Management of atypical and anaplastic meningioma

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Incidence and Prevalence

The annual incidence of meningioma is approximately 6 per 100,000. These tumors occur mostly in the middle-aged or elderly patients, but they can also occur in younger patients, mainly with neurofibromatosis Type 2. Atypical and anaplastic meningiomas represent a small subgroup with histological and clinical features suggesting aggressive behavior. Due to the lack of one clear histopathological classification in the past, there are numerous inconsistencies in the literature. Therefore the rates of atypical and anaplastic meningiomas reported in the literature vary considerably, ranging from 4.7% to 19.8% for atypical and from 1% to 7.2% for anaplastic tumors. It is known that the prevalence of benign meningiomas is higher in women. In atypical meningiomas there is an equal male:female ratio or even a slight female predominance. In contrast, anaplastic meningiomas seem to be more common in male. Furthermore, atypical and anaplastic meningiomas appear earlier in life.

Most studies either do not present exact data about the location of atypical and anaplastic meningiomas or mix the two types of tumors. Looking at the reported cases one can say that atypical meningiomas are located in 65% over the convexity, the falx or the parasagittal region, in 31% on the skull base, in 2% on the tentorium, and in 2% in the posterior fossa. For anaplastic meningiomas, the percentages change to 77% (convexity, falx, and parasagittal), 18% (skull base), 3% (tentorium), and 2% (posterior fossa). Sade et al. report that 75% of atypical and 80% of anaplastic meningioma are found over the convexity and 25% and 20% respectively on the skull base. There are only a few reports of atypical and malignant spinal meningiomas, suggesting that tumors in this location have a different pathological behavior as they rarely show malignant transformation or recurrence even if not totally resected. The differential meningeal embryogenesis may result in the predominance of one arachnoidal cell type over the other at certain location. Metastases for meningiomas are rare, even for anaplastic meningiomas.
The lungs are the most common site for seeding but metastases were also found in the bone, liver, skin and subcutaneous tissue.\textsuperscript{12,29-31}

Atypical and anaplastic meningioma can occur after cranial irradiation for tumor or other conditions, especially in younger patients.\textsuperscript{32} It is reported that 2% of patients with a meningioma have a prior history of high dose radiotherapy for intracranial neoplasm, including pituitary adenomas, medulloblastomas, astrocytomas, and acoustic neuromas.\textsuperscript{12,33} The incidence of 76% benign, 19% atypical and 4% malignant among radiation-induced meningioma with high dose therapy and 90% benign and 10% atypical after low dose radiotherapy is reported.\textsuperscript{34} As radiation induced atypical and anaplastic meningiomas show a different clinical course and seems to be different pathology they are discussed in a separate chapter.

Pathology

As mentioned, the histopathological classification or grading of atypical and anaplastic meningioma has been a topic of debate. Nowadays most studies refer to the 2000 WHO criteria for their classification, which have not changed with the 2007 edition (Table 1).\textsuperscript{14}

Meningioma classify for the atypical type if they show increased mitotic activity or three or more of the following histological features: increased cellularity, small cells with a high nuclear: cytoplasmic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of ‘spontaneous’ or ‘geographic ‘ necrosis. Increased mitotic activity is defined as 4 or more mitoses per 10 high-power (40x) fields (defined as 0.16mm\(^2\)) (figure 1). Anaplastic meningioma exhibit histological features of frank malignancy far in excess of the abnormalities present in atypical meningioma. These include either obviously malignant cytology resembling that of carcinoma, melanoma or high-grade sarcoma, or a markedly elevated mitotic index of 20 or more mitoses per the high-power fields (defined as 0.16mm\(^2\)) (figure 2).\textsuperscript{14} Brain invasion, characterized by irregular, tongue-like protrusions of
meningioma cells infiltrating underlying parenchyma, without an intervening layer of
leptomeninges connotes a greater likelihood of recurrence and can occur in histologically
benign, atypical and anaplastic meningioma. It is estimated as an adverse prognostic factor for
tumor recurrence and is associated with a significant decrease in survival.\(^{35,36}\)

The clinical course and prognosis of atypical and anaplastic meningiomas seems to be
heterogeneous.\(^{9,10}\) For example, the clinical behavior of radiation-induced meningiomas
differs from similar meningiomas of the same pathological grade.\(^ {32}\) A differentiation of ‘de
novo’ atypical and anaplastic meningiomas versus meningiomas with progression has been
proposed as they seem to have different clinical courses.\(^{9,35}\) It is accepted that atypical and
anaplastic meningiomas evolve by the accumulation of cytogenetic aberrations and that
subsequent genomic changes result in a poorer clinical outcome. Also the hormone receptor
status may play a role to predict the outcome. Therefore a future classification may consider
genetic as well as hormone receptor studies as part of the diagnosis.

**Progression**

Meningiomas can progress from benign to atypical or anaplastic variants, as is well
documented with gliomas.\(^ {1,2,4,9,24,35}\) This phenomenon, in which a neoplasm changes
irreversibly in one or more characteristics, has been termed *tumor progression*.\(^ {37}\) Such a
biological and clinical progression reflects the sequential appearance of cytogenetically
acquired changes.\(^ {38,39}\) Glioblastomas can develop *de novo* or progress from a low-grade or
anaplastic astrocytoma termed primary and secondary glioblastoma.\(^ {14,40}\) Recently, the
differentiation of such ‘de novo’ and ‘transformed’ types of atypical and anaplastic
meningiomas has been proposed as they show a significant different overall survival.\(^ {9,35}\)
Between 0.16-2% of all meningiomas experience malignant progression and the rate of
progression in recurring tumors is higher in atypical than in benign meningiomas.\(^ {2,4,10,24,35,41}\)
Up to 28.5% of recurrent meningiomas transform to malignant varieties,\(^ {1,2}\) and the risk of
progression from atypical to malignant ranges from 26% to 33%. The period of time that elapses between the appearance of a tumor and its progression to malignancy is variable. Some describe it shorter for tumors progressing to the anaplastic variant than for tumors progressing from benign to atypical. Yang et al found a mean period for malignant progression of 70.0 months from benign to atypical meningiomas and of 89.7 months from benign to anaplastic meningiomas. The period of progression from atypical to anaplastic is described to be considerably shorter (39.8 months), a fact that is confirmed by other studies. Tumors with malignant progression occur in atypical meningiomas in 35-38% and in 65-70% of anaplastic meningiomas. On the other hand ‘de novo’ atypical meningiomas occur in 62-75% in atypical and 25-30% in anaplastic meningiomas. Meningioma located over the convexities or of the parasagittal location seem to progress more often to malignancy than meningiomas of the skull base. The average number of operations performed in meningiomas with malignant progression is higher than in ‘de novo’ aggressive meningiomas, which is due to their more aggressive behavior (Figure 3 and 4).

Several studies show that progression in meningioma is associated with cytogenetic alterations and changes in the hormone receptor status, which might also be markers of malignant potential that influence tumor recurrence and poor prognosis.

**Hormone receptors and proliferation indices**

Progesterone receptor expression in meningiomas relates to the tumor’s grade and recurrence. A Progesterone receptor-positive status is more frequent in benign than malignant tumors and there is an association between recurrence and Progesterone receptor-negative status. Overall survival and tumor recurrence in atypical and anaplastic meningiomas seem to be associated with a high Ki-67 labeling index. But significant overlap exists in the ranges for benign, atypical and anaplastic meningiomas. Proliferative indices in Progesterone receptor-positive meningiomas are lower than those in Progesterone receptor-
negative tumors. $^{47,52}$ Thus, negative Progesterone receptor and a higher mitotic activity, indicate more aggressive behavior. $^{43,46-49,52}$ Atypical meningiomas with progression from a benign tumor often have negative Progesterone receptor and a higher proliferative index, which may explain the more aggressive behavior than the de novo atypical meningioma. $^9$

Estrogen receptors seem to be more present in atypical and anaplastic Meningiomas. $^{43,52}$

**Genetics**

Genetic alterations in meningiomas are known to increase as the tumors become more aggressive. $^{45,53,54}$ In general, karyotypic abnormalities are more extensive in atypical and anaplastic meningiomas including multiple translocations between different chromosomes and monosomy of multiple chromosomes. In addition to abnormalities of the chromosome 22, which were among the first cytogenetic alterations recognized in solid tumors, $^{14}$ alterations of chromosomes 1, 6, 9, 10, 14, 16, 18, 19 and sex chromosomes are most often detected in atypical and anaplastic meningiomas. $^{44,53,54-60}$ Partial loss or monosomy of chromosomes 1, 10, and 14 is associated with more aggressive behavior in meningiomas. $^{53,54,60-70}$ Loss of chromosome 18 and loss of part or monosomy of chromosome 10 and an increased monosomy or derivative chromosome 1 in combination with monosomy of chromosome 14, which may represents a bad prognosis, occurs more frequently in meningiomas with progression. $^9$ (Figure 5) Two of the most frequent early events in meningioma tumorigenesis involve the loss of expression of the neurofibromatosis 2 (NF2) and 4.1B genes. The 4.1B gene is shown to interact with the tumor suppressor in lung cancer-1 (TSLC1) protein expression, which was shown to be absent in 48% of benign, 69% of atypical, and 85% of anaplastic meningiomas. $^{71}$ Over-expression of p53, which is probably a surrogate for p53 mutations, $^{72,73}$ is described to be a predicting factor for the progression in meningioma. $^{35,74,75}$ It is known that the expression of several genes linked to cell cycle regulation are upregulated in atypical and anaplastic meningiomas and that expression of several members
of the insulin-like growth factor (IGF) and wingless (WNT) signaling cascade is increased in atypical and anaplastic meningiomas with loss on chromosome 10 and 14, suggesting that aberrations of these pathways may also play a role in progression. Cai and colleagues found that the combination of the deletion of 1p and 14q correlated with decreased survival in patients with atypical meningiomas. The WHO 2007 classification determines a stepwise change in the genetic characteristics of benign meningioma, as these become anaplastic (Table 2).

**Imaging**

Until today there is no specific imaging modality to diagnose atypical or anaplastic meningioma. Several features on their appearance in computed tomographic scanning have been described, but all of them are non specific and can also be seen in benign meningioma: Marked edema, heterogeneous appearance, homogenous dense contrast enhancement, irregular or nodular cerebral surface, mushrooming on the outer edge of the lesion, bone destruction and absence of calcification. But computed tomography still has a role to define the extent of bone invasion in preoperative planning.

Unfortunately magnetic resonance imaging (MRI) does not allow a precise diagnosis either. But recently, perfusion MR imaging was evaluated to differentiate benign and malignant meningiomas on the basis of the differences in perfusion of tumor parenchyma and/or peritumoral edema by measuring the cerebral blood volume (rCBV) and the corresponding relative mean time to enhance (rMTE) (in relation to the contralateral normal white matter) in both tumor parenchyma and peritumoral edema. Statistical significance was only found in the rCBV and rMTE in peritumoral edema with higher values in malignant meningiomas. Also diffusion-weighted MRI findings of atypical/malignant meningiomas and benign meningiomas differ. Atypical/malignant meningiomas have lower intratumoral ADC values than typical meningiomas. Mean ADC values for peritumoral edema do not differ
between benign and atypical meningiomas. Magnetic resonance spectroscopy (MRS), which helps in the diagnosis and differentiation between lesions on MRI, has also been used to distinguish higher grade from benign meningiomas. But no specific spectral characteristics could be found for these subtypes of meningiomas, except for a peak in lactate and a probable increased choline/creatin ratio in higher-grade meningiomas.

**Surgical treatment**

The grade of surgical resection of all types of meningioma is the most important prognostic factor for recurrence. It allows definitive diagnosis and reduces the mass effect. As with benign meningiomas, the surgical excision should be as complete as possible including if possible a margin of the dura mater around the tumor, any infiltrated soft tissue and the bone infiltrated by the meningioma. The likelihood of gross-total resection varies considerably by primary sites. Careful preoperative planning should include MRI in combination with MR-angiography/venography if needed to evaluated dislocation and stenosis of parent vessels and the pattern of venous draining. CT scan should be performed for the evaluation of bony infiltration by the tumor. Digital substraction angiography should be used, if the arterial or venous system cannot properly be evaluated by MRI or if a revascularization procedure is considered during surgery. As „the first time is the best time“ the first surgery is the most important one, especially in higher-grade meningiomas. In further operations a complete excision is getting more difficult without significant morbidity due to the fact that most patients underwent high dose or stereotactic radiation therapy which in combination with a lack of an arachnoidal plane leads to significant adhesion of the meningioma to the brain parenchyma and the surrounding neurovascular structures. It is described that, once recurrence develops, prognosis is poor because of a high likelihood of treatment failure. In skull base atypical and anaplastic meningiomas appropriate skull base approaches should be used for better exposure of the tumor. It should allow early
devascularization of the tumor, removal of infiltrated bone, less or no brain retraction and a short working distance. Rarely preoperative embolization is needed in these cases, but the decision should be made on a case-by-case basis. Eventually cerebral revascularization with a bypass should be considered, if tumor infiltration of the wall of the internal carotid artery is presumed or if a total tumor excision is only achievable with the sacrifice of an important vessel.

**Radiation Therapy**

Historically, meningiomas were considered resistant to irradiation. Moreover, there has been apprehension regarding the malignant degeneration of irradiated tumors as well as about the relationship between irradiation and the ultimate development of meningiomas. The effect of radiation therapy on atypical and anaplastic meningioma is difficult to analyze. Because of the small numbers a distinction between these two types is often not made. Moreover, because of the variation of histopathological classification a comparison of the different studies is difficult. Unfortunately, the exact grade of resection is often lacking or imprecise.

**Conventional fractionated Radiation Therapy**

Although there is no prospective study to compare early postoperative radiation with radiation of recurrent tumor, the consensus in the literature favors early fractionated radiation therapy. The largest series of 119 patients with atypical and anaplastic meningiomas shows 5- and 10-year overall survival rates of 65% and 51%, respectively, with age >60 years (p=0.005), Karnofsky performance status (p=0.01) and high mitotic rate (p=0.047 being significant factors for the outcome. The grade of surgical resection in this study was not a significant prognostic factor, probably due to the difficulty to retrospectively assess the completion of resection. Others show significant better outcome in patients with gross total
resection and adjuvant radiation therapy. Goyal et al. showed a local tumor control of 87% at 5 and 10 years with external-beam radiation therapy in 8 patients with atypical meningioma following gross total resection.

**Stereotactic Radiosurgery**

The role of stereotactic radiosurgery is nowadays well defined for benign meningiomas. For higher-grade meningiomas most studies report fairly good results with low complications. Local tumor control in atypical meningiomas is described to be between 64% and 68% at 5-year follow-up. Others report a 3-year survival rate of atypical and anaplastic meningiomas to be 24.4 and 13.9 months, respectively. Harris et al. reported their treatment results for 18 atypical and 12 anaplastic meningiomas that had undergone radiosurgery. Atypical meningiomas had 5- and 10-years survival rates of 59%, whereas anaplastic meningiomas had rates of 59% and 0%, respectively. Ojemann et al. treated 37 lesions in 19 patients with recurrent atypical and anaplastic meningioma with 2- and 5-year progression rates of 48% and 34%, respectively.

Stereotactic radiosurgery has its role in the treatment of atypical and anaplastic meningiomas for nodular residual or recurrent tumor, this in combination with fractionated radiation therapy.

**Brachytherapy**

Brachytherapy may play a role in the therapy of atypical and anaplastic meningioma, but the data available in the literature are limited. Ware et al. report 22 patients with recurrent atypical and anaplastic meningioma, which were treated by surgery, and brachytherapy with implantation of I-125 into the tumor bed. The median survival was 2.4 years, but 27% showed wound problems.
**Proton Beam Therapy**

Proton beam therapy seems to be promising as it allows high dosages of radiation delivery to region near critical structures, but it has limited availability and its costs are high. Moreover there are implicit limits to the size of tumor that can be treated. The delivery of higher target doses by 3D-treatment planning assisted combined photon and proton beam therapy with target doses >60y photon significantly improved local control rates and survival. Especially in atypical and anaplastic meningioma proton beam therapy should be considered as other treatment modalities have a high failure rate.

**Chemotherapy**

The role of chemotherapy in the treatment of atypical and anaplastic meningiomas remains unclear. Several chemotherapeutic agents have been used, mainly for meningiomas with progression or recurrence after radiotherapy or for unresectable tumors. The use of conventional chemotherapy with intravenous cyclophosphamid, adriamycin and vincristine as well as the treatment with interferon α-2B showed moderate success and the use of Tamoxifen has been shown to be ineffective. The use of the antiprogesterone agent mifepristone (RU-486) was first thought to be successful in stabilizing the disease, but in a phase III placebo-controlled trial no significant evidence of activity was found.

Hydroxyurea, which inhibits meningioma cell growth in vitro by causing apoptosis, has been used as a treatment for recurrent and rapidly growing meningiomas. It has shown modest clinical activity against inoperable or recurrent benign meningioma with clinical and radiological stabilization, but it probably seems to be ineffective in higher-grade meningiomas. Novel therapeutic drugs like anti-platelet derived growth factors and anti-epidermal growth factor compounds are under investigation and may be used in the future for atypical and anaplastic meningiomas.
Outcome

It is difficult to give clear answers about the clinical outcome of atypical and anaplastic meningiomas because in a lot of studies they were combined for outcome analysis or no clear differentiation was made between the two types due to the small number of tumors. Median survival time for anaplastic meningioma is described by Perry et al. to be 1.5 years, with a 5-year mortality rate of 68%. Yang found that the median survival rate for anaplastic meningiomas is $39.8\pm7.8$ months, and the 3- and 5-year survival rates are 55% and 35%, respectively. The mean overall and mean recurrence-free survivals in atypical meningiomas are reported to be $142.5\pm6.0$ months and $138.5\pm7.0$ months, respectively. Krayenbühl et al. report an overall average survival time for patients with atypical and anaplastic meningiomas to be 4.54 years (range 0.07-15.95 years) and 1.48 years (range 0.18-13.26 years), respectively. Recently differences in outcome in ‘de novo’ atypical and anaplastic meningiomas and tumors with malignant progression were found. Overall survival and recurrence-free survival are significantly worse in patients with malignant progression than in those without malignant progression ($p=0.007$ and $p=0.005$, respectively). The average survival time for patients with ‘de novo’ atypical meningiomas was 5.36 years (range 1.02-15.95 years) compared with 1.95 years (range 0.07-7.71 years) for those with malignant progression ($p=0.01$).

Treatment algorithm

The treatment of anaplastic meningioma should comprise in every case beside complete tumor resection adjuvant radiation therapy, either with fractionated radiation therapy, stereotactic radiosurgery or proton beam irradiation. In atypical meningioma the situation is more complex due to the difference in clinical course among subtypes. A ‘de novo’ atypical meningioma with progesterone positive receptor status and low proliferation
index can be observed when surgical excision was complete. Otherwise radiation therapy should be considered.

**Conclusion**

Atypical and anaplastic meningiomas are distinct subgroups of meningiomas. They can be further divided into ‘de novo’ tumors and tumors with progression, which has influence on their outcome. These subgroups need further investigation in the future to better define the clinical prognosis and to understand the pathway of progression. Surgery remains the main therapeutic option for these tumors, but adjuvant radiotherapy should be recommended. The role of proton beam therapy as primary adjuvant therapy should be evaluated. Chemotherapy currently has a limited role in the treatment strategy of atypical and anaplastic meningioma but new agents should be developed for these difficult to treat lesions.
References


controlled study of mifepristone (RU) for the treatment of unresectable meningioma.

ASCO Proceedings 20:56a, 2001

Table 1

Classification and grading of meningiomas according to the histological subtype

<table>
<thead>
<tr>
<th>Grade I (benign)</th>
<th>Grade II (aggressive)</th>
<th>Grade III (malignant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningothelial</td>
<td>Atypical</td>
<td>Anaplastic</td>
</tr>
<tr>
<td>Fibrous (fibroblastic)</td>
<td>Clear cell</td>
<td>Rhabdoid</td>
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<tr>
<td>Transitional (mixed)</td>
<td>Chordoid</td>
<td>Papillary</td>
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<td>Psammomatous</td>
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<td></td>
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<tr>
<td>Angiomatous</td>
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<td></td>
</tr>
<tr>
<td>Microcystic</td>
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<td></td>
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<tr>
<td>Secretory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoplasmacyte-rich</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metaplastic</td>
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</table>
Table 2

Genetic model of meningioma tumorigenesis and malignant progression according to the WHO\textsuperscript{14}

<table>
<thead>
<tr>
<th>Arachnoidal (meningothelial cell) or precursor cell</th>
<th>Benign Meningioma</th>
<th>Atypical Meningioma</th>
<th>Anaplastic Meningioma</th>
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<tbody>
<tr>
<td>- 22q (40-70%)</td>
<td>-1p (40-75%)</td>
<td>-1p (70-100%)</td>
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</tr>
<tr>
<td>NF2 mutations (30-60%)</td>
<td>-6q (30%)</td>
<td>-6q (50%)</td>
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<tr>
<td>Loss of 4.1B expression (20-50%)</td>
<td>-10 (30-40%)</td>
<td>-9p21 (60-80%)</td>
<td></td>
</tr>
<tr>
<td>Loss of TSLC 1 expression (30-50%)</td>
<td>-14q (40-60%)</td>
<td>-10 (40-70%)</td>
<td></td>
</tr>
<tr>
<td>PR expression (50-90%)</td>
<td>-18q (40%)</td>
<td>-14q (60-100%)</td>
<td></td>
</tr>
<tr>
<td>EGFR, PDGFRB activation</td>
<td>+1q, 9q, 12q, 15q, 17q, 20q, (30-50% each)</td>
<td>-18q (60-70%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of TSLC 1 expression (70%)</td>
<td>NDRG2 hypermethylation (70%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of PR expression (60-80%)</td>
<td>Loss of TSLC 1 expression (70%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telomerase / hTERT activation (60-95%)</td>
<td>Loss of PR expression (80-90%)</td>
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<tr>
<td></td>
<td>Notch, WNT, IGF, VEGF activation</td>
<td>17q23 amplification (40%)</td>
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**Figure Legends**

Figure 1: Histopathological images (hematoxylin and eosin stain) of an atypical meningioma showing increased cellularity with area of necrosis (A), high nuclear: cytoplasmic ratio with prominent nucleoli (B). Increased mitotic activity on MIB-1 labeling (C).
Figure 2: Histopathological images (hematoxylin and eosin stain) of an anaplastic meningioma showing sarcoma-like morphology with mitotic figures (A and B), and signs of brain invasion (C). High mitotic activity on MIB-1 labeling (D).

Figure 3: A de novo atypical meningioma before (A) and after (B) resection and at the 4-year follow-up exam (C). The tumor did not recur.
Figure 4: Atypical meningioma with progression at the time the progression was diagnosed. The patient had had two previous recurrences. (A) Before resection; (B) After resection. The tumor recurred for the fourth time 15 months later (C), and again 9 months after resection (D). Rapid growth was evident again within 3 months (E). Two months after another resection (F), a new recurrence appeared (G, H).
Figure 5: Cytogenetic findings of a de novo atypical meningioma (A) and an atypical meningioma with progression (B and C). The transformed meningioma shows additional monosomy of chromosomes 10 and 18, derivative chromosome 1 and monosomy of chromosome 14.