Oligodendroglioma

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8.1 Epidemiology

Approximately 5% of all primary brain tumors are oligodendroglial tumors. Their incidence is in the range of 0.5 per 100,000 per year. The median age at diagnosis is 40–45 (www.cbtrus.org).

8.2 Symptoms and Clinical Signs

Oligodendrogliomas are infiltrative, mostly supratentorial tumors that frequently originate in the frontal lobes (50%), often bilaterally affecting the white matter. Corpus callosum and basal ganglia may also be involved. Seizures are the most common mode of presentation (50–70%), followed by focal neurological signs such as aphasia and personality changes. The tumors tend to spread within the central nervous system, but extraneural metastases are rare.

8.3 Diagnostics

8.3.1 Synopsis

Although neuroimaging (CT, MRI) can be highly suggestive of an oligodendroglial tumor, the diagnosis can only be made histologically. Thus, a surgical procedure, resection or biopsy, is always required.

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8.3.2 Body

Neuroimaging plays a central role in the diagnosis and follow-up of oligodendroglial tumors (Fig. 8.1). MRI is superior to CT because of a better delineation of tissue structure and the availability of imaging in all planes, and is therefore the imaging method of choice. CT may aid in the detection of calcification, which is a common feature (70–90%). T1-weighted MRI or CT delineates areas of contrast enhancement, whereas T2-weighted images are sensitive for the detection of tumor extension into the brain parenchyma. Oligodendrogliomas

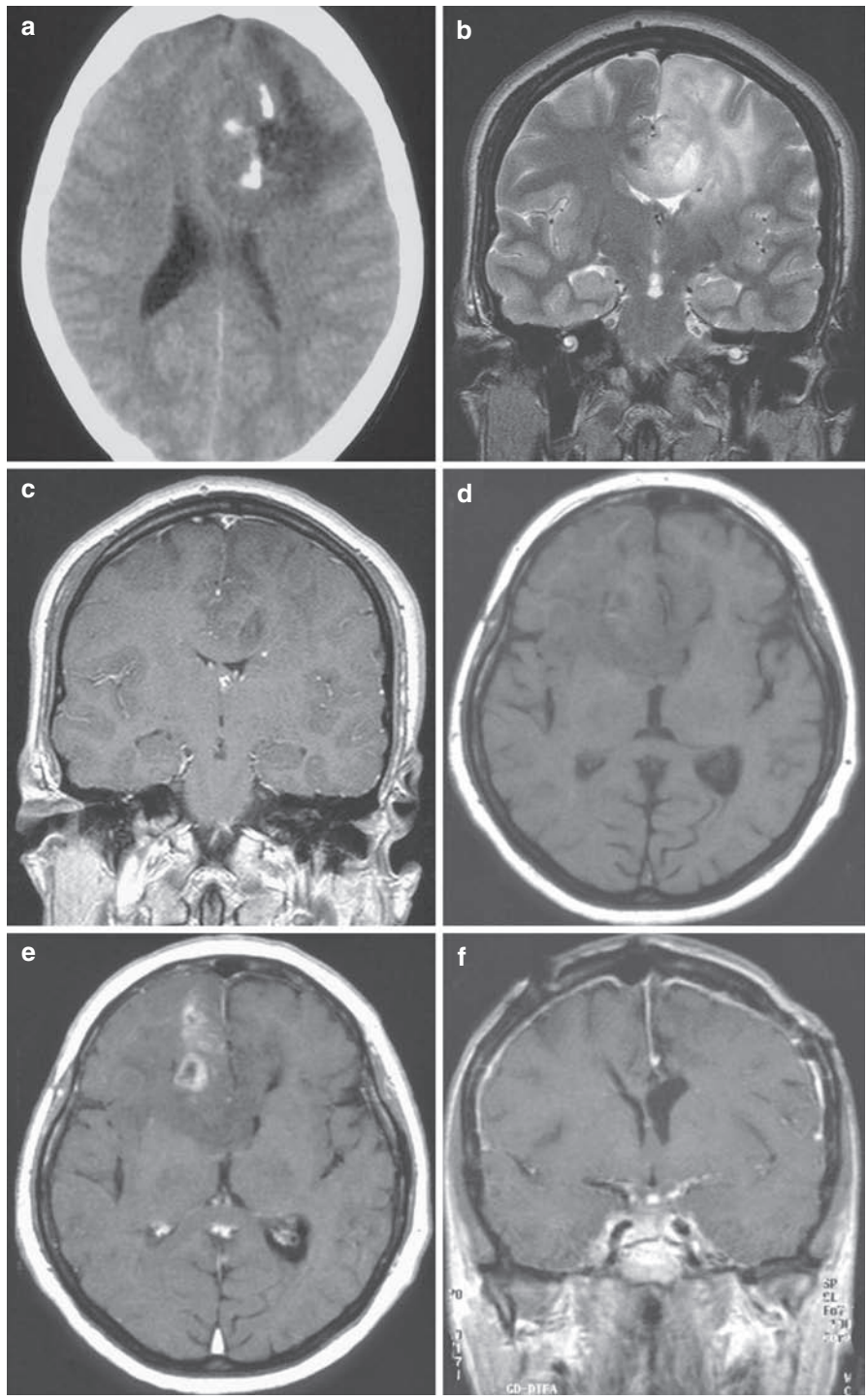

Fig. 8.1 (**a–f**) Typical neuroimaging features of oligodendroglioma. (**a**) Axial CT of a left frontal oligodendroglioma characterized by calcification. (**b**) Coronary T2-weighted MRI of a left frontal oligodendroglioma with thickening of the cortex and spread into the corpus callosum. (**c**) The corresponding contrast-enhanced T1-weighted sequence shows no enhancement in the tumor. (**d**) T1-weighted MRI of a right frontal anaplastic oligodendroglioma with tumor extension crossing the midline. (**e**) Contrast enhancement delineates areas of cystic regression in this tumor. (**f**) Coronary T1-weighted MRI after resection of a left frontal oligodendroglioma shows meningeal enhancement across the convexity of both hemispheres and in the basal subarachnoid space, suggestive of leptomeningeal tumor cell dissemination (U. Ernemann, Tübingen, Germany)

and oligoastrocytomas may not be differentiated by imaging, but can be distinguished from astrocytomas by the higher frequency of calcification, cystic regressive changes, and hemorrhages. Perifocal edema and contrast enhancement are more often found in anaplastic (grade III) than in grade II tumors, but are not reliable parameters for the differential diagnosis. PET and SPECT are experimental imaging techniques that have no role in the standard care of these tumors. Cerebral angiography is performed prior to surgery as requested by the surgeon. Although the tentative diagnosis of an oligodendroglial tumor may be made by neuroimaging criteria, the diagnosis should always be confirmed histologically. The key morphological features are defined by the WHO classification [10] as detailed below.

In the course of disease, the response to therapy is assessed by neuroimaging using the Macdonald criteria, which emphasize contrast enhancement [11] or modifications thereof for nonenhancing tumors. These response criteria may experience further modifications as antiangiogenic agents are moving into the clinic (see below).

8.4 Staging and Classification

8.4.1 Synopsis

Oligodendroglial tumors are classified as pure oligodendroglial or oligoastrocytic (mixed) and assigned the WHO grades II (low grade) or III (anaplastic) [10]. Molecular markers, notably 1p/19q status and MGMT status, are increasingly used for molecular stratification, but have not yet assumed a firm place in clinical decision making.

8.4.2 Body

The distinction of WHO grade II oligodendrogliomas and oligoastrocytomas and their anaplastic variants (WHO grade III) is made by histopathological criteria [10]. Oligodendrogliomas are well-differentiated, diffusely infiltrating lesions that consist of cells resembling oligodendrocytes. The typical features of these tumors may only be appreciated in paraffin-embedded tissue. Oligoastrocytomas contain two distinct cell populations that correspond to tumor cells characteristic of oligodendrogliomas and grade II astrocytomas (Fig. 8.2). Immunohistochemical markers for the diagnosis of the oligodendroglial component have not been identified. Anaplastic tumors exhibit higher cellular density, pleomorphic cells, and an increase in mitoses and microvascular proliferation. Importantly, according to the current WHO classification, the detection of necroses in an anaplastic oligodendroglial tumor per se does not make this tumor a glioblastoma.

The loss of genetic material on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is a common finding in oligodendroglial tumors that predicts favorable responses to radiotherapy or chemotherapy [5, 8]. However, there may be no difference in progression-free survival of patients with or without 1p/19q loss who receive no further radiotherapy or chemotherapy [16], suggesting that 1p/19q loss is a predictor of response to genotoxic therapies. The genes mediating this differential course of the disease in histologically indistinguishable tumors have not been identified. The lower frequency of 1p and 19q losses in temporal tumors compared with frontal,

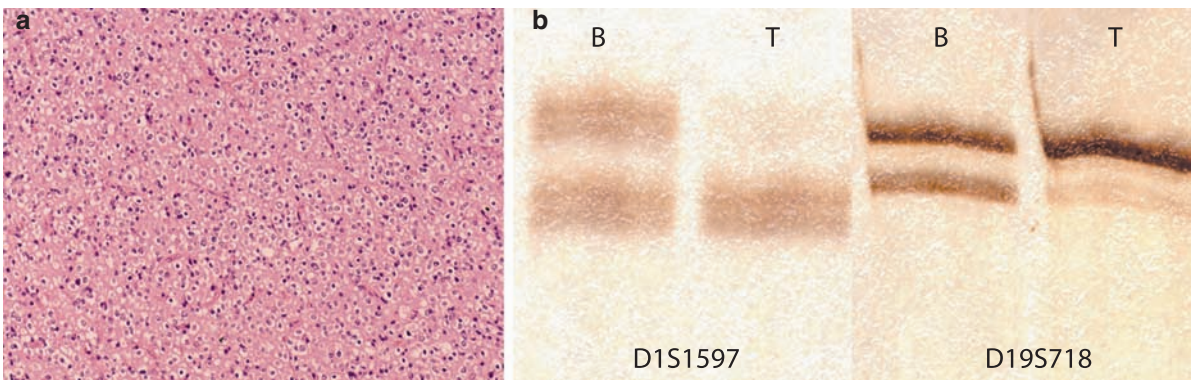

Fig. 8.2 (**a**, **b**) Histological and molecular diagnostics of oligodendrogliomas. (**a**) Typical histological features of oligodendroglioma; (**b**) allelic losses on chromosomes 1p and 19q in an oligodendroglioma: two microsatellite markers, D1S1597 and D19S718, demonstrate two (heterozygous) parental alleles in the DNA of peripheral blood leukocytes (blood, *B*), but only one allele in the DNA of the oligodendroglioma (loss of heterozygosity; *T*, tumor) (W. Müller and A. v. Deimling, Berlin, Germany)

parietal, and occipital tumors may be responsible for a less benign course of temporal tumors [18].

Silencing of the O^6-methylguanine methyltransferase (MGMT) gene by promoter methylation results in the loss of MGMT protein in the tumor cells and has been associated with favorable responses to alkylating chemotherapy in astrocytic gliomas. The role of MGMT promoter methylation in oligodendroglial tumors is less well defined, but it is probably rather common in these tumors and may contribute to their chemosensitivity [6, 12]. Preliminary results from the German NOA-04 trial indicate that MGMT promoter methylation predicts prolonged disease control in response to either chemotherapy with alkylating agents or to radiotherapy [17].

8.5 Treatment

8.5.1 Synopsis

Surgery, radiotherapy, and chemotherapy have a role in the treatment of oligodendroglial tumors. Neither treatment should be considered curative, but disease control for many years and even decades may be achieved.

8.5.2 Body

WHO grade II oligodendrogliomas and oligoastrocytomas should be treated accordingly since the presence of the oligodendroglial component in a mixed glioma probably determines the better prognosis for mixed tumors compared with pure astrocytic gliomas. Histologically confirmed WHO grade II tumors, which are asymptomatic except for seizures, may be managed using a wait-and-see strategy, especially in younger patients (<40 years) [13]. Symptomatic and, by radiology, well-circumscribed lesions in accessible locations should be resected microsurgically. If surgery has a high risk of neurological morbidity, symptomatic or radiologically progressive lesions should be treated with radiotherapy or chemotherapy. The ongoing EORTC trial 22033-26033 compares focal radiotherapy at 50 Gy with a protracted 3 weeks on/1 week off regimen of temozolomide at 75 mg/m^2 in low-grade gliomas including oligodendroglioma and oligoastrocytoma. Outside clinical trials, younger patients with low-grade tumors are often considered candidates for primary chemotherapy using PCV [7] or temozolomide [14]. When the tumor shows a complete or partial response or remains stable [11], chemotherapy may be discontinued after four cycles of nitrosourea-based chemotherapy or eight cycles of temozolomide, although some centers prefer to administer chemotherapy for 1 year or even until relapse or prolonged myelosuppression. Elder patients or patients with contraindications for chemotherapy should receive radiotherapy (54 Gy, 1.8–2-Gy fractions) as the first-line therapy. These recommendations are based on the assumption that younger patients survive longer and are therefore more likely to experience the neurotoxic side effects of radiotherapy, whereas the long-term toxicity of chemotherapy is considered to be less prominent and is at least less well defined. Treatment options at recurrence include second surgery and, depending on prior treatment, radiotherapy or chemotherapy. Radiotherapy should not be withheld when one first-line chemotherapy has failed, and a second-line chemotherapy should be considered only after radiotherapy has failed. Grade II tumors often exhibit imaging and histological features of anaplastic (grade III) lesions at recurrence.

WHO grade III anaplastic tumors should not be managed with surgery alone because of their less benign natural course. First-line treatment options include radiotherapy or chemotherapy. Combined modality treatment using radiotherapy plus PCV is not considered standard of care because the associated toxicity and the lack of an impact on overall survival seem to outweigh the moderate gain in progression-free survival [5, 9].

Conversely, temozolomide alone as the up-front treatment is probably as effective as PCV alone or radiotherapy alone [17]. Whether temozolomide plus radiotherapy is superior to radiotherapy alone will be tested separately for anaplastic gliomas, including pure anaplastic astrocytomas, *without* 1p/19q loss in the CATNON trial (EORTC 26053-22054) and in anaplastic gliomas *with* 1p/19q loss probably in the NCCTG N0577 trial, which has not started enrollment at this time. The options at recurrence depend on the first-line therapy as outlined for the grade II tumors above.

8.5.2.1 Surgery

The surgical procedure required to make the histological diagnosis of an oligodendroglial tumor can be a stereotactic biopsy with a purely diagnostic intent or an effort at a gross surgical resection. Stereotactic biopsies are performed at locations that preclude resection, with

multiple lesions possibly representing primary cerebral lymphoma or metastatic disease or in elderly, high-risk patients. Surgical resections aim at a reduction of overall tumor volume, relieve elevated intracranial pressure and thereby restore neurological function. The high response rates of oligodendroglial tumors with a favorable molecular profile of 1p/19q loss and MGMT promoter methylation to radiotherapy and chemotherapy suggest that the extent of neurosurgical resection in oligodendroglial tumors is less critical for the outcome than in astrocytic gliomas. This consideration, however, is limited by the failure to diagnose oligodendroglioma with certainty from nonembedded specimens during surgery. Surgeons will therefore either require a biopsy prior to the decision for the type of resection approach or will be guided by neuroimaging features. The result of resection should be verified by postoperative MRI or CT within 48–72 h after the procedure.

8.5.2.2 Radiotherapy

A prospective randomized trial to affirm that radiotherapy, compared to observation, is an effective treatment for oligodendroglial tumors has not been, and will probably never be, performed. There is nevertheless little doubt that radiotherapy at doses of 54–60 Gy administered in 1.8–2 Gy fractions provides enduring local control for many patients with low-grade [4] as well as anaplastic [5, 9] oligodendroglial tumors. The target volume encompasses the tumor area defined by T2-weighted MRI or by the contrast-enhancing lesion where applicable plus a safety margin of 2 cm. Despite the high incidence of leptomeningeal seeding in the course of the disease of up to 30%, prophylactic craniospinal radiotherapy is not recommended because high doses would be required for tumor control and because craniospinal irradiation is poorly tolerated in adult patients in terms of myelosuppression. The latter is particularly relevant because of the well-defined activity of systemic chemotherapy in oligodendroglioma.

8.5.2.3 Chemotherapy

The most established chemotherapy protocols for oligodendroglial tumors include the nitrosourea-based protocol, notably PCV, or monotherapy using temozolomide. The classical PCV regimen consists of procarbazine (60 mg/m^2 p.o. days 8–21), lomustine/CCNU (110 mg/m^2 p.o. day 1), vincristine (1.4 mg/m^2 i.v. days 8 + 29), in 6–8 weekly cycles and produced response rates of more than 50% and median survival times of 15–24 months in patients with recurrent oligodendroglial tumors [8]. Response rates for anaplastic tumors may be even higher when chemotherapy is administered prior to radiotherapy [3]. The most important side effects of PCV chemotherapy other than myelosuppression include allergy for procarbazine, pulmonary fibrosis for nitrosoureas, and polyneuropathy for vincristine.

Mainly because of the easier mode of administration and a more favorable safety profile, temozolomide (150–200 mg/m^2 D1–D5 in 4-weekly cycles) has largely replaced PCV, both for recurrent disease [1, 2] and for first-line treatment [17]. Experimental chemotherapeutic approaches for oligodendroglial tumors failing conventional treatments include, among others, carboplatin (300 mg/m^2 day 1) plus etoposide (VP16, 150 mg/m^2 days 2–3) in 4-week cycles, or bevacizumab plus irinotecan [15]. Intensified PCV regimens plus autologous stem cell transplantation are no longer used.

8.5.2.4 Other

A role for treatments other than surgery, radiotherapy, or chemotherapy has not been defined. Inhibition of migration, invasion, or angiogenesis, or gene therapy should preferentially be performed after the established treatment options have failed and in the context of clinical trials.

8.6 Prognosis/Quality of Life

Younger age, frontal localization, macroscopic resection, high Karnofsky performance score, and lack of contrast enhancement on neuroimaging are favorable prognostic factors. After the tumor-specific treatment has been completed, patients with grade II tumors should have clinical and radiological examinations at 6-month intervals, and patients with grade III lesions at 4-month intervals, at least for the first 3–5 years. The quality of life is often unaffected for years. The morbidity associated with neurosurgery has steadily decreased. Long-term survivors may experience neurotoxic side effects from radiotherapy and chemotherapy, but their incidence in patients treated according to current standards of care is probably low. The survival

rates at 2 and 5 years are in the range of 70–80% and 50–60% with grade II and 60% and 30–40% with grade III lesions.

8.7 Follow-Up/Specific Problems and Measures

Oligodendroglial tumors spread within the central nervous system and cause leptomeningeal seeding in up to 30% of the patients. MRI of the spinal cord and cerebrospinal fluid analysis are therefore necessary when clinical symptoms or signs suggest leptomeningeal disease. The outcome for patients with leptomeningeal disease from oligodendroglial tumors is not inevitably poor compared with other malignancies. The management should follow the recommendations summarized above and may sometimes require craniospinal radiotherapy. Gliomatosis cerebri is defined as the diffuse growth of neoplastic cells, verified by histology, in more than two cerebral lobes, verified by neuroimaging, and has been attributed WHO grade III. Histology may show a diffuse oligodendroglial tumor. Responses to treatment and course of the disease are highly variable, but median survival is only 1 year for all patients and certainly better for patients with focal oligodendroglial as compared with astrocytic histology. Some younger patients may be managed by observation alone whereas symptomatic or progressive lesions should be treated with chemotherapy or large volume radiotherapy to 45–54 Gy in 1.8–2 Gy fractions as outlined above.

8.8 Future Perspectives

The NOA-04 trial has indicated an equal effectivity of radiotherapy and chemotherapy with temozolomide in newly diagnosed anaplastic gliomas [17]. The next trials will pool all anaplastic gliomas by histology, but will separate them according to 1p/19q status. Establishing whether the combination of temozolomide and radiotherapy is better than radiotherapy (or chemotherapy) alone will be the next question to be addressed in large cooperative trials (CATNON, NCCTG N0577). Ultimately, it will be essential to establish therapeutic approaches with a curative intention for these tumors.

References

1. Bent van den MJ, Chinot O, Boogerd W et al (2003a) Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972. Ann Oncol 14:599–602
2. Bent van den MJ, Taphoorn MJ, Brandes AA et al (2003b) Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971. J Clin Oncol 21:2525–2528
3. Bent van den MJ, Kros JM, Heimans JJ et al (1998) Response rate and prognostic factors of recurrent oligodendroglioma treated with procarbazine, CCNU, and vincristine chemotherapy. Neurology 51:1140–1145
4. Bent van den MJ, Afra D, de Witte O et al, for the EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council. (2005) Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet 366:985–990
5. Bent van den MJ, Carpentier AF, Brandes AA et al (2006) Adjuvant procarbazine, lomustine, and vincristine improve progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol 24:2715–2722
6. Brandes AA, Tosini A, Cavallo G et al (2006) Correlations between O6-methylguanine DNA methyltransferase promoter methylation status, 1p and 19q deletions, and response to temozolomide in anaplastic and recurrent oligodendroglioma: a prospective GICNO study. J Clin Oncol 29:4746–4753
7. Buckner JC, Gesme D Jr, O'Fallon JR et al (2003) Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. J Clin Oncol 21:251–255
8. Cairncross JG, Macdonald D, Ludwin S et al, for the National Cancer Institute of Canada Clinical Trials Group (1994) Chemotherapy for anaplastic oligodendroglioma. J Clin Oncol 12:2013–2021
9. Cairncross G, Berkey B, Shaw E et al (2006) Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 24:2707–2714
10. Louis DN, Ohgaki H, Wiestler OD et al (2007) WHO Classification of Tumours of the Central Nervous System. IARC Press, Lyon, France
11. Macdonald DR, Cascino TL, Schold SC et al (1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277–1280
12. Möllemann M, Wolter M, Felsberg J et al (2005) Frequent promoter hypermethylation and low expression of the MGMT gene in oligodendroglial tumors. Int J Cancer 113:379–385

13. Pignatti F, Bent van den MJ, Curran D et al (2002) Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 20:2076–2084
14. Quinn JA, Reardon DA, Friedman AH et al (2003) Phase II trial of temozolomide in patients with progressive low-grade glioma. J Clin Oncol 21:646–651
15. Vredenburgh JJ, Desjardins A, Herndon 2nd JE et al (2007) Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 13:1253–1259
16. Weller M, Berger H, Hartmann C et al, for the German Glioma Network (2007) Combined 1p/19q loss in oligodendroglial tumors: predictive or prognostic biomarker? Clin Cancer Res 13:6933–6937
17. Wick W, Weller M, for the Neurooncology Working Group of the German Cancer Society (2008) NOA-04 randomized phase III study of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. J Clin Oncol 2008, ASCO Proceedings, #LBA2007
18. Zlatescu MC, Tehrani Yazdi AR, Sasaki H et al (2001) Tumor location and growth pattern correlate with genetic signature in oligodendroglial neoplasms. Cancer Res 61: 6713–6715