Review Article

Animal models of meningiomas

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Abstract: Meningiomas are frequent intracranial and intraspinal tumors. They are tumors of the elderly, and meningioma growth at certain localizations, as well as recurrent tumors or primary aggressive biology may pose a therapeutic challenge. To understand the growth characteristics of meningiomas, animal models can provide insights both from a biological and therapeutical point of view. Using genetically-engineered mouse models (GEMM), it has been proven that alterations of the neurofibromatosis type 2 (*NF2*) gene are key steps for benign meningioma development. Aggressive meningiomas can be induced by simultaneous activation of Nf2 and the PDGF (platelet-derived growth factor)/-PDGF-Receptor (R) system, or inactivation of Tp53 and cdkn2ab in mice. However, mechanisms acting in *NF2* wild-type meningiomas are poorly understood so far, because appropriate models are lacking. Xenograft models have been used either by implantation of primary cultures derived from human meningiomas, or immortalized human cell lines, respectively. While the value of primary cells is limited due to low rate of overall tumor growth and slow proliferation, xenograft approaches have been shown to be helpful for the evaluation of potential medical treatment options. Future studies must incorporate new molecular meningioma tumor drivers, as well as potential treatment options based on recurrent genetic alterations into the generation of meningioma models.

Keywords: Neurofibromatosis type 2 (*NF2*); nude mice; xenograft; imaging; genetically-engineered mouse model (GEMM)

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Introduction

Meningiomas are the most frequent intracranial neoplasms. Meningiomas are tumors of the elderly, with a clearly increased incidence after the age of 65 years (1). Meningiomas preferentially affect women with a female : male ration of 3.5:1 (2). Other risk factors are ionizing radiation, diabetes mellitus, hypertension, and possibly smoking (3-6). Meningiomas in children and young adults are rare, however, in patients suffering from germline mutations in the neurofibromatosis type 2 (*NF2*) gene, single or even multiple meningiomas may be present (7).

Approximately 90% of meningiomas arise in the cranial meninges, while 10% occur in the spinal meninges. Within the cranial cavity, sites of meningioma growth can be separated into tumors of the convexity and tumors growing in the anterior, middle, or posterior skull base. Especially skull base meningiomas may cause considerable morbidity and may be challenging for the neurosurgeon, and the clinical course is at least partly dependent on the localization of the tumor (8,9).

While the tumor resection by the neurosurgeon is regarded as standard therapy for meningiomas, a fraction of tumors may be resected only incompletely, with subsequent tumor regrowth and/or recurrence. Moreover, meningiomas in difficult locations may be not eligible for resection. In these cases or in patients with recurrent tumors, additional treatment options may be required. Another limitation for surgery might be caused by the overall health condition of the patient or other co-existing diseases, a scenario which is not infrequent within the typical meningioma patient age

Table 1 Key questions for meningioma modeling

Tumor localization
Cranial cavity: skull base (anterior/posterior) or convexity
Spinal
Genetics
NF2 (merlin)-dependent/ *NF2*-independent
Skull-base related alterations (*SMO*, *AKT1*)
Progression-associated alterations (*CDKN2A* mutation)
Growth characteristics
Epidemiology (age, gender)
Tumor irradiation applicable
Monitoring of orthotopic tumor growth

group.

As an additional treatment option for aggressive, recurrent or inaccessible meningiomas, radiotherapy is recommended [reviewed in (10)]. In aggressive meningioma subtypes, radiotherapy can achieve good results (11).

Beside radiotherapy, additional medical treatment for meningiomas has shown only limited efficacy so far (12). This is based partly on the limited knowledge regarding molecular alterations with relevance to treatment in meningiomas, but also on the lack of animal models with gene-specific alterations, covering the spectrum of known or supposed driver mutations, to study treatment efficacy.

Meningiomas are characterized by a high diversity of histopathological features. The dominating histological subtypes among the WHO (World Health Organization) grade I meningiomas are the meningothelial and fibroblastic subtype, or a mixture from both designated as transitional meningiomas. While most of the meningioma subtypes belong to the WHO grade I, about 20 percent are diagnosed as atypical or anaplastic meningiomas (13). Grade II and grade III meningiomas have substantial impact on morbidity and mortality (14). These tumors display aggressive biological features with high proliferation activity and infiltrative growth. In the recently updated WHO classification of brain tumors, brain invasion by meningiomas qualify them for the grade II designation (15).

Genetic alterations in meningiomas as basis for model development

The molecular biology of meningiomas is complex and determined by the age group affected, the localization of the tumor, and the histological subtype. The key molecular alterations present in sporadic meningiomas are allelic losses and/or mutations in the *NF2* gene at chromosome 22q (16,17). *NF2* alterations are preferentially found in meningiomas of the convexity and of fibroblastic/ transitional subtype. In patients suffering from *NF2*, multiple meningiomas may arise in children or young adults. Vice versa, occurrence of a meningioma during childhood is a strong indicator for the presence of *NF2* (18). Recently, a number of other genetic alterations have been identified mostly on *NF2*-wild type intracranial meningiomas. They affect the genes *Smo*, *AKT1*, *TRAF7*, *KLF4*, *POLR2A*, *PI3K*, *SMARCB1 and BAP1*. The frequency of these alterations is much lower than the one seen for *NF2*, but they show a surprising preference for certain localizations or histological subtypes (19-26). Additionally, for meningiomas with clear-cell WHO-grade II subtype located either intracranially, or in the majority of cases in the spinal cord, mutations in the *SMARCE1*-Gen have been identified as tumor-initiating event (27). However, the modeling especially of the newly-identified genetic alterations to evaluate the tumor-initiating or at least tumor-accelerating properties has not been developed thus far.

Meningioma modeling: questions and challenges

Based on the various clinical, pathological, molecular, and therapeutical characteristics and challenges associated with meningiomas, appropriate modeling requires addressing of a number of key issues which are listed in *Table 1*.

The first point is related to the *NF2* gene. Given the high frequency of *NF2* alterations in sporadic meningiomas, understanding growth characteristics and treatment efficacy should include this essential gene. *NF2* (with the gene product merlin) is a tumor suppressor and a member of the 4.1/FERM gene family (4.1, ezrin, radixin, moesin). FERM domain proteins are linker between plasma membrane receptors and the actin cytoskeleton (28). Merlin regulates receptor-mediated signaling processes essential for cell proliferation, cell adhesion, and survival. Relevant pathways affected by merlin include PI3K/Akt, mTOR (mammalian target of rapamycin), small GTPases, and the hippo pathway [reviewed in (29)]. Merlin action might therefore affect all drug-based treatment options targeting one of the above-mentioned pathways.

Another aspect is related to the tumor location. Beside the fact that the frequency of certain molecular alterations

is related to the localization of the tumor (convexity, skull base, spinal cord), the neurosurgical treatment especially for skull base meningiomas can be challenging (9). Therefore, skull base-located tumors are prone to incomplete resection and subsequent early tumor recurrence. It is well-known that certain histological subtypes preferentially occur at certain sites. For instance, psammomatous or clear cell meningiomas are frequently found within the spinal cord, while meningothelial meningiomas favor the skull base and fibroblastic meningiomas the convexity (10). Embryonically, the meninges at the skull base are derived from the mesoderm, while telencephalic meninges are neural crest-derived, explaining the different histological subtype development at least partly (30). Therefore, tumor location is relevant both from a clinical and biological point of view.

The site of tumor growth in a given meningioma model is moreover relevant for the potential application of radiation therapy, which can potential enhance drug sensitivity (31). Meningiomas growing at the convexity are easier accessible for irradiation then meningiomas growing at the skull-base in an animal model. This tackles the question of monitoring tumor growth in model systems in addition, because meningiomas growing at the convexity might be monitored by luciferase-base techniques, while skull-base related models require magnetic resonance imaging (MRI) examination for follow-up.

Finally, most meningiomas are naturally slow-growing tumors which develop in elderly patients (32,33). There seems to be a phase of minimal growth, but over the age of 60 years an accelerated tumor growth may occur (32). Although the tumor initiation within a very restricted time window after birth have been demonstrated in mice (34) (see below), it is unclear why meningiomas need a surprisingly long time until relevant tumor growth is going to be started. Taken together, meningioma modeling is complicated by a plethora of different clinical and biological features.

Genetically-based meningioma models

Driven by the observation that *NF2* inactivation is frequently found in sporadic meningiomas, and that in patients with *NF2* meningiomas arise early in life and sometimes in multiplicity, the first convincing meningioma model using genetically-engineered mice (GEMM) has targeted the *NF2* gene.

Michel Kalamarides and his group demonstrated that *Nf2* inactivation in leptomeningeal cells of conditional *Nf2* knockout mice ($Nf2^{flox/flox}$) by Cre-recombinase injection induces meningiomas (34). The injection of Cre-recombinase was performed in two ways: intraorbitally, or subdural injection into the frontal convexity area of newborn pubs. Most of these mouse tumors they could induce recapitulated the meningothelial, fibroblastic, or transitional subtype of human meningiomas, and there characterized by reduced merlin expression. However, the tumor induction was restricted to a narrow window of Cre-recombinase injection around postnatal day 2–3. Moreover, the efficiency of tumor induction was limited (29% for transorbital induction and 19% for convexity injection). Regarding the tumor burden, mice died beginning at the age of approximately 8 months. These features indicate that despite the proof for a fundamental role of *NF2* in meningioma induction, other factors might operate to end up with the frequency of ~50% sporadic meningiomas with *NF2* alterations in humans. The authors could indeed shorten the time to tumor induction and death of mice by introducing with heterozygous p53 loss ($Nf2^{flox/floxp53+/-}$). However, *TP53* alterations are rare in human meningiomas (35,36), indicating that additional genes might be affected. This was further elucidated in a subsequent study by the same group, addressing the question whether inactivation of the *Cdkn2ab* gene in mice might accelerate the meningioma formation. The *CDKN2A* gene with its gene product p16 is frequently altered during meningioma progression; alterations on chromosome 9p21 during meningioma progression have been found to represent losses of the tumor suppressor genes *CDKN2A* ($p16^{INK4a}$), $p14^{ARF}$, and *CDKN2B* ($p15^{INK4b}$) (37,38). In anaplastic grade III meningiomas, deletions of *CDKN2A*/*CDKN2B* are associated with reduced survival (39). The group from Michel Kalamarides indeed could show that additional deletion of *Cdkn2a*, together with *Nf2* inactivation, results in increased meningioma frequency and development of grade II/grade III meningiomas in mice, proving that loss of *CDKN2A* and *CDKN2B* is a feature for aggressive meningioma development (40,41).

As mentioned above, the meningothelial and fibroblastic subtype are the dominating histological subtypes among the WHO grade I meningiomas. Thus, it would be interesting to model the development of these major subtypes in mice. The knowledge regarding the development of WHO grade I-subtypes could be improved recently by generating a mouse model based on inactivation of meningeal *NF2* by using the prostaglandin D2 synthase (*PGDS*) gene promoter. PGDS is a specific marker of arachnoidal cells (42). It was nicely shown that *Nf2* inactivation in PDGS-positive

Table 2 Meningioma cell lines widely used for xenograft meningioma models

Name	Source	Immortalization	Genetics	Ref.
BenMen1	Meningothelial meningioma (I)	hTERT	–22q	(57)
IOMM-Lee	Anaplastic intraosseous meningioma (III)	–	No 22q loss	(58)
F5	Anaplastic meningioma (III)	–	–22q	(59)
KT21	Anaplastic meningioma (III)	–	–22q	(60)

WHO grading is given in brackets.

meningeal progenitor cells was capable to give rise to both meningothelial and fibroblastic meningiomas in 38% of mice (43).

One of the key mitogens in meningiomas is platelet-derived growth factor (PDGF) (44,45). Using the PGDS system again, the group from Michel Kalamarides could demonstrate that PDGF overexpression in arachnoidal cells using the RCAS-TVA system (46) could induce meningiomas independent from *Nf2* inactivation (47). Furthermore, malignant transformation of meningiomas could be modeled by combined Nf2 inactivation and PDGF overexpression.

Taken together, using mice with floxed *Nf2* (including the use of PGDS as a meningeal promoter) and meningeal inactivation of *Nf2* it could be established that *NF2* is critical for the induction of a relevant fraction of meningiomas, and that meningioma aggressiveness can be recapitulated by additional *CDKN2ab* inactivation. Based on the site of *NF2* inactivation, both predominating histopathological meningioma subtypes can be generated. Unfortunately, the induction of non-*NF2*-based meningiomas is not well understood. This is especially relevant because several new genes have been identified in *NF2* wild-type meningiomas (*SMO*, *KLF4*, *TRAF7*, *AKT1*), while their potential as true meningioma tumor drivers is unclear so far. Moreover, some drugs targeting these mutations have shown promising results, as recently demonstrated for the AKT inhibitor AZD5363 successfully administered in a patient with metastatic *AKT1*-mutated meningioma (48).

Xenograft models using patient-derived tumor tissue and meningioma cell lines

As shown before, the GEM model available so far have some disadvantages, including the low rate of tumor induction and the long time necessary until substantial tumor growth is recognized. The latter further complicates the evaluation of potential medical treatment strategies.

Implantation of human tumor cells into immune-compromized ("nude") mice is a well-established method to evaluate tumorigenicity and potential treatment efficacy (49). For meningiomas, however, the human tumor cells need to be delivered at sites prone to develop meningiomas in order to respect the environmental factors which modulate tumor growth. These environmental factors include cerebral spinal fluid, arachnoidal, brain, or bone tissue, as well as space differences evident between convexity, skull base, and spinal cord, respectively. Moreover, implantation of cells should not be limited by substantial animal mortality or morbidity do to the operation procedure itself.

There are several papers reporting the implantation of primary meningioma cells or cell lines into the flank of nude mice for monitoring meningioma tumor cell growth and potential treatment effects [for instance (50-54)]. Generally, this process is enhanced by matrigel-based tumor cell formation (55). However, it is debatable whether a subcutaneous flank model can serve as a real meningioma model or not. Thus, details of flank model-derived data will not be discussed in detail in this review.

Characteristics of meningioma cell lines used for xenograft experiments

The use of primary meningioma cultures is restricted to early passages due to cellular senescence, but expression of the telomerase catalytic subunit (hTERT), together with expression of the human papillomavirus *E6* and *E7* oncogenes in cells derived from WHO grade I tumors, may overcome this limitation (56). On the other hand, some established cell lines derived from highly aggressive meningioma variants are available, and the majority of xenograft studies indeed are using the latter. *Table 2* gives an overview about the essential characteristics of widely used

meningioma cell lines.

The best characterized line derived from a benign WHO grade I meningioma is the line BenMen1 (57). The cells are derived from a WHO grade I meningothelial meningioma and show a loss of chromosome 22. The majority of the other reported cell lines used for orthotopic xenograft studies are derived from anaplastic malignant meningiomas, while the line IOMM-Lee unfortunately does not contain the typical loss of chromosome 22q (58) (*Table 2*). The other malignant lines have unlimited growth potential and harbor alterations of the *NF2* gene at chromosome 22, making them eligible for meningioma studies with inclusion of the characteristic *NF2* alterations seen in sporadic meningiomas.

A major limitation of these cell lines is based on the fact that no *NF2* wild-type control cell is available. Therefore, it would be desirable to generate (ideally) patient-derived cell lines from *NF2* wild-type tumors with unlimited growth and subsequent inactivation of *NF2*. Indeed, these cell pairs have been generated in the past. Striedinger *et al.* (61) reported a cell pair called MENII-1, which is derived from a WHO grade II meningioma and have been immortalized by *E6/E7* human papilloma genes. These cells were used to knockdown *NF2*/merlin using NF2-siRNA constructs, yielding a genetically comparable pair of MENII cells with and without merlin expression. However, the usefulness of these paired cells for orthotopic xenografts to model the effect of merlin loss for meningioma growth is unclear. The same group reported the alternative strategy in the same paper (61): malignant KT21 cells with chromosome 22q loss (*Table 2*) were used to overexpress wild-type *NF2*, with successful re-expression of the *NF2* gene product merlin. However, studies using pairwise *NF2* wild type/*NF2* mutant cells with stable merlin loss or merlin overexpression have been not been reported in the context of mouse xenografts.

Cerebral convexity and skull base models

Implantation of primary, non-manipulated cells derived from benign meningiomas was demonstrated to result in a reliable growth of tumors (93% of mice with implanted tumors) after 3 months (62). In this approach, tumor cells were implanted into the convexity of the prefrontal cortex. The tumors exhibited showed typical meningioma features, and in a subsequent study this model was used to test whether celecoxib treatment might affect tumor growth, with only limited success (63). Implantation of meningioma cells directly below the skull to model meningiomas of the convexity have been reported from several groups. Cargioli *et al.* (54) generated two different meningioma cell lines (Me3TSC and Me10T) by hTERT immortalization and observed after a period of 16 weeks that all mice with injected meningioma cells harbored meningioma-like tumors. Michelhaugh *et al.* (64) generated a cell line from a WHO grade I meningioma which was spontaneously immortal and observed orthotopic tumor growth, while the observation time of these animals was not described in detail. Our group has performed several studies with injection of IOMM-Lee cells for modeling convexity meningiomas, and animals were subsequently treated with different systemic drugs either by intraperitoneal injection, or by oral application. Normally, untreated mice are alive for 12–16 days in this model, while significant extension of survival can be achieved by systemic drug treatment (31,65,66). Moreover, the explanted tumors can be used for biochemical analyses, mostly immunohistochemistry and western blotting, to prove the orthotopic downregulation of the desired drug target. However, a major drawback is the fact that the tumor growth of IOMM-Lee cells is fast, prohibiting longer observation periods with ongoing treatment, or after cessation of drug application. Recently, xenografts (tumorspheres) derived from malignant meningioma were implanted into the convexity and successfully treated with oncolytic herpes simplex virus by another group, with a surprisingly low number of implanted cells necessary for tumor induction (67). It should be mentioned that convexity-based xenograft models open the opportunity to irradiate the tumor in order to evaluate possible radiation-associated treatment augmentation (31).

To model growth of meningiomas at the skull-base, a number of studies have been published. Earliest reports showed successful growth at both convexity and skull base of immortalized cell lines (CH-157-MN and IOMM-Lee). Tumor growth was successful in the majority of implantation procedures (68). Other groups have implanted meningioma cells (IOMM-Lee) into the region of the temporal fossa to model the growth of skull base meningiomas (69,70). In one study, mice with implanted IOMM-Lee cells at the skull base were treated with Temozolomide, and significant survival benefit was seen (71). In general, a major disadvantage of xenograft models is the dependency on an immunocompromised host, deleting potential important immune-cell based antitumor processes. Moreover, the growth characteristics may not recapitulate the situation in humans completely, and it

Table 3 Orthotopic meningioma xenograft models

Site of injection	Cell type*	Treatment	Survival (days)	Ref.
Convexity (Subdural)	P (I)	Celecoxib	>90	(62,63)
Skull base & Convexity	IOMM-Lee, CH-157-MN (III)	–	23 (#)	(68)
Convexity (Subdural)	Me3TSC (I), Me10T (I)	–	112 (#)	(54)
Convexity (Subdural)	KCI-MENG1 (I–III)	–	26 (#)	(64)
Convexity (Subdural)	P (I-III)	Oncolytic HSV	90	(67)
Skull base	IOMM-Lee	Temozolomide	up to 43	(71)
Convexity (Subdural)	IOMM-Lee	Temsirolimus, cilengitide, sorafenib, regorafenib	up to 20	(31,65,66)
Convexity (Subdural)	BenMen1 (I)	–	NA	(57)
Convexity (Subdural), Skull base	P (I–III), IOMM-Lee	–	>84	(69)
Skull base	KT21 (III)	–	Up to 35	(72)
Skull base	BenMen1 (I)	Diet (AR-42)	Up to 24	(73)
Convexity (Subdural)	IOMM-Lee & CH157MN	Pre-irradiation of cells	Up to 28	(74-76)
Convexity (Subdural)	IOMM-Lee	Verotoxin-1	Up to 49	(70)

CL-cell line (immortalized); WHO grading is given in brackets. *, P-primary tumor cell; #, animals were killed.

is not completely clear how closely related the immortal meningioma cell lines are in fact to the human tumors. *Table 3* summarizes the key features of orthotopic meningioma xenograft models.

Monitoring of mouse meningioma tumor growth

It is highly desirable to have monitoring options for meningioma mouse models available. In case of GEMM, the rate of tumor induction *per se* needs to be evaluated, and, in case of successful tumor induction, growth rate and potential treatment effects can be followed. For xenograft models, the induction rate is usually high, but a true orthotopic growth and potential treatment effects need to be evaluated. Two principle ways are available: imaging using small-animal MRI, and bioluminescence-based (BL) methods.

MR imaging to detect the rate of tumor induction in GEMM for meningiomas have been reported by Kalamarides *et al.* (34). Additionally, the same group has successfully applied BL to detect the growth of genetically-induced meningioma (40). The most widely used cells for xenograft imaging are IOMM-Lee and KT21 (71,72). MRI monitoring as a valuable tool for monitoring of growth and treatment response has been reported by several groups (64,66,77,78) (*Figure 1*). On the other hand, a less invasive (and less expensive) method is the use of BL for cells which have been labeled before with GFP (green fluorescent protein) or other fluorescence dyes. Iwami and colleagues (79) used green fluorescence (GFP)-labeled IOMM-lee cells and could show nice tumor growth within 14 days. Both MRI and BL surveillance is an essential requirement for the study of meningioma growth in mice.

Conclusions

Mouse models, either based on the inactivation of specific meningioma-associated genes, or based on orthotopic implantation of human xenograft meningioma cells in mouce, provide valuable insight into growth kinetics and treatment effects. Incorporation of newly identified genes altered in meningiomas in both models is challenging, but will enhance the knowledge about the impact of these genes and their potential treatment. For an overall assessment of a mouse meningioma model, all relevant clinical features of meningiomas should be considered.

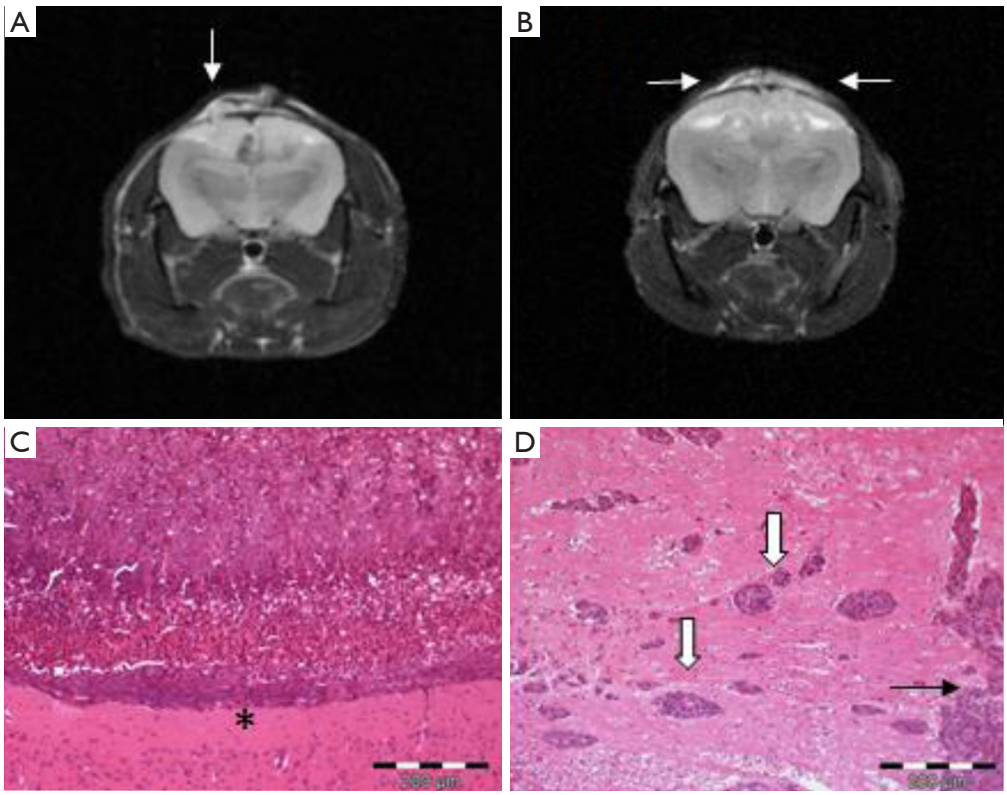

Figure 1 Characteristics of orthotopic IOMM-Lee xenografts into nude mice. (A,B) MRI pictures demonstrating a nodular (A, arrow) or plaque-like (B, arrows) growth pattern at the convexity (Courtesy of Marcus Tuchen, Magdeburg); (C,D) histology reveals either tumor growth in the subarachnoid space without brain (*) infiltration (C), or islands of infiltrating meningioma cells from the surface (arrow) or using the Virchow-Robin space (D) (open arrows). MRI, magnetic resonance imaging.

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Footnote

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