR inhibitor, appears to hold some promise. This review provides an overview of the current rationale and evidence base for the various medical therapy approaches tested.

Keywords: meningioma, systemic treatment, chemotherapy, immunotherapy, hormonal therapy, targeted therapies

Introduction

Meningioma is the most frequently diagnosed primary brain tumour, accounting for nearly 35.5% of all primary brain tumours [1]. The prevalence of pathologically confirmed meningioma is estimated to be approximately 97.5/100,000 with an incidence rate of 7.1/100,000/year in the United States [1]. Meningioma is more than twice as common in females than in males (female: male ratio: 2.2:1) and it is also more common in the black population (black: white ratio 1.2:1). Moreover, the incidence increases progressively with age [1].

The majority of meningiomas are classified according to the World Health Organization (WHO) as grade I or so-called benign meningioma (nearly 80%). They present a prolonged progression-free survival (PFS) and overall survival (OS) (PFS and OS of 90% at 5 years). In contrast, high-grade meningioma, including atypical or WHO grade II and anaplastic or WHO grade III, differ in important aspects from their benign counterparts [2]. They represent up to 20–35% of all meningiomas, largely WHO grade II (approximately 20–30%). WHO grade-III meningioma represents only approximately 2% of all meningiomas. High-grade meningiomas exhibit an earlier peak incidence, with a small male predominance, and they present a worse PFS (60% and 30% at 5 years, for grades II and III, respectively) and OS (80% and 40% at 5 years for grades II and III, respectively) [3–5]. Atypical meningiomas carry a 7–8-fold increased risk of recurrence and about a 2-fold increased risk of death at 3–5 years compared to benign meningioma [3, 6].

Although there are scarce data regarding meningioma aetiology, 2 risk factors, ionizing radiation and genetic predisposition [7], have been described. Genetic aberrations such as focal chromosomal deletion of the NF2 (type-2 neurofibromatosis) gene on chromosome 22 and other more complex genetic changes have been associated with sporadic meningioma. Moreover, the complexity of genetic aberrations clearly increases with tumour grade [8].

Meningioma results from a clonal outgrowth derived from arachnoid cap cells and it presents some differential facts compared to other brain tumours. First, the natural history of meningioma is relatively unknown. This is due to the fact that meningioma has a prevalence of nearly 3% of subclinical disease as suggested by autopsy studies, and it is frequently discovered incidentally, introducing a detection bias [8]. Second, research regarding the molecular pathogenesis has been limited in comparison to gliomas. All these disadvantages, together with a lack of data from prospective series, make meningioma research a challenging area of study.

Standard therapy for meningioma includes extensive surgical resection for grade I followed by radiation therapy at front line for high-grade meningioma and at recurrence for grade I [9]. Although radiation therapy following surgical resection is the standard and recommended therapy for high-grade meningioma, there is still some controversy among studies [9]. Two currently ongoing phase-II trials (RTOG-0539, EORTC 22042-26042) are expected to provide better evidence to define optimal therapy in high-grade meningioma patients. Recurrence after completion of both therapies is managed by re-resection or re-irradiation when feasible [10, 11]. Unfortunately, there is no well-established treatment for meningioma patients with a good performance status who suffer recurrence after completion of these therapies. However, meningiomas have some particularities that make them susceptible and potential good candidates to respond to systemic therapies. The tumour is located outside the blood-brain barrier, it presents high vascularity supply, and it over-expresses a variety of potential therapeutic targets, including growth factors and their receptors, such as PDGF, EGFR, and IGF, angiogenesis factors such as VEGF and VEGF receptor, and hormonal receptors such as oestrogen, progesterone, androgen, growth hormone, and somatostatin receptors. In this setting, several approaches have been assessed, although most of them have yielded disappointing results [12]. Nevertheless, 3 of these tested systemic treatments – hydroxyurea, alpha-interferon, and somatostatin analogue – are recommended for the treat-
ment of recurrent meningioma by the Central Nervous System National Comprehensive Cancer Network (CNS NCCN, 2012) guidelines [13].

The aim of the present review is to provide an up-to-date survey of the advances of systemic treatments in recurrent meningioma patients.

Systemic Therapies

Several systemic therapies have been evaluated in recurrent meningioma patients, especially over the last 10 years. The systemic treatment attempts may be grouped according to the mechanism of action and the targets of the drug or combination of drugs assessed. The most relevant clinical trials are summarized in Table 1.

Chemotherapy

Treatment strategy using classic systemic cytostatic drugs has been based on 3 different approaches. First, the drugs and the chemotherapy schedules tested were selected according to the activity and the results obtained in experimental studies. Secondly, assuming that a meningioma has histopathogenic similarities with soft-tissue sarcomas, combined chemotherapeutic regimens used in these patients were reproduced in meningiomas. Lastly, chemotherapy regimens normally employed in glioma treatment have also been explored. Unfortunately, the antineoplastic agents studied, presented very limited results [26–29].

The first evidence from testing chemotherapy in recurrent meningioma came from combined chemotherapeutic regimens, including ifosfamide and mesna [27], cisplatin and doxorubicin [26], cyclophosphamide, adriamycin, and vincristine (CAV [28]), and, more recently, high-dose chemotherapy (carboplatin, etoposide, and thiopeta) followed by hematopoietic stem cells [29]. These case reports and small clinical series yielded disappointing results [26–29]. Cham-

berlain et al treated 14 WHO grade-III meningioma patients with CAV therapy just 2–4 weeks after adjuvant radiotherapy. Despite a substantial survival benefit of a median of 4 years, the authors suggested that this benefit was more related to the effects of radiotherapy than chemotherapy itself [28].

On the other hand, hydroxyurea (HU) is an antineoplastic drug that has demonstrated potent inhibition of cultured meningioma cells by inducing apoptosis in vitro [29]. The first phase-II trial with 4 recurrent meningioma patients resulted in prolonged disease-free survival (PFS at 6 months [PFS6] 100 %) with a 50-% partial radiographic response [14]. After these promising preliminary results, several subsequent phase-II clinical trials in recurrent meningioma patients suggested modest efficacy with an acceptable toxicity profile. The interval of PFS6 in these studies was 13–77 months [30–36]. The most important limitation of these studies is that patients were neither previously treated with radiotherapy nor were the drugs administered concomitantly [30–36]. Conversely, a large retrospective case series study with recurrent grade-I and high-grade meningioma treated with HU after surgery and radiotherapy demonstrated a median PFS of 2 months with no radiographic responses [15, 16]. In 2012, a phase-II trial combining HU with imatinib, a PDGF inhibitor, was published [17]. Recurrent grade-I and high-grade meningioma patients were included. Although there were no radiographic responses, median PFS was 7 months (14 and 5.3 months for grade-I and high-grade meningioma, respectively) and median OS was 5.5 and 1.5 years for grade-I and high-grade meningioma, respectively. Thus, although these results are modest and not directly comparable, combined treatment seems better in terms of PFS and OS compared to the studies with HU alone. In addition, another phase-II trial combining HU with verapamil, a calcium channel antagonist, is ongoing (Table 2). Calcium channel antagonists block the stimulatory growth effects by inhibiting calcium-dependent secondary messenger pathways of multiple growth factors, and it has been demonstrated that they increase the inhibitory growth

Table 1. Summary of the most relevant medical therapies tested in recurrent meningioma patients previously treated with surgery and radiotherapy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study design</th>
<th>n</th>
<th>WHO grade (n grade I/n high grade)</th>
<th>PFS (months)</th>
<th>PFS (%)</th>
<th>OS (years)</th>
<th>RRR (%)</th>
<th>Best RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea [14]</td>
<td>Phase II</td>
<td>4</td>
<td>3/1</td>
<td>nr</td>
<td>100</td>
<td>nr</td>
<td>75</td>
<td>nr</td>
</tr>
<tr>
<td>Hydroxyurea [15]</td>
<td>Retrospective</td>
<td>60</td>
<td>60/0</td>
<td>2</td>
<td>10</td>
<td>nr</td>
<td>0</td>
<td>SD 35</td>
</tr>
<tr>
<td>Hydroxyurea [16]</td>
<td>Retrospective</td>
<td>35</td>
<td>0/35</td>
<td>2</td>
<td>3</td>
<td>nr</td>
<td>0</td>
<td>SD 43</td>
</tr>
<tr>
<td>Hydroxyurea and imatinib [17]</td>
<td>Phase II</td>
<td>21</td>
<td>8/13</td>
<td>7</td>
<td>62</td>
<td>5.5</td>
<td>0</td>
<td>SD 67</td>
</tr>
<tr>
<td>CPT-11 [18]</td>
<td>Phase II</td>
<td>16</td>
<td>16/0</td>
<td>5</td>
<td>0</td>
<td>nr</td>
<td>0</td>
<td>SD 81</td>
</tr>
<tr>
<td>Mifepristone [19]</td>
<td>Phase III</td>
<td>160</td>
<td>160/0</td>
<td>10</td>
<td>nr</td>
<td>nr</td>
<td>2</td>
<td>nr</td>
</tr>
<tr>
<td>Interferon-α [20]</td>
<td>Phase II</td>
<td>35</td>
<td>35/0</td>
<td>7</td>
<td>54</td>
<td>0.7</td>
<td>0</td>
<td>SD 74</td>
</tr>
<tr>
<td>Octreotide [21]</td>
<td>Phase II</td>
<td>16</td>
<td>8/8</td>
<td>5</td>
<td>44</td>
<td>0.6</td>
<td>31</td>
<td>PR 31</td>
</tr>
<tr>
<td>Octreotide [22]</td>
<td>Phase II</td>
<td>12</td>
<td>3/9</td>
<td>4</td>
<td>17</td>
<td>2.7</td>
<td>0</td>
<td>SD 75</td>
</tr>
<tr>
<td>Imatinib [23]</td>
<td>Retrospective</td>
<td>9</td>
<td>1/8</td>
<td>16</td>
<td>67</td>
<td>3.5</td>
<td>0</td>
<td>SD 78</td>
</tr>
<tr>
<td>Bevacizumab [24]</td>
<td>Retrospective</td>
<td>15</td>
<td>0/15</td>
<td>6.5</td>
<td>44</td>
<td>1.3</td>
<td>0</td>
<td>SD 87</td>
</tr>
<tr>
<td>Bevacizumab and chemotherapy</td>
<td>Retrospective</td>
<td>14</td>
<td>6/8</td>
<td>18</td>
<td>86</td>
<td>nr</td>
<td>7</td>
<td>SD 79</td>
</tr>
</tbody>
</table>

WHO: World Health Organization; PFS: median progression-free survival; PFS6: progression-free survival rate at 6 months; OS: median overall survival; RRR: rate of radiographic response; Best RR: best radiographic response; nr: not reported; SD: stable disease; PR: partial response.
effects of HU in experimental studies [37]. Lastly, several drugs that are able to cross the blood-brain barrier have also been tested. Temozolomide, an alkylating agent that reacts with DNA bases and represents the current antineoplastic cornerstone drug in high-grade glioma treatment, did not demonstrate efficacy against meningioma in a phase-II trial (median PFS 5 months) [38]. This result may be explained by the high levels of activity in meningioma cells of O6-methylguanine-DNA-methyltransferase, the DNA repair enzyme responsible for creating a resistant phenotype to alkylating agents [39, 40]. Similarly, other drugs have been tested with disappointing results. Irinotecan, which also demonstrated activity in further studies. The combination of hydroxyurea and imatinib showed the best results in a well-designed phase-II trial.

Immunotherapy

Interferon-α (IFN-α) is a biologic agent with efficacy in a variety of systemic malignancies due to its antiproliferative and antiangiogenic activity [45]. Moreover, preclinical studies have documented that IFN-α inhibits the growth of cultured human meningioma cell lines [46]. Based on this rationale, small clinical studies using IFN-α in patients with recurrent meningioma were conducted, resulting in promisingly long stabilization periods [47, 48]. Hence, in 2008, Chamberlain et al conducted a phase-II trial in grade-I recurrent meningioma patients treated with IFN-α administered subcutaneously every other day. This resulted in moderate toxicity but with promising outcome results. Median PFS was 7 months and PFS6 was 54 %. However, no patients presented a radiographic response and stable disease was the best response in 74 % of patients. Thus, this study demonstrated moderate but noteworthy results in grade-I recurrent meningioma patients [20]. Nevertheless, as mentioned above, due to the unknown natural history of meningioma, especially the growth ratio of recurrent meningiomas, these results have to be interpreted with caution.

Hormonal Therapy

Progesterone receptors (PR) are more frequently expressed in grade-I meningioma (in nearly 80 %) and their presence diminishes with higher histological grade. Likewise, the PR status has been associated with specific gene expression located on the long arm of chromosome 22 near the NF2 gene [49]. This means that meningioma patients with a positive PR status have significant up-regulation of these genes and patients with negative PR status are more likely to have a 22q loss [49]. In this setting, several studies have evaluated the efficacy of

<table>
<thead>
<tr>
<th>Table 2. Summary of the most relevant ongoing trials in recurrent meningioma patients. Source: clinicaltrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Hydroxyurea plus verapamil</td>
</tr>
<tr>
<td>Interferon-α</td>
</tr>
<tr>
<td>Pasireotide (SOM230B/SOM230C)</td>
</tr>
<tr>
<td>Erlotinib</td>
</tr>
<tr>
<td>Gefinitib</td>
</tr>
<tr>
<td>Sunitinib</td>
</tr>
<tr>
<td>Imatinib mesylate</td>
</tr>
<tr>
<td>Imatinib mesylate</td>
</tr>
<tr>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Valatanib</td>
</tr>
<tr>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Everolimus</td>
</tr>
<tr>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Ispinesib</td>
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<tr>
<td>Antineoplastona</td>
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</table>
the anti-progestosterone agent mifepristone (RU486) in recurrent meningioma patients. Although initial small phase-II trials showed promising results, a further phase-III trial in WHO grade-I recurrent meningioma patients failed to demonstrate any benefit (PFS was 10 months in the treatment arm vs 12 months in the placebo arm) with no radiographical responses [19, 50–52]. In contrast, a recent phase-II trial using mifepristone in recurrent meningioma patients (most of them grade I) demonstrated a minor radiographic response in 29 % of patients [53].

Recently, there has been particular interest in the potential therapeutic action of somatostatin (SST) analogues. SST is a neuropeptide that plays an important role in several relevant cancer pathways, such as the inhibition of angiogenesis and tumour invasion, and in the induction of apoptosis [54]. SST receptors are composed of 5 subtypes of receptors (sstr1–5). Meningiomas show a high frequency of SST receptor expression (nearly 90 %), most frequently of the sstr2a subtype, but their functional role remains unclear [55]. Due to the short half-life of SST, a number of SST analogues with longer half-lives have been developed. A prototype of a long-acting SST analogue agonist, with a clear preference for sstr2a, is octreotide. Since 2007, there have been anecdotal reports of octreotide improving meningioma-related signs and symptoms with no radiographic improvement [56–58]. Recently, 3 phase-II trials yielded contradictory results in terms of radiographic responses [21, 22, 59]. A first trial using sustained-release intramuscular SST administered monthly in 16 patients with recurrent grade-I and high-grade meningioma showed a median PFS of 5 months (PFS6 44 %). Moreover, partial radiographic response was found in 31 % [21]. The second phase-II trial, using daily subcutaneous octreotide, treated 11 patients with recurrent grade-I and high-grade meningioma and found a median PFS of 4.2 months (PFS6 33 %) with no radiographic response [22]. Lastly, a phase-II trial exclusively performed in recurrent high-grade meningioma patients using sustained-release intramuscular SST demonstrated a median PFS of 4 months (PFS6 43 %) with no radiographic response [59]. In addition, pasireotide, a novel SST analogue with a wider SST receptor spectrum (including subtypes 1, 2, 3, and 5) and greater affinity (particularly for subtypes 1, 3, and 5), has been developed [60]. However, preliminary results of a phase-II trial, using long-acting pasireotide LAR in 26 patients with recurrent grade-I and high-grade meningioma, did not show promising results, yielding a median PFS of 5 months (PFS6 29 %) [61].

**Targeted Molecular Agents**

Targeted molecular agents are drugs that block some of the cell signalling pathways involved in neoplastic transformation by interfering with specific targeted molecules needed for carcinogenesis. Our understanding of brain tumour biology and recognition of the importance of the dysregulation of cell signalling pathways as a cause of neoplastic transformation have grown in recent years. In contrast to the extensive research on glioma, little is known about meningioma biology [62–65]. Preclinical studies have identified aberrant expression of critical signalling molecules in meningioma cells [66, 67]. Based on this approach, several studies using targeted molecular agents have recently been performed in recurrent meningioma patients. These trials have been classified into 5 groups depending on their main target: (1) cellular signal transduction tyrosine kinases, (2) intracellular signalling kinases, (3) tumour vasculature, (4) other molecular targets, and (5) multitargeted or combined therapies [68].

Tyrosine kinase inhibitors are drugs against tyrosine kinases or their receptors. Tyrosine kinases are a group of protein kinases that are critical to many cellular signal transduction pathways involved in cell proliferation, growth, survival, adhesion, motility, and differentiation [69]. In addition, receptor tyrosine kinases are transmembrane proteins containing an extracellular binding domain and an intracellular kinase domain that activates intracellular signalling pathways. This group includes the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptor (PDGFR).

The EGFR is over-expressed in > 60 % of meningiomas and studies in vitro have demonstrated that EGF and TGF-α activate these receptors, thereby stimulating meningioma growth [44, 63, 70–75]. Recently, 2 phase-II trials with 2 EGFR inhibitors, erlotinib and gefitinib, in recurrent grade-I and high-grade meningioma patients did not find any objective radiographic responses. Median PFS of the analysis of pooled data in both studies was 2.5 months with a PFS6 rate of 25 % for grade-I and 29 % for high-grade meningioma, respectively. These studies concluded that neither gefitinib nor erlotinib alone appeared to have a significant activity against recurrent meningioma [76].

In addition, most meningiomas also express PDGF and PDGF receptor [77–80]. PDGFR is a fundamental driver of cell proliferation in many tumours, thus supporting meningioma cell growth and maintenance. Expression levels of both PDGF and PDGFR are higher in atypical and malignant meningiomas than in benign meningiomas [78]. Moreover, meningioma cell culture studies provide evidence that the administration of PDGF results in the stimulation of tumour growth and activation of intracellular signalling kinases, while proliferation of meningioma cells can be inhibited by anti-PDGF antibodies [81–83]. The first phase-II study with a PDGFR inhibitor, imatinib mesylate, conducted in grade-I and high-grade recurrent meningioma patients, did not show any radiographic response. Median PFS was 2 months and the PFS6 rate was 29 % (45 % for grade I but 0 % for high grade); there was, therefore, minimal activity against recurrent meningiomas [84]. Conversely, a recent retrospective study conducted in preselected recurrent grade-I and high-grade meningioma patients with positive immunohistochemical PDGFR staining confirmation and treated with imatinib showed promising results. Although no complete or even partial radiographic response was observed, median PFS was 16 months with a PFS6 rate of 67 % [23].

The second group of targeted therapies includes drugs that interact with intracellular kinases, a family of enzymes involved in the phosphorylation of serine and threonine residues of their substrates. Many of these kinases serve as intermediaries in important signalling pathways. This group includes phosphatidylinositol 3-kinase/AKT PI3k/Akt inhibitors, ras-mitogen-activated protein kinase (MAPK) inhibitors and protein kinase C inhibitors. MAPK and PI3k/Akt path-
The third group of targeted therapies is related to tumour angiogenesis. This process is critical for the growth of many solid tumours and meningiomas, which are highly vascular tumours that derive their blood supply predominantly from meningeal vessels [88]. Thus, the inhibition of angiogenesis is a potentially important approach in treating meningioma patients. Vascular endothelial growth factor (VEGF) plays a central role in tumour angiogenesis, and there is increasing evidence that inhibition of soluble VEGF or VEGFR can lead to significant anti-tumour effects [89, 90]. VEGF and VEGFR are expressed in meningiomas and the level of expression increases with the tumour grade [91–93]. VEGF expression is 2-fold increased in atypical meningiomas and 10-fold in malignant meningiomas compared to benign meningiomas [91]. After the first case report of partial remission of a high-grade recurrent meningioma induced by anti-angiogenic therapy, 2 clinical studies using bevacizumab were reported on in 2012 [24, 25, 94]. Bevacizumab is a monoclonal antibody that inhibits VEGF with demonstrated activity in other systemic cancers as well as in glioblastoma [89, 90, 95]. A retrospective case series study of high-grade recurrent meningioma patients treated with bevacizumab demonstrated a median PFS of 6.5 months with a PFS6 rate of 44 %. However, no complete or partial radiographic responses were observed, although minor response was documented in 2 patients. In terms of toxicity, bevacizumab was relatively well-tolerated although 3 patients (20 %) developed non-fatal intratumoural haemorrhage. These results suggest that bevacizumab may be an effective therapeutic approach for high-grade recurrent meningioma patients [24]. The second retrospective case series study in recurrent meningioma patients reported this year also supported the use of bevacizumab for this indication [25]. In this study, patients received bevacizumab alone (n = 4) or combined with chemotherapy (n = 10), including etoposide- (n = 6) or temozolomide-based regimens (n = 4), and demonstrated a median PFS of 17.9 months with a PFS6 rate of 85.7 %. However, no complete radiographic responses were observed, although one patient treated with bevacizumab and etoposide presented partial response. Despite these promising results, this study has some limitations. It was retrospective in nature and the majority of patients received chemotherapy plus bevacizumab.

Following this line, the multitargeted agents sunitinib and vatalanib, which inhibit several kinases such as VEGFR and PDGFR, have demonstrated strong cytostatic and anti-migratory effects on human meningioma cells [96]. To date, preliminary results have been published for 2 phase-II trials. The first study included mostly recurrent high-grade meningioma patients treated with sunitinib. This study showed a median PFS of 4.6 months with a PFS6 rate of 36 %, with one patient demonstrating partial radiographic response. However, patients presented important toxicities (34 events of grade-3–4 toxicity) [97]. The other phase-II trial tested vatalanib in high-grade recurrent meningioma patients and observed a median PFS of 3.7 months with a PFS6 rate of 37.5 %. However, one patient presented a partial response, and vatalanib seems to have been better tolerated (10 events of grade-3–4 toxicity) than sunitinib [98].

Finally, other therapies designed to act on new molecular targets involved in tumourigenesis such as IGFR, histone deacetylases, ubiquitin-proteasome system, heat shock proteins, cytokines like TGF-β, and DNA repair proteins have not been evaluated in recurrent meningioma patients so far although one recent report has documented a response in an incidental meningioma of a patient treated with chemotherapy combined with an IGFR inhibitor [99].

## Conclusions

Recurrent meningioma patients are a relevant although not very large group of patients who have made recourse to surgery, radiation therapy, and even to radiosurgery. Therefore, these patients require further treatment options. In this setting, systemic drugs have a potential role in the therapeutic armamentarium. Up to now, most studies have shown disappointing or limited results with only one drug tested in phase-III trials.

Clinical trials in meningioma have several unresolved problems, making it difficult to draw clear conclusions. One limitation is the heterogeneity of the patients included. Almost all studies assumed that the behaviour of recurrent grade-I meningiomas was similar to grade II or III, though in fact the natural history and the growth rate of untreated meningioma is unknown. This point becomes crucial when the endpoint of the phase-II trial is PFS or the PFS6 rate or when a biological agent is tested, the main action of which is the slowing down or blocking of tumour growth. Thus, based on this background, the radiological response rate would be a more reliable endpoint than PFS.

Alternatively, the use of comparative randomized phase-II designs may be in order. Actually, the control group of the only phase-III study published showed a better PFS than the most promising phase-II studies. However, the details of this study are scarce because it has only been reported in a congress abstract. Moreover, data provided by retrospective studies are not useful as screening proof, because PFSs of phase-II studies are clearly worse than the inevitably biased retrospective studies.

Even though several studies have provided in recent years better understanding of the molecular characteristics of meningioma, identifying novel targets for therapy, researching molecular pathogenesis, and learning about the critical molecular changes driving tumour growth need to be addressed if we want to increase the likelihood of success of either single or combined drug selection.

In conclusion, although systemic therapy research on recurrent meningioma patients has substantially increased over the last years, further basic and clinical research is needed to clearly elucidate the most effective systemic therapy options for recurrent meningioma patients.

## Conflict of Interest

The authors state that no conflict of interests exists.
References:


Systemic Treatment of Recurrent Meningioma

recurrent meningo[...](84); 35: 222–43.
Case Report: Long-Term Epilepsy-Associated Giant Lobar Collision Tumour

Karl Rössler¹, Roland Coras², Ingmar Blümcke²

¹Department of Neurosurgery, ²Department of Neuropathology, University Hospital Erlangen, Germany

A 20-year-old male had been suffering from psychomotor retardation and chronic grand mal epilepsy since childhood. Because of a right-sided hemiparesis, a cranial CT scan had been performed at the age of 14 months, showing a porencephalic cyst in the left peri-insular region, obviously a remnant of an early ischemic event (Figure 1). Because of an increase in seizure frequency, new epileptological work-up was recently performed.

At physical examination, the 20-year-old man presented with chronic right-sided spastic hemiparesis, which rendered him unable to walk by himself – a limitation well-documented from his childhood days on. Striking at first sight was a yet unnoticed bulging of his forehead on the left side, which his parents had known well for many years, but which had considerably grown during the last years according to their description.

Surprisingly, cranial MRI demonstrated a giant intrinsic tumour mass of the left frontal lobe, infiltrating the contralateral hemisphere (Figures 2, 3). On MRI, the tumour appeared half cystic, half solid, with slight contrast enhancement of the solid parts, and showed large areas of calcification. This had led to the aforementioned bony bulging of the forehead. Thus, a slow-growing tumour (Figure 4) was suspected.

What Is Your Diagnosis?

Histological examination revealed an anaplastic neuroepithelial tumour with calcifications and focal necrosis, MIB1 index 10–15 % (Figure 5). The tumour showed areas with 2 different histo-morphological phenotypes with distinct characteristic immuno-histochemical staining patterns: on the one hand, areas with a dysplastic neuronal component within a glial tu-

Figure 1. Cranial CT scan at the age of 14 months.
Figure 2. T1 gadolinium-enhanced axial MRI.
Figure 3. T2 axial MRI, calcification in black.
Figure 4. Macroscopic appearance of the tumour.
Figure 5. Increased proliferation activity as indexed by MIB1 labelling.
Mour matrix in terms of a ganglioglioma (Figures 6, 7) were evident; on the other hand, ependymal differentiation was noticed (Figure 8). Both lesions were well discriminable from each other, but intermingled at different sites. The patient did not suffer from any genetic syndrome. This case illustrates the extremely rare occurrence of a brain collision tumour composed of a ganglioglioma and an ependymoma, which has not been reported for those entities so far. After surgery, MRI verified successful resection of the tumour. Focal radiotherapy with 60 Gy total tumour dose and 6 cycles of concomitant temozolomide were applied. During a time period of 18 months, no recurrence was noticed in the MRI follow-up.

**Further Reading:**

**Correspondence to:**
Karl Rössler, MD,PhD
Department of Neurosurgery
University Hospital Erlangen
Schwabachanlage 6
91054 Erlangen
Germany
E-mail: karl.roessler@uk-erlangen.de
A 30-year-old woman was admitted to our hospital because of a generalised tonic-clonic seizure. Her past medical history was unremarkable except for a biopsy-confirmed Tierfell naevus located on the posterior side of the pelvic region. After the seizure she complained of headache and nausea.

On clinical neurological examination the patient showed no abnormalities except for non-fluent aphasia. In order to exclude underlying structural abnormalities a magnetic resonance imaging (MRI) scan was performed which showed a contrast-enhancing lesion located on the left frontal lobe.

What Is Your Diagnosis?

Diagnosis: primary leptomeningeal melanoma in a patient with neurocutaneous melanosis (Figures 1, 2).

PET-CT scan and dermatological examination showed no melanoma outside the central nervous system. Because of the mass effect from the tumour and the neurological abnormalities surgery was performed and the tumour was removed 8 days after admission. Surgical appearance of the leptomeninges displayed several large, dark brown lesions. A postoperative MRI scan showed complete removal of the tumour without contrast enhancement. Histopathological examination of the resected tissue revealed a circumscribed malignant melanocytic lesion with an increased number of non-atypical melanocytes in the surrounding leptomeninges.

Primary melanocytic neoplasms of the central nervous system are rare and arise from leptomeningeal melanocytes. They include benign circumscribed or diffuse tumours (melanocytoma, melanocytosis) and their malignant counterparts (melanoma, melanomatosis) [1]. The diagnosis is mainly based on histopathological findings. The incidence for melanocytoma is estimated to be 1 case per 10 million; for primary CNS melanoma 0.5 cases per 10 million [2].

A preoperative diagnosis of melanocytic neoplasms is generally difficult to establish. On MR imaging, most tumours have a low T2-weighted signal and a high T1 signal with contrast enhancement and FLAIR but tumours with higher percentages of melanin-containing cells might show hyperintensity on T1- and hypointensity on T2-weighted images [3]. Macroscopically, the tumour usually appears as a brown-to-black lesion that is firmly attached to the underlying meninges. Microscopically, a variable amount of melanin pigment is seen in the tumour cells at various stages of development [2].

Although meningeal melanocytoma is a benign condition, relapse and malignant transition into melanoma have been reported. Wang et al reported a case of a primary meningeal melanocytoma located at the temporal lobe in which malignant transformation was confirmed histopathologically 3 years after resection of the tumour [4]. For that reason, adjuvant radiation therapy is advised in both complete and incomplete resection. The 5-year survival rate for patients

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**Figure 1.** Intraoperative photograph after opening of the dura, showing a black leptomeningeal tumour in the left frontal region. Of note is the spotty black appearance of the arachnoid, which is not continuous with the tumour, consistent with neurocutaneous melanosis.

**Figure 2.** Transversal section of contrast-enhanced T1 MRI demonstrating a left frontal, inhomogeneously contrast-enhancing, and space-occupying lesion with oedema in the surrounding brain tissue.
with incomplete resection in combination with radiation therapy was 100 %, but only 46 % without radiation therapy [5].

Primary CNS melanoma is an aggressive tumour and may metastasise throughout the neuraxis and sometimes even to other organs [2]. Patients with complete resection have a better outcome, post-operative radiation therapy is advised in all cases [3]. Primary malignant melanoma of the CNS may be found in isolation or (as in our patient) in the context of neurocutaneous melanosis.

Our patient underwent postoperative radiation therapy. Three months after surgery the patient was free of symptoms and an MRI scan showed no recurrence.

References:
Patient advocacy as well as provision of support and information about disease and its treatment for patient and caregivers are important aspects of a nurse’s coordinating role. As a consequence, in many European countries, the role of the oncology nurse has developed to the extent that in many centres oncology nurses take a lead role in the care of oncology patients.

In several European countries, specialised neuro-oncology nurses are included in care teams to act as the most direct contact for patients, their caregivers, and all healthcare professionals involved in the clinical management of brain tumour patients. Nurses deal with clinic scheduling, symptom management, medication/steroids, psychological support, and referral to other agencies as part of the process of advancing patient care.

**Is There a Function for the Nurse Within the Multidisciplinary Care Process?**

The Dutch Health Care Inspectorate stated that for every cancer patient, an accessible health care professional should be appointed in the interest of the patient [1]. Furthermore, good documentation of the process and pathway makes clear to every professional who is responsible at what time. Like other health care professionals the nurse has a clear place within the care process of, in the described case, the neuro-oncology patient, clear to both the patient and all other health care professionals within the multidisciplinary team. If it is decided to assess case management (in The Netherlands, this is a trend in oncologic care) to improve care, this cannot be the responsibility of one person. Oncologic care is provided for by multiple participating professionals within one hospital and can be quite complex. It is the task of a multidisciplinary team to clarify the total care process and to decide on which health care professional is responsible and accessible for which part of the process. Managing a case – defined as care for the individual patient – is in my opinion one of the competences of the specialised nurse.

**Specialized Nurse or Nurse Practitioner?**

Competences of both health care professionals include coordinating and organizing care for the benefit of all disciplines and are aimed at guarding continuity of oncologic care, with consultation and reporting as important requirements. Reallocation of tasks and responsibilities has led to the function of the NP (master degree in nursing) with competences such as clinical reasoning, the ability to perform physical examination, delegated tasks which previously belonged exclusively to medical health care professionals, such as ordering diagnostic tests, prescription of medication, and performing minor procedures. To realize continuity within multidisciplinary care, the care process can be coordinated by the oncology nurse or NP to prevent gaps, overlaps, and contradictions. Advanced practice nurse outcomes show that these professionals have an increasing role as providers in the health care system, which leads to an important improvement of quality of patient care [2]. Neurological nurse specialists provide cost-effective care and research in the United Kingdom on the influence of budget costs on care delivered by specialized nurses shows that not only are there several cost benefits but nursing care also contributes to the wellbeing of patients with neurological disorders and their families, including reduced waiting time, avoidance of unnecessary hospital admissions, and reduced postoperative care [3].

**Implementation in Practice, Barriers, and Limitations to the Function**

With the start of a new health care professional within the multidisciplinary team such as the specialized nurse, one of the barriers to be taken is the unfamiliarity and resistance to work with the nurse. Clinicians might ask themselves what they can expect of such a professional, how they are educated, if the qualification is of a high-enough standard, if they want to collaborate with specialized nurses, if they want to delegate/allocate tasks and responsibilities to the nurse, and in which way these tasks and responsibilities are verified.

In daily practice, it is often difficult to establish confidence and belief in new players within the multidisciplinary team, sometimes the newly created function is connected to a person of whom physicians may have high expectations. To meet those expectations and to be recognized by the multidiscipi-
plinary team is another issue. Is this new player after implementation (ir)replaceable? One of the important aspects of introducing a new function is that its holder is being acknowledged by the entire medical team. If any other health care professional offers resistance against the introduction it is more difficult to start and implement the function. Besides, it is important to communicate tasks and responsibilities so that they can be taken over by someone else with the same competences.

For new specialized nurses it is important to be able to be trained on the job by the physicians they are collaborating with in patient care. A plan of introduction before starting is a must: what is expected of the nurses, what tasks will they perform, what responsibilities will they have, how will this be evaluated, how is it guaranteed that the nurses will be able to continue to deliver quality of care? NPs have their own responsibilities but will always have to be able to get back-up from physicians. Protocols, standards, and guidelines will guide NPs. If there are situations not covered by these NPs have to know their limits and ask for support.

To be able to perform the job, the department and multidisciplinary team have to create certain conditions, such as a good job description, support by the management, workspace (desk, computer etc) for the nurses, access to patient files, and authorization to perform the allocated tasks. It will help if the nurses get to know the key players in the care process they will participate in.

### Recommendations

Nurses have a clear place within the care process of a specific patient group, they have expertise and knowledge of disease, diagnostics, treatment, signs and symptoms, the working methods of different disciplines, the key players in the health care process, and the referral structure within the institution. They know and participate in the total care process: from diagnostics to death, from possible treatments to clinical scientific research. Running the function is only possible because of the acknowledgement and support by the institution and various participating disciplines, united in a multidisciplinary board with the responsibility to identify the individual care process and to initiate policy. Specialized nurses or NPs function as “spiders in the web” and improve the quality of patient care by coordination and continuation of care.

### Suggested Reading:


**Correspondence to:**

Hanneke Zwinkels, RN, MA ANP
Medical Center Haaglanden
PO Box 432, NL-2501CK The Hague
e-mail: hannekezwinkels@eano.eu
A Patient Advocacy Perspective

In his fascinating “biography of cancer”, *The Emperor of All Maladies*, author and Pulitzer Prize winner Dr Siddhartha Mukherjee quotes the 20th-century American surgeon William Bainbridge who wrote: “Throughout the centuries the sufferer from this disease has been the subject of almost every conceivable form of experimentation. The fields and forests, the apothecary shop and the temple have been ransacked for some successful means of relief from this intractable malady. Hardly any animal has escaped making its contribution, in hair or hide, tooth or toenail, thymus or thyroid, liver or spleen, in the vain search by man for a means of relief” [1].

As patients, caregivers, researchers, medical professionals, academics, and representatives of industry, we desperately search for that “means of relief” from cancer in all its devastating forms, whether common or rare, primary or metastatic.

Mukherjee also quotes the American surgeon-writer Sherwin Nuland who described the cancer cell as “a desperate individualist” and “in every possible sense, a nonconformist” [1].

Mukherjee goes on to say, “The word metastases, used to describe the migration of cancer from one site to another, is a curious mix of meta and stasis – ‘beyond stillness’ in Latin – an unmoored, partially unstable state” [1].

The Default Support and Information System

Many of the symptoms of metastatic brain tumours, as well as the physical and emotional impact from them, are similar to those of primary brain tumours.

But where would a person turn for information and support when first diagnosed with a metastatic brain tumour?

For example, if they lived in the UK and had brain metastases from lung cancer, would they immediately phone the Roy Castle Lung Cancer Foundation, or would they phone The Brain Tumour Charity? If they lived in Canada and had brain metastases from kidney cancer, would they contact Kidney Cancer Canada or Brain Tumour Foundation of Canada? If they lived in Belgium and were diagnosed with brain metastases from breast cancer, would they get in touch with the breast cancer charity Europa Donna or Werkgroep hersentumoren – the Belgian brain tumour association?

Sarah Lindsell, Chief Executive of The Brain Tumour Charity (UK), said, “Having looked at our figures for the first 6 months of the year, I can see that only 5 of the individuals who contacted us did so in relation to a secondary tumour. This represents less than 1% of all our enquiries. Furthermore, looking at our online support presence we are not aware of anyone who accesses support in this way for a secondary brain tumour. When we do receive such contacts, emotional support is provided in the same way as we would support someone with a primary brain tumour. Information is given in relation to the nature of secondary tumours and ... in relation to possible treatments such as stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT).”

She added, “… people who have a secondary brain tumour are often already receiving support from charities who supported them through their [original] cancer diagnosis and treatment of the primary tumour site ...” [2].

Patient advocacy colleagues in the European and North American kidney cancer community have also confirmed to us that their patients generally default to their primary diagnosis support and information systems at kidney cancer organisations rather than necessarily contacting a brain tumour patient organisation [3].

Based on anecdotal evidence such as this, it would appear that patients diagnosed with metastases to the brain think of themselves as breast cancer patients with metastatic disease; kidney cancer patients with metastatic disease; lung cancer patients with metastatic disease, etc, and not necessarily brain tumour patients. Patients may also identify themselves as having “advanced cancer” which may well not elicit the same horror and stigma as the term “metastases to the brain”.

Nevertheless, this is not to say that brain tumour patient organisations are irrelevant regarding metastatic brain tumour patients. Far from it. They can provide much-needed information and support and fulfil the advocacy role in a similar way that they do for primary brain tumour patients.

Seeking Information – A Predominant Theme

In a paper published in *NeuroOncology* in 2006 by Jane Schubart et al, “Caring for the Brain Tumour Patient: Family Caregiver Burden and Unmet Needs”, the authors suggest that information-seeking has emerged as a distinctly predominant theme during this devastating journey. The authors note: “The research on information needs and chronic illness suggests that almost all cancer patients want to be fully informed about...
the various aspects of their disease and treatment and, in increasing numbers, are assuming a proactive role in their own care.

A growing body of research finds that when patients and families have a better understanding of their diagnosis and treatment, they are more able to cope with their problems, use the health system more effectively, and have less psychological distress. Improved coping strategies, in turn, generally result in better adjustment to a cancer diagnosis” [4].

There is a very important role for brain tumour patient organisations in helping people with brain metastases. This does not involve replacing a patient’s connection with his or her primary cancer site support network. Instead it means forging new partnerships and collaborative initiatives between brain tumour and other site-specific cancer patient organisations to ensure that people with metastatic brain tumours receive the most comprehensive information available.

Sharing Support

On the support front, every metastatic brain tumour patient should be given a “systems navigator”. This could be a specialist neuro-oncology nurse, a social worker, or other trained person who can signpost relevant support groups, facilitate access to social welfare payments/services, and assist with access to specialist support, ie, physical therapy, psychosocial support, and help in dealing with side effects like epilepsy and fatigue.

Again, brain tumour patient organisations can become involved by working in partnership with primary cancer site patient organisations and provide assistance with support groups specifically for metastatic patients, dedicated telephone helplines, and maintaining morale.

Coping with uncertainty and a reduced life expectancy; the need for practical support and help in returning to pre-treatment responsibilities or preparing for longer-term care; overcoming social isolation, stigma, and discrimination are some of the major themes identified by Monika Janda et al relating to the supportive care needs of patients with primary brain tumours and their carers [5]. These themes may also be relevant for those suffering from brain metastases.

Brain tumour patient organisations already have substantial experience in understanding and delivering support for primary brain tumour patients. By collaborating with other site-specific cancer patient organisations, we can share our experiences so that secondary brain tumour patients can also benefit and get the support they need.

Patient Advocacy Brings Change

The National Cancer Institute (NCI) defines cancer advocacy groups as organisations which “try to raise public awareness about important cancer issues, such as the need for cancer support services, education and research. Such groups work to bring about change that will help cancer patients and their families” [6].

In a paper on patient advocacy by Melissa Gilkey and JoAnne Earp, the authors say that “a specific definition of patient advocacy is difficult to articulate, in part because the term has been used in many different ways”. But they say that the concept of patient advocacy “generally refers to efforts to support patients and their interests within the context of the health care system” [7].

Whether we come from brain tumour organisations or those dealing with kidney cancer, bowel cancer, melanoma, lung cancer, or breast cancer, we all have the same goal in mind – to help improve the situation for our patients and to provide them with the best, most hopeful, and comfortable journey possible.

There are numerous issues affecting metastatic brain tumour patients which could be addressed through advocacy efforts by brain tumour patient organisations working collaboratively with primary cancer site organisations to put pressure on governments, regulators, and health authorities.

Advocacy Issues and a Force for Change

First, every metastatic brain tumour patient should be assigned to a multi-disciplinary team (MDT) just as primary brain tumour patients are. All treating centres for brain metastases should have appropriate MDT pathways and the correct capacity to ensure that brain metastases patients are treated quickly and optimally.

Second, where national or international guidelines exist to treat metastatic brain tumour patients – and there are a number of these already in place (see reference list) – are they being adhered to on a regional or local level? If not, why not? [8, 9].

Third, if stereotactic radiosurgery (SRS) is appropriate, are the waiting times on national health services for accessing this treatment acceptable? If SRS is not available in a particular region or country, how can this situation be changed/improved?

Fourth, in these cash-strapped times who will fund research into metastatic disease? Will members of the public – who currently provide a large percentage of brain tumour research funding through donations to brain tumour charities in different countries - continue to do so in these economically challenging times?

And finally, do statistics about brain metastases need to be quantified more accurately so that we can better identify service, treatment, and support requirements? How can we efficiently serve a community of metastatic brain tumour patients when we do not even know how many of those there really are? How can we budget for their needs?

Patient advocates can help address all of these challenges and more by being a force for change. We can put pressure on governments, regulators, industry, and the healthcare sector to achieve improvements in access to treatments and support because even in the richest and most powerful countries on
this planet, patients can be lost in a maze of uneven and inequitable care.

Brain tumour patient groups are crucial in ensuring that people with brain tumours – whether they are primary or metastatic – are treated equally and have every opportunity to access the highest possible level of care and support.

References:
2. Personal correspondence, Sarah Lindsell to Kathy Oliver, July 2013.

Correspondence to:
Kathy Oliver
International Brain Tumour Alliance
PO Box 244, Tadworth, Surrey KT20 5WQ, United Kingdom
e-mail: kathy@theibta.org
## Calendar of Events

### 2013

<table>
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<th>Date</th>
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<td>November 21–24</td>
<td>World Federation for Neuro-Oncology Meeting</td>
<td>San Francisco, CA, USA</td>
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<tr>
<td>December 13–15</td>
<td>The 8th International SFO-Conference</td>
<td>Kathmandu, Nepal</td>
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<td>ESTRO 33</td>
<td>Vienna, Austria</td>
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<td>June 12–14</td>
<td>16th Biennial Canadian Neuro-Oncology Meeting</td>
<td>Halifax, Canada</td>
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<td>July 3–6</td>
<td>20. Jahrestagung der Deutschen Gesellschaft für Radioonkologie</td>
<td>Düsseldorf, Germany</td>
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<td>July 26–30</td>
<td>5th World Congress – IFHNOS and Annual Meeting AHNS</td>
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<td>September 7–11</td>
<td>18th International Conference on Cancer Nursing (ICCN)</td>
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<td>November 18–21</td>
<td>EORTC – NCI – AACR International Symposium on Molecular Targets and Cancer Therapeutics</td>
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EANO Neuro-Oncology Online Magazine

Instructions for Authors

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Published since September 2011, EANO Magazine is the official open-access online journal of the European Association of Neuro-Oncology (EANO).

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  - indicate in a statement of submission that all authors have read and approved submission of the manuscript, and that the manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract.
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- Type manuscripts double-spaced, including references, figure legends, and tables, on one side of the page only. Original contributions generally should not exceed 6 pages when typeset. As a reference for manuscript length, there should be no more than 1 figure or 1 table for every 750 words. The manuscript should not exceed 30,000 keystrokes including title page, abstract, key words, references, legends, and tables. Authors should eliminate redundancy, emphasise the central message, and provide only the data necessary to convey their message. Manuscripts may exceed 6 pages when exigencies of design or complexities of research require it and length is approved by editors.
- Leave 1-inch margins on all sides. Do not use justified margins.
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EUR ASSOC NEUROONCOL MAG 2013; 3 (3) 149
In 2013, after 4 years of absence, the 3rd National Conference of Neuro-Oncology with International Participation was organized from April 17–20, 2013, at the Hotel Golden Tulip in Cluj-Napoca, Romania, under the generous patronage of the University of Medicine and Pharmacy “Iuliu Hatieganu” Cluj-Napoca, “Prof. Dr. Ion Chirircuta” Oncology Institute Cluj-Napoca, the Romanian Society of Neurosurgery, the Society for the Study of Neuroprotection and Neurorecovery, and last but not at least the Romanian Medical Academy.

The first edition of the National Conference of Neuro-Oncology with International Participation took place in Cluj-Napoca in 2007. This national conference was a great success in attempting to unite under the same roof multiple, and apparently different, medical specialties involved in the diagnosis and treatment of tumours of the nervous system.

Encouraged by the success of our action, and wishing to expand our work in this demanding field by stressing the newest scientific acquisitions in a domain of medicine in which multidisciplinary collaboration is mandatory, we organized the 2nd National Conference of Neuro-Oncology with International Participation which took place from November 20–22, 2008, in Cluj-Napoca under the same generous patronage of the University of Medicine and Pharmacy “Iuliu Hatieganu” Cluj-Napoca, “Prof. Dr. Ion Chirircuta” Oncology Institute Cluj-Napoca, the Romanian Society of Neurosurgery, the Romanian Society of Radiation Oncology, and Medical Oncology, and the Romanian Society of Neuro-Oncology, under the auspices of the European Association for Neuro-Oncology.

The 3rd National Conference of Neuro-Oncology with International Participation in 2013 gathered more than 180 active participants from the fields of neurosurgery, neurology, oncology, and pathology and covered the following main topics:
- Molecular therapies in malignant gliomas
- Cerebral metastases
- Palliative care
- Controversies in the surgery of spinal tumours
- Low-grade gliomas: how to deal with?
- Varia

This year’s edition was honoured with the presence of distinguished invited speakers from Europe such as Wolfgang Grisold, MD (Austria), Jürgen Piek, MD (Germany, co-president of the conference), Vladimir Benes, MD (Czech Republic), Sotirios Bisdas, MD (Germany), Olivier Chiotis, MD (France), Yavor Enchev, MD (Bulgaria), Marc-Eric Halatsch, MD (Germany), Ralf Ketter, MD (Germany), Christian Matula, MD (Austria), Nyary Istvan, MD (Hungary), Kathy Oliver (UK, International Brain Tumour Alliance), Ferenc Pongracz (Hungary), Lukas Rasulic, MD (Serbia), Apostolos Stathopoulos, MD (Belgium), Francesco Tomasello, MD (Italy), Steffi Urbschat, MD (Germany), and Istvan Valalik, MD (Hungary).

The high standard of the presentations as well as the novelty and various projects presented offered to all participants the chance of a fruitful exchange of ideas and widening their professional horizons.

As a take-home message I would like to include the following quotation by Kathy Oliver, Co-Director, International Brain Tumour Alliance: “I do believe that one day we will defeat brain tumours as long as we maintain a truly collaborative approach between patients and doctors and across disciplines, geographic borders, and generations.”

In our attempt to do so, we warmly welcome you to join us for the 4th National Conference of Neuro-Oncology with International Participation to be held in 2015 in Cluj-Napoca, Romania.

Correspondence to:
Ioan Stefan Florian, MD
Sectia Clinica Neurochirurgie
Str. Victor Babes nr 43
400012 Cluj-Napoca
Jud. Cluj, Romania
e-mail: stefanfloriannch@gmail.com
Brain metastases (BM) are the most common intracranial malignancy in adults with an incidence 10 times higher than in primary malignant brain tumours. Besides the high and rising incidence, brain metastases have an impaired and poor prognosis with survival times of only several weeks to a few months. However, treatment options, especially in terms of systemic therapy approaches, are very limited. The number of brain metastases (>3 metastases) as well as their sizes (>3 cm diameter) are groundbreaking for further treatment approaches. Patients with ≥3 brain metastases are candidates for an either surgical (brain metastases >3 cm) or radiosurgical (brain metastases <3 cm) treatment approach with facultative adjuvant whole-brain radiation therapy. Patients with >3 brain metastases are usually treated with whole-brain radiation. Therefore, brain metastases pose a great clinical need for improved treatments that is, however, not reflected by the number of studies investigating brain metastases.

The Annual Meeting of the American Society of Clinical Oncology (ASCO) is one of the most prominent scientific conferences. The plenary session is followed by >25,000 participants and the results presented have high impact on clinical practice. In the following, we give a short overview concerning the presented articles on BM at the ASCO 2013 meeting.

**Prognostic Assessment in Patients with Brain Metastases**

Several prognostic scores for estimation of survival time upon first diagnosis of brain metastases exist. The diagnostic, specifically graded prognostic assessment takes clinically prognostic factors into account as well as the histology of the primary tumour, resulting in a specific prognostic score for each primary tumour [1]. The graded prognostic assessment for breast cancer includes age, receptor (eg, oestrogen receptor, HER2 receptor) expression, and Karnofsky performance status and was once more validated for a cohort of patients treated at a tertiary care centre [2]. Another study on breast cancer brain metastases tried to identify clinically prognostic factors for long-term survival over 36 months. However, none of the common clinical factors showed a significant association with long-term survival [3]. In a further retrospective cohort of breast cancer patients who underwent craniotomy for brain metastases, only age showed prognostic impact on overall survival [4].

Graded prognostic assessment was validated in a real-life cohort of patients with non-small lung cancer brain metastases [5]. Presence of EGFR mutation was identified as an independent prognostic factor upon diagnosis of non-small cell lung cancer brain metastases [6]. A population-based study investigated factors associated with the risk of brain metastases at first diagnosis of non-small lung cancer. A score including age >60, non-squamous histology, size >5 cm, grade II–IV, and lymph node involvement was postulated to stratify for patients with an increased risk for brain metastases [7].

As no specific prognostic score exists for renal cell carcinoma, the value of the graded prognostic assessment including the factors age, Karnofsky performance score, number of brain metastases, and status of extracranial disease was evaluated for renal cell carcinoma brain metastases. However, no significant correlation of the graded prognostic assessment score and overall survival was evident and a new prognostic assessment based on the factors time from diagnosis of primary tumour to brain metastasis, haemoglobin level, age, number of brain metastases, and status of extracranial disease was postulated [8]. Another study postulated the MSKCC (Memorial Sloan Kettering Cancer Center) risk group, histology (clear-celled vs other), and number of brain metastases as prognostic factors in a similar, independent cohort of patients with renal cell carcinoma brain metastases treated with various targeted therapies (anti-angiogenic, mTOR inhibitor) [9].

Graded prognostic assessment was validated for brain metastases from melanoma, indicating that the presence of liver metastases and haemorrhagic metastases adds additional prognostic value [10].

**Rare Primary Entities of Brain Metastases**

Lung cancer, breast cancer, and melanoma are the most common primary tumours of brain metastases and brain metastases are very rare in other primary tumours. However, some studies presented at ASCO 2013 focused on prognostic factors and development of brain metastases in rare primary entities [11–15].

Although colorectal cancer is a frequent cancer entity patients rarely develop brain metastases as most patients die due to
systemic progression before the development of brain metastases. Data of a large retrospective study postulated an increased risk for brain metastases of colorectal cancer in patients with lung metastases and KRAS mutation [11].

Brain metastases of non-seminomatous germ cell tumours are rare. However, up to 15 % of patients might eventually develop brain metastases. Patients with elevated hCG levels > 500 IU/l, multiple (< 3) and large (< 2 cm) pulmonary metastases, and a poor IGCCCG prognosis score are at a higher risk of brain metastases and screening in this patient population was suggested to be feasible [12]. In addition, the possibility of long-term survival for patients with brain metastases of germ cell tumours irrespective of their time of occurrence (synchronous or metachronous to the first diagnosis of germ cell tumour) was postulated [13].

The incidence of brain metastases was evaluated in a rare series of 21 patients with primary cardiac sarcoma. 33 % developed brain metastases, although brain metastases are very rare in sarcoma patients – commonly, they occur only in about 8 % [14]. Similarly, the incidence of 1.8 % for brain metastases was reported for a retrospective cohort of patients with metastatic urothelial carcinoma, an entity that rarely metastasizes to the brain. Survival upon diagnosis of brain metastases was poor with a median of only 3 months [15].

**Pathobiology of Brain Metastases**

The understanding of the metastatic cascade and the molecular function involved is crucial to direct further development of treatment approaches [16].

Melanocytes and glial cells share their ectodermal origin, an instance that is commonly used to explain the high propensity of melanoma to metastasize to the brain. Herein, a high expression of neutral factors, namely the p75 neurotrophin receptor, was observed in cell lines of melanoma brain metastases, supporting the theory of neurotrophin receptor involvement in the brain metastatic cascade [17]. Another study on the pathobiology of melanoma brain metastases investigated alterations in DNA methylation patterns, which are recognized markers of metastasis initiation. Significant genome-wide hypomethylation and CpG island hypermethylation were observed [18].

An autopsy study focused on the invasion of brain metastases into the surrounding brain parenchyma. Herein, 3 different invasion patterns were postulated: (1) well-demarcated (clearly distinct border of brain metastases and brain parenchyma), (2) vascular co-option (growth along pre-existing vessels), and (3) diffuse infiltration (single-cell infiltration of the surrounding brain parenchyma) [19].

A preclinical mouse model study of melanoma brain metastases examined the potential role that the drug efflux transporters p-glycoprotein and breast cancer-resistant protein play in the treatment response of melanoma brain metastases harbouring the BRAF V600E mutation to the BRAF inhibitor vemurafenib, indicating that these might be involved in mechanisms of resistance [20].

The RAF-MEK-ERK and the PI3K-Akt pathways play a crucial role in the progression and metastatic spread of melanoma. A preclinical study therefore investigated the value of a new PI3K inhibitor. Herein, the PI3K inhibitor BKM120 produced a significant reduction of cell growth in the metastatic melanoma cell line and in a melanoma brain metastases mouse model [21].

Molecular features like the EGFR status in non-small cell cancer were postulated to influence the propensity of brain metastasis development. A multivariate model including EGFR mutation, young age, and lymph node involvement was shown to predict for patients at a higher risk for brain metastasis development [22].

**Treatment of Brain Metastases**

Patients with brain metastases have been systematically excluded from clinical trials in the past and clinical trials on the specific treatment of brain metastases are rare [23]. However, the inclusion of patients in clinical trials is the key approach in improving treatment strategies. Only few studies presented at the ASCO 2013 focused on treatment options in brain metastases and even less clinical trials including patients with brain metastases were presented.

Only one phase-III study including patients with brain metastases from non-small cell lung cancer was presented. Herein, the value of additional oral systemic therapy with topotecan in addition to whole-brain radiation therapy in patients with non-small cell brain metastases was evaluated. However, no significant impact of additional therapy with topotecan but significantly higher rates of adverse events were evident [24].

The combination of stereotactic radiosurgery followed by immunotherapy with the CTL4A antibody ipilimumab was shown to be active and safe in 2 independent small cohorts of patients with melanoma brain metastases [25, 26].

Systemic therapy with the BRAF mutation inhibitor vemurafenib was investigated in several, independent small cohorts of patients with melanoma brain metastases harbouring a BRAF mutation. A response rate of up to 50 % was observed, however, a discordance of the response in intra- and extracranial lesions was evident in some patients [27, 28]. The high impact of BRAF inhibitors in the treatment of patients with melanoma brain metastases was further emphasized by a retrospective evaluation, indicating that patients treated with a BRAF inhibitor experience median survival times of up to 23.2 months compared to 6.7 months in patients not treated with a BRAF inhibitor [29].

A response rate of up to 80 % with a very favourable toxicity profile was shown in a phase-II study of icotinib, a new epidermal growth factor receptor tyrosine kinase inhibitor, in combination with concomitant whole-brain radiation therapy for brain metastases of non-small cell lung cancer [30].

Vorinostat showed promising radiosensitizing effects in preclinical models. Hence, the safety of vorinostat as a radio-
sensitizer in brain metastasis patients undergoing whole-brain radiation was shown [31].

The value of the epidermal growth factor receptor tyrosine kinase inhibitors suntinib and sorafenib was further evaluated in a very small, single-centre cohort with renal cell cancer brain metastases. Herein, an overall response rate of 27 % was observed [32].

Two phase-II studies investigated bevacizumab-based systemic therapy in patients with brain metastases. (1) A non-comparative study showed promising results and safety for the combination of bevacizumab with carboplatin and paclitaxel as first-line treatment or erlotinib and bevacizumab as second-line treatment in patients with asymptomatic non-small cell lung cancer brain metastases [33]. This result was further supported by (2) a small study postulating an intracranial response rate of 78 % and an extracranial response rate of 40 % for bevacizumab-based treatment [34].

A phase-II trial of carboplatin and bevacizumab in patients with breast cancer brain metastases showed promising results with an overall response rate of 63 % and a progression-free survival of 5.7 months. Based on this data, a phase-III trial is being considered by the authors [35].

While the studies mentioned so far concentrated on the treatment of established brain metastases, 2 independent studies focused on the potential of bevacizumab-based treatment to prevent the occurrence of brain metastases in patients with advanced non-small cell lung cancer. A statistically significant reduction of the propensity of brain metastases was observed in patients receiving bevacizumab-based therapy compared to patients treated with chemotherapy only in both retrospective series [36, 37].

Similarly, a preventive value of erlotinib therapy in terms of brain metastasis development was postulated at patients receiving erlotinib-based therapy had less brain metastases and developed them later during the course of their disease than patients treated with chemotherapy only [38].

The penetration at active concentrations and the passage through the blood-tumour/brain barrier is one of the major obstacles in the systemic treatment of brain metastases. The value of the blood-tumour/brain barrier in brain metastases is currently under discussion. Therefore, somewhat surprisingly a study investigating the drug concentration of bevacitabine and lapatinib in resected brain metastases from breast cancer postulated concentrations of 21–142 % of the serum concentration, underscoring the already known clinical activity of these drugs in the treatment of breast cancer brain metastases [39].

**Conclusion**

In conclusion, the further inclusion of patients with brain metastases in randomised clinical trials and further basic research on the brain metastatic cascade are urgently warranted to identify drugable targets.

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Correspondence to:
Anna Sophie Berghoff, MD
Department of Medicine I & Comprehensive Cancer Center – CNS Unit (CCC-CNS), Medical University of Vienna
A-1090 Vienna, Währinger Gürtel 18-20
e-mail: anna.berghoff@meduniwien.ac.at
Interview with Dr Michael Weller (Zurich) about the Phase-III EGFRvIII Vaccine Trial on Newly Diagnosed EGFRvIII-Positive Glioblastoma

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Dr Weller, what can you tell us about the ongoing “ACT IV” trial on newly diagnosed glioblastoma? What is its background and objective?

A: ACT IV is a randomized, phase-III study investigating the efficacy and safety of the addition of rindopepimut to the current standard of care, temozolomide, in patients with recently diagnosed EGFRvIII-positive glioblastoma who have had surgery and radiotherapy plus concomitant temozolomide. The trial is designed to see whether there is an improvement in overall survival in patients treated with the vaccine in addition to maintenance temozolomide compared with maintenance temozolomide alone in patients with gross total resection. Secondary analyses will evaluate the activity of the vaccine in patients with incomplete resection.

Q: How is the trial designed? Which patients are eligible for this trial?

A: Glioblastoma patients who have had attempted surgical resection are eligible to have their tissue evaluated for EGFRvIII expression. Patients with EGFRvIII expression confirmed by the sponsor’s laboratory are eligible for entry into the ACT IV trial if their disease does not progress on their chemoradiotherapy following surgery. All patients must be enrolled into this trial within 2 weeks of finishing concomitant chemoradiotherapy and prior to starting their maintenance temozolomide (Figure 1).

Q: Why did you choose gross total resection (GTR) as an inclusion criterion?

A: Initial studies evaluating rindopepimut assumed that an immune approach would have its greatest effect in patients with minimal residual disease. All of the phase-II data supporting the ACT IV study include only patients with GTR, hence ACT IV is focused on this population in its primary analysis. However, ACT IV will accrue patients with bulkier disease in a separate cohort and could show efficacy in that population as well.

Q: What are the schemes and durations of treatment in both arms?

A: Patients enrolled into the ACT IV trial are randomized to receive either rindopepimut (study vaccine) or a control injection in a blinded fashion. Two priming injections of the study vaccine are given during the first month of treatment and then patients receive monthly injections thereafter until disease progression or intolerance. All patients receive the 5-day regimen of maintenance temozolomide for 6–12 cycles based on local standards of care.

Q: What are the stratification factors?

A: Patients are stratified according to MGMT status, EORTC RPA class, and geographical region.

Q: How is the EGFRvIII expression status assessed in the trial? Do you have any trial-specific difficulties?

A: EGFRvIII expression status is assessed at a sponsor-designated laboratory in the USA. The laboratory is running the validated PCR-based EGFRvIII test under an investigational device exemption (IDE) from the US FDA. This assay has provided reliable and consistent results and should be readily used as a selection assay if rindopepimut is found to be efficacious.

Q: Do you have any planned translational studies?

A: Molecular studies will be conducted at European centres to correlate response to therapy and outcome with soluble biomarkers and miRNA profiles. A smaller number of European centres will also perform immune phenotyping to determine enzymatic activities as a measure for suppressive activity and the frequencies of regulatory T cells and myeloid-derived suppressor cell subsets. In addition, any correlation between immune response or extent of EGFRvIII expression and clinical outcome will be evaluated.

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**Figure 1. Trial scheme**
Q: How is response assessed in this trial? Do you use the RANO criteria?

A: Response is assessed using the RANO criteria. Patients have restaging assessments every 8 weeks for the first 6 months, every 12 weeks through the second year, and then they are spaced further apart in subsequent years.

Q: How is the accrual and when do you expect to reach the accrual goal? When can we get the first results?

A: Accrual is going well, suggestive of the significant unmet medical need in this patient population. Since the endpoints are event-driven, it is too soon to tell when results will be available.

Thank you very much!

Dr Michael Weller is the coordinating investigator of the trial entitled, “An International, Randomized, Double-Blind, Controlled Study of Rindopepimut/GM-CSF with Adjuvant Temozolomide in Patients with Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma (The “ACT IV” Study”).

EudraCT number 2011-006068-32.
Combined Analysis of O\textsuperscript{6}-Methylguanine-DNA Methyltransferase Protein Expression and Promoter Methylation Provides Optimized Prognostication of Glioblastoma Outcome


Methylation of the promoter region of the O\textsuperscript{6}-methylguanine-DNA methyltransferase (MGMT) gene is a predictive biomarker for benefit from alkylating-agent chemotherapy in glioblastoma. The MGMT status is commonly determined by methylation-specific PCR. In the March issue, Lalezari et al challenged the notion that immunohistochemical assessment of MGMT in tumour tissue is of no prognostic or predictive value. These authors compared MGMT test results obtained by genetic testing and immunohistochemical assessment, trying to make sure that the MGMT signal on immunohistochemistry was obtained from tumour cells and not from tumour-infiltrating host cells. They conclude that combined MGMT testing using methylation-specific PCR and immunohistochemistry is superior to methylation-specific PCR alone because high MGMT protein levels were associated with poor outcome irrespective of genetic MGMT status, whereas low protein was not associated with a favourable outcome in the absence of MGMT promoter methylation. Although these observations are interesting and enhance our understanding of the significance of MGMT in the outcome of glioblastoma, this study argues for supplementing genetic testing with protein testing, not for replacing it.

A Multi-Disciplinary Consensus Statement Concerning Surgical Approaches to Low-Grade, High-Grade Astrocytomas and Diffuse Intrinsic Pontine Gliomas in Childhood (CPN Paris 2011) Using the Delphi Method


Defining widely accepted standards of care for rare brain tumours has been notoriously difficult. Most national or international guidelines do not include such tumours. In the April issue, Walker et al, on behalf of the Consensus Conference on Paediatric Neurosurgery, Paris, France, 2011, published a multidisciplinary consensus statement on surgical approaches to low- and high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood. They used the Delphi method, that is, they drafted statements which were then subjected to an online voting procedure. A 70-% agreement was looked for, statements achieving lower agreement were modified and re-evaluated. The consensus group comes up with 27 statements which should be very helpful, especially for sites or countries where no large cooperative networks are available to standardize approaches to these tumours in childhood. The approach pursued can be realized with a reasonable effort and may be applied successfully to other areas of controversy in clinical neuro-oncology.

Glutamine Synthetase Expression as a Valuable Marker of Epilepsy and Longer Survival in Newly Diagnosed Glioblastoma Multiforme


The biological determinants of symptomatic epilepsy in intrinsic brain tumours including glioblastoma remain controversial. Expression of glutamine synthetase has previously been linked to inferior outcome, but decreased risk of epilepsy. Glutamine synthetase is an enzyme expressed by astrocytes which catalyzes the conversion of glutamate and ammonia to glutamine. In the May issue, Rosati et al from Italy expand on this topic by performing a retrospective study of glutamine synthetase expression in a series of 83 consecutive patients with newly diagnosed glioblastoma. Staining intensity and homogeneity of this distribution for glutamine synthetase were inversely correlated with epilepsy. Moreover, absent or low intensity of glutamine synthetase expression was associated with prolonged survival on uni- and multivariate analyses. This interesting study appears to confirm a link between glutamine synthetase, risk of epilepsy, and outcome and provides an explanation for the association of tumour-associated symptomatic epilepsy with better outcome in glioblastoma.

Patterns of Care and Outcome for Patients with Glioblastoma Diagnosed During 2008–2010 in Spain


Several efforts have recently been made to assess the changing management and outcome patterns in patients with glioblastoma on a population-based level, based on the assumption that the introduction of concomitant and adjuvant temozolomide in 2005 resulted in an overall improvement of outcome. In the June issue, Graus et al from Spain report the results of a retrospective analysis of such data collected via questionnaires, covering patient files from 19 Spanish hospitals. A total of 834 patients were studied. One quarter of the patients was older than 17 and ⅓ of the patients was initially managed by biopsy rather than resection. One quarter received no further treatment beyond surgery. Three quarters of the patients who were treated after surgery received radiotherapy plus temozolomide. Age was confirmed as an impor-
tant prognostic factor. Surgery-associated morbidity was identified as a significant factor linked to cessation of further treatment measures in patients with newly diagnosed glioblastoma, notably in the elderly. Median overall survival was 11.8 months which conforms to other larger contemporary studies, overall suggesting a moderate improvement in survival since the introduction of temozolomide. Yet, similar to other studies, also this series is not truly population-based, rendering it very likely that a fraction of poor-prognosis patients was not captured in this survey.

Phase 2 Study of Dose-Intense Temozolomide in Recurrent Glioblastoma


Dose-intense temozolomide regimens are among the most commonly used treatment regimens for recurrent glioblastoma in many countries in Europe, notably where bevacizumab is not available. Moreover, the repertoire of nitrosourea compounds has been reduced over the last years, mostly to CCNU (lomustin), which is available in most countries. In the July issue, Norden et al reported results from a phase-II study of dose-intense temozolomide at 21 out of 28 days in patients with glioblastoma at first relapse. 58 patients were enrolled, 65 % of assessed patients had MGMT promoter methylation. The partial response rate was 13 %, and progression-free survival at 6 months was disappointingly low with 11 %. This figure is lower than with CCNU in recent randomized trials or continuous dosing of temozolomide according to the “rescue” regimen. Although this is a small study, it increases the series of publications questioning the overall strategy of dose-intense temozolomide in newly diagnosed or recurrent glioblastoma. Data from the randomized DIRECTOR trial comparing the 21-out-of-28 and 7-out-of-14 days regimens will soon be available and may allow for a more definitive conclusion on the future of this regimen for patients with recurrent glioblastoma.

Correspondence to:
Michael Weller, MD
Department of Neurology, University Hospital Zurich
Frauenklinikstrasse 26
8091 Zurich, Switzerland
e-mail: michael.weller@usz.ch
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