

Abstract The term oligodendroglioma was created by Bailey, Cushing, and Bucy based on the observation that these tumors share morphological similarities with oligodendrocytes (Bailey and Cushing 1926; Bailey and Bucy 1929). However, a convincing link between oligodendrocytes and oligodendrogliomas still needs to be shown. Oligoastrocytomas or mixed gliomas are histologically defined by the presence of oligodendroglial and astrocytic components. According to the WHO classification of brain tumors, oligodendroglial tumors are separated into oligodendrogliomas WHO grade II (OII), anaplastic oligodendrogliomas WHO grade III (OIII), oligoastrocytomas WHO grade II (OAII), anaplastic oligoastrocytomas WHO grade III (OAIII), and glioblastomas with oligodendroglioma component WHO grade IV (GBMo) (Louis et al. 2007). The perception of oligodendroglial tumors has changed in recent years. The diagnosis of oligodendroglioma or

oligoastrocytomas is made much more frequently than 10 years ago. Treatment modalities have been advanced and novel concepts regarding the origin of oligodendroglial tumors have been developed. This review focuses on recent developments with impact on the diagnosis and understanding of molecular mechanisms in oligodendroglial tumors.

2.1 Epidemiological, Neuroradiological, and Clinical Features

Oligodendrogliomas occur 1.5–2.1 times more frequently in men than in women (Mork et al. 1986; Zulch 1986). The average age of onset of oligodendrogliomas is between 35 and 55 years with a peak incidence around 45 years (Mork et al. 1986; Zulch 1986). Often OII occur in patients under 40 years of age and OIII arise in patients over 40 years of age (Ludwig et al. 1986). The incidence of oligodendrogliomas has risen over the last few years, reaching levels of 25% of primary brain tumors. This rise is most likely due to the improvement in the therapy of oligodendroglial tumors and the feeling of the diagnostician not to withhold potentially effective treatment for patients with glioma containing any feature reminiscent of

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oligodendroglial tumors (Coons et al. 1997; Ironside et al. 2002). The frequency of anaplastic tumors among the oligodendroglial gliomas varies strongly between 3.5% and 50% (Winger et al. 1989; Shaw et al. 1992). The incidence of oligoastrocytomas also ranges from 2% to 19%, which is most likely a consequence of the lack of stringent diagnostic criteria (Jaskolsky et al. 1987; Louis et al. 2007).

The etiology of oligodendrogliomas remains unclear with only few studies and some case reports pointing to tumor-initiating factors. None of the hereditary tumor syndromes is associated with oligodendrogliomas. However, familial oligodendrogliomas were reported in single cases (Ferraresi et al. 1989; Kros et al. 1994). In rabbits, application of *N*-methyl-*N*-nitrosourea induced tumors with histological features of oligodendrogliomas (Kleihues et al. 1970). The involvement of SV40 and JS viruses in the induction of oligodendrogliomas is uncertain and conflicting data have been reported (Herbarth et al. 1998; Huang et al. 1999). In one patient an oligodendroglioma might have been induced by radiation therapy (Huang et al. 1987). In two patients that sustained head injuries, oligodendrogliomas arose at the site of brain damage due to contusion (Perez-Diaz et al. 1985). Furthermore, a few case reports proposed an association between multiple sclerosis and oligodendrogliomas (Giordana et al. 1981; Sega et al. 2006).

Within the group of gliomas, epileptic seizures are most frequently encountered in oligodendrogliomas. Often an epileptic seizure is the first symptom of an oligodendroglioma. Other typical clinical symptoms of oligodendrogliomas are headaches in combination with signs of increased intracranial pressure. Depending on the location of the tumor, varying focal neurological symptoms occur. OII are slowly growing tumors. Cases with seizures as a first symptom usually present a clinical history of about 1 year. Intervals of more than 5 years are not uncommon and in children more than 10 years between onset of seizures and diagnosis of oligodendroglioma has been reported (Greenfield et al. 2002).

Compared to white matter, oligodendrogliomas usually appear on computed tomography (CT) images as a well-demarcated hypo- or isodense lesion. Frequently calcifications can be found, mostly around the periphery of the tumor in a so-called gyriform or ribbon-like pattern. On magnetic resonance imaging (MRI) oligodendrogliomas typically appear as hypointense lesions on T1 and hyperintense on T2 images. The margins are sharply demarcated and perifocal edema is rather small. Varying signal intensities are found in rare cases due to hemorrhages or cystic degeneration. Gadolinium contrast enhancement shows low accuracy in predicting OIII. Enhancement was also found in OII, and on the other hand lack of enhancement was seen in OIII (Ginsberg et al. 1998; Lebrun et al. 2004; White et al. 2005). However, noninvasive grading of oligodendrogliomas appears to be more promising with techniques such as proton magnetic resonance spectroscopic imaging (MRSI) (Rijpkema et al. 2003; Xu et al. 2005). In a small series FDG-PET showed raised glucose utilization within the tumor in six of eight WHO Grade II gliomas with 1p/19q LOH and in none of the WHO Grade II gliomas without this genetic alteration (Stockhammer et al. 2007).

2.2 Pathology

Usually oligodendrogliomas arise in the white matter of the cerebral hemispheres. They occur with a distribution frequency of 3:2:2:1 in the frontal, parietal, temporal, and occipital lobes (Chin et al. 1980; Lee and Van Tassel 1989; Tice et al. 1993). Only in rare cases oligodendrogliomas can be observed in the cerebellum, brainstem, or spinal cord (Greenfield et al. 2002).

Macroscopically, oligodendrogliomas appear as soft, gelatinous grayish-pink masses with relatively well-delineated borders compared with astrocytic gliomas. A gritty texture in unfixed

tissue indicates calcification, characteristically in the periphery of the tumor and in adjacent cortical structures. Regions of cystic degeneration can be found in large tumor masses, necrosis only in OIII (see below). Hemorrhages can be found even in OII. Oligodendrogliomas exhibit a tendency to infiltrate adjacent leptomeningeal structures. More rarely, infiltration of the dura might occur, thereby leading to an initial impression of a meningioma.

2.2.1

Oligodendrogliomas WHO Grade II

OII are monomorphous gliomas with moderate cellularity, isomorphic round to oval nuclei and, on paraffin section, a clear perinuclear halo, a so-called honeycomb or fried egg appearance. The typical perinuclear halo is based on an artifact due to tissue fixation (Ironsides et al. 2002). These perinuclear halos cannot be observed in unfixed tissue sections such as smear preparations or frozen sections. Furthermore, numerous delicate, branching vessels with a ‘chicken wire’ or ‘retiform’ appearance are characteristic of oligodendrogliomas (Fig. 2.1a). Frequently calcification is seen in OII (Fig. 4.1b). Some mitoses are allowed according to the definition of OII (Louis et al. 2007).

2.2.2

Anaplastic Oligodendrogliomas WHO Grade III

OIII are defined by increased cellularity, cytological atypia with pleomorphic cells or multinucleated giant cells, brisk mitotic activity, vascular proliferation ranging from increased cellularity of branching vessels, microvascular proliferation (Fig. 4.1d) to glioblastoma-like garlands or glomeruloid vessels, and necrosis that may show geographic aspects or exhibit perinecrotic palisading of tumor cells (Louis et al. 2007).

2.2.3

Oligoastrocytomas WHO Grade II

OAI are defined as tumors composed of components resembling both oligodendroglioma and astrocytoma. Different authors suggested various cut-off values for the astrocytic component to separate oligodendrogliomas from oligoastrocytomas. Values between 1% (Kim et al. 1996), 25% (Mork et al. 1986), and 50% (Hart et al. 1974) have been proposed. For good reasons, WHO did not define a cut-off value to separate oligoastrocytomas from oligodendrogliomas and astrocytomas. The evaluation of slides is based on the assumption that the plane visualized is representative of the entire tumor. However, the proportion of astrocytic and oligodendroglial components may vary considerably in different planes. Further, due to surgical procedures not all tumor material is evaluated by histological examination. Two groups of oligoastrocytomas defined by different morphology have been described: The “biphasic” tumors with two clearly distinct components and the “diffuse” neoplasm with astrocytic tumor cells scattered in between oligodendroglial cells (Hart et al. 1974). However, it needs to be shown that these scattered astrocytic tumor cells are indeed neoplastic cells and not reactive and hypertrophic astrocytes. Another problem in the diagnosis of OAI is the presence of an increased mitotic rate in absence of other clearly anaplastic features. The WHO allows a higher rate of mitoses in OII than in astrocytoma WHO grade II. It is not yet been resolved whether a moderately increased mitotic activity in oligoastrocytomas requires different grading depending on whether the mitoses are predominantly seen in the oligodendroglial or in the astrocytic component, i.e., WHO grade II or WHO grade III. Several reports indicated that the presence of some mitoses in oligoastrocytomas are WHO grade III and require more aggressive treatment (Miller et al. 2006; van den Bent et al. 2006).

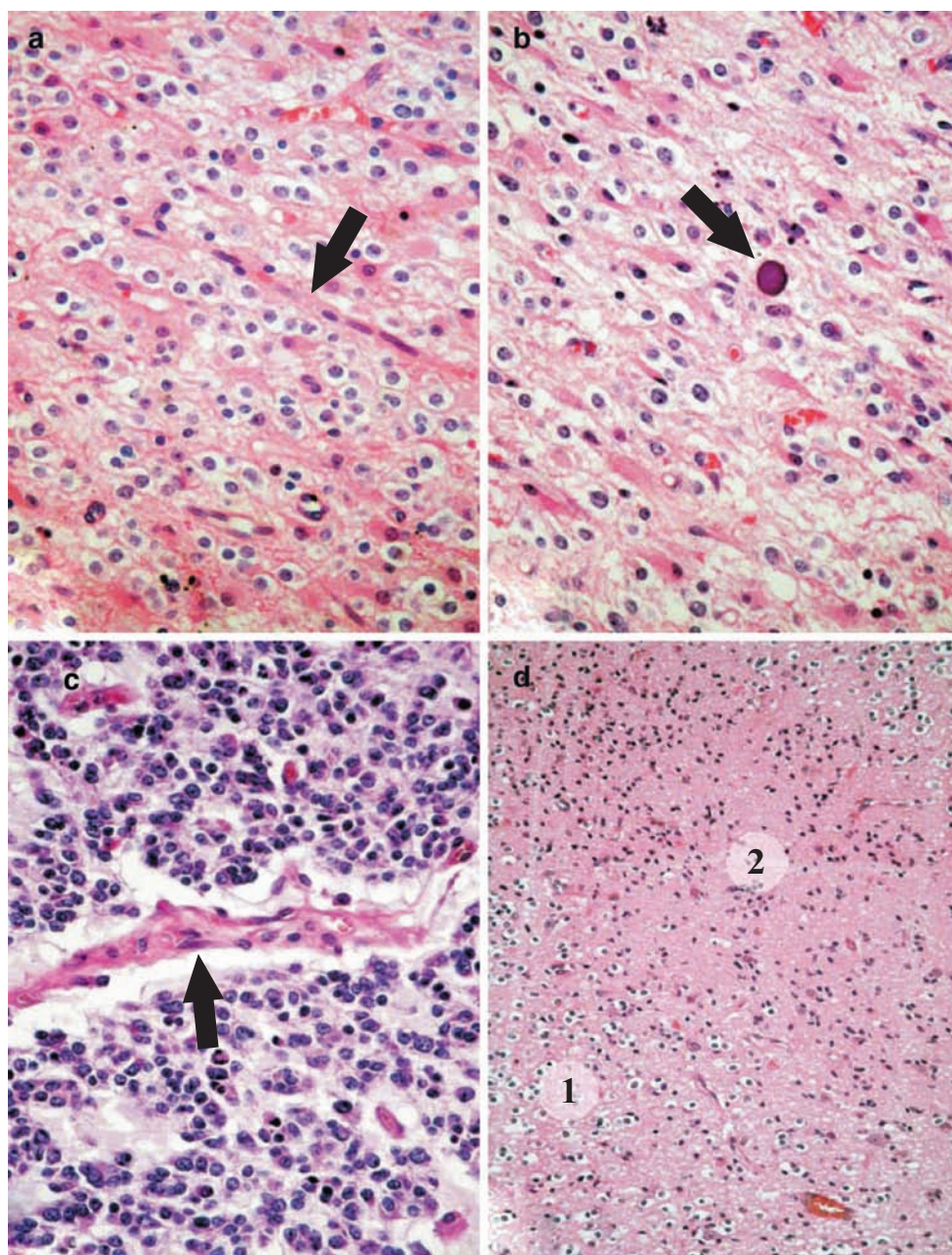


Fig. 2.1 Histological appearance of oligodendroglial tumors. (a) Oligodendroglioma WHO grade II with delicate branching capillaries. (b) The same tumor with small calcifications. (c) Anaplastic oligodendroglioma

WHO grade III with microvascular endothelial proliferation. (d) "Biphasic" oligoastrocytoma WHO grade II with an oligodendroglial component (1) and an astrocytic component (2)

2.2.4

Anaplastic Oligoastrocytomas WHO Grade III

OAI show histological features of anaplasia including nuclear and cellular atypia, high cellularity, and high mitotic activity. Microvascular proliferation may be present; however, the issue of necrosis is not sufficiently addressed by the WHO. Recent studies showed that patients with OAI containing necrosis had a shorter overall survival than patients with OAI not containing necrosis (Miller et al. 2006; van den Bent et al. 2006). Therefore, the current WHO classification suggests classifying and grading anaplastic tumors with oligodendrocytic and astrocytic differentiation and with necrosis as glioblastoma (GBM) with oligodendroglial component WHO grade IV (Louis et al. 2007). On the other hand, a recent study demonstrated that in such tumors necroses were not of prognostic significance if the oligodendroglial component showed the classical features of oligodendroglioma. In that study, the classic features of oligodendroglioma were highly associated with combined 1p and 19q deletions (Giannini et al. 2008).

2.2.5

Glioblastomas with Oligodendroglioma Component WHO Grade IV

Anaplastic oligoastrocytomas with necrosis may be termed glioblastomas with oligodendroglial component WHO grade IV (GBM). This diagnosis was introduced in the WHO 2007 brain tumor classification based on the observation that such tumors have a poorer clinical performance than anaplastic oligoastrocytomas without necrosis. GBM seem to have a better prognosis than ordinary GBM (He et al. 2001; Kraus et al. 2001; Homma et al. 2006). However, according to the WHO GBM is not yet an established GBM variant but is seen as a pattern of differentiation (Louis et al. 2007).

2.3

Immunohistochemistry

Multiple immunohistochemical markers have been proposed to distinguish oligodendrogliomas from astrocytomas. However, due to inconsistent results none of these markers has been established for routine diagnostics. Specific immunohistochemical markers would be very helpful for reducing the high interobserver variation in the diagnosis of OI (Giannini et al. 2001). Based on the concept of a link between oligodendrocytes and oligodendrogliomas, multiple immunohistochemical markers were evaluated that are expressed in oligodendrocytes. For example, expression of the myelin basic protein (MBP) (Tanaka et al. 1988; Kashima et al. 1993), galactocerebroside (Kennedy et al. 1987; de la Monte 1989), and myelin-associated glycoprotein (MAG) (Perentes and Rubinstein 1987) was found only in some oligodendrogliomas or in portions of the tumors. Furthermore, no oligodendroglioma-specific expression of the oligodendrocytic lineage markers platelet-derived growth factor receptor alpha (PDGFRα), proteolipid protein (PLP), and chondroitin sulfate proteoglycan (NG2) was found (Landry et al. 1997; Shoshan et al. 1999). Recently, the transcriptional activity of the oligodendrocytic lineage genes 1 and 2 (OLIG1, OLIG2) raised new hope for separating oligodendrogliomas from astrocytomas (Lu et al. 2001; Marie et al. 2001; Hoang-Xuan et al. 2002). However, multiple follow-up studies found Olig-1 and Olig-2 expression in astrocytic tumors as well (Ohnishi et al. 2003; Aguirre-Cruz et al. 2004; Ligon et al. 2004). Nevertheless, it was shown that Olig-expressing tumor cells do not express GFAP (Azzarelli et al. 2004; Mokhtari et al. 2005). Nuclear expression of endothelin beta receptors (EDNRB) was described in oligodendroglial tumors and only rarely in glioblastomas (Angelova et al. 2005). However, an independent study confirming these data has not been reported yet. Due to these

frustrating efforts to establish oligodendroglioma-specific immunohistochemical markers, glial fibrillary acid protein (GFAP) which binds to cells of astrocytic differentiation but not to typical oligodendroglial cells is used as a “negative” marker. However, strong expression of GFAP is also seen in so-called mini-gemistocytes, well compatible with the diagnosis of oligodendroglioma (Louis et al. 2007). Recently, strong expression of cartilage glycoprotein-39/YKL-40 (CHI3L1) has been described in glioblastomas and no or weak binding only in anaplastic oligodendrogliomas WHO grade III. The distinction of both glioma entities by YKL-40 was better than that achieved with GFAP (Nutt et al. 2005). However, further studies are required to demonstrate the value of YKL-40 in routine diagnostics (Louis et al. 2007).

2.4

Molecular Genetics

2.4.1

Combined Losses on Chromosome 1p and 19q in Oligodendroglial Tumors

The genetic hallmarks of oligodendroglial tumors are combined chromosomal deletions on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). Up to 90% of all OII carry this alteration (von Deimling et al. 1992; Bello et al. 1994, 1995a, b; Reifenberger et al. 1994; Kraus et al. 1995). The rate of combined losses on 1p and 19q is lower in OIII with approximately 50–70% of tumors carrying this alteration (Cairncross et al. 1998; Smith et al. 2000; Mueller et al. 2002). It has been pointed out that oligodendrogliomas with combined losses on 1p and 19q demonstrate a more “classical” histological phenotype. In contrast, oligodendrogliomas without losses on 1p and 19q exhibited more frequently astrocytic features (Burger et al. 2001; Sasaki et al. 2002; Ueki et al. 2002; McDonald

et al. 2005). These findings reflect the high inter-observer variation in the diagnosis of oligodendroglial tumors and indicates that molecular analysis for 1p and 19q deletions is a helpful diagnostic parameter.

Oligodendroglial tumors with combined losses on 1p and 19q typically occur at an extratemporal location. In contrast, oligodendroglial tumors with an intact 1p/19q status accumulated in the temporal lobe (Zlatescu et al. 2001; Mueller et al. 2002).

A higher apoptotic index was observed in oligodendrogliomas with combined losses on 1p and 19q than in oligodendrogliomas without losses. This variation in apoptotic activity might explain the differences in clinical behavior in both oligodendroglioma variants (Wharton et al. 2007). Because of the frequency of combined 1p and 19q deletions in low-grade oligodendroglial tumors, it is assumed that these alterations have an initiating role in tumorigenesis. The high rate of combined 1p and 19q losses prompted speculations on defining OII by molecular rather than by histological criteria (Reifenberger and Louis 2003). The lower frequency of 1p and 19q deletions in OIII may point to a higher degree of genetic heterogeneity possibly due to the difficult distinction of OIII from other malignant gliomas such as GBMo.

Combined losses of 1p/19q are found in approximately 50% of oligoastrocytomas (von Deimling et al. 2000; Mueller et al. 2002). These losses are mutually exclusive to LOH 17p and *TP53* mutations (Maintz et al. 1997; von Deimling et al. 2000; Mueller et al. 2002; Ueki et al. 2002), indicating either an oligodendroglioma genotype characterized by losses on 1p/19q or an astrocytoma genotype characterized by *TP53* mutations (Fig. 2.2). In oligoastrocytomas 1p/19q losses occur in the oligodendroglial and astrocytic component, thereby indicating a clonal origin of oligoastrocytomas and supporting the concept of at least two genetic variants of oligoastrocytomas (Kraus et al. 1995). However, in a few cases differing genetic alterations were observed in the oligodendroglial and astrocytic tumor component (Dong et al. 2002; Qu et al. 2007). This implies

that oligoastrocytomas are predominantly of monoclonal origin. Furthermore, *TP53* mutations were seen mostly in temporal oligoastrocytomas but not in extratemporal tumors (Mueller et al. 2002). At least two models might explain these findings. The environment of the temporal and extratemporal location might vary and, thereby, provide different growth advantages for oligodendroglial tumors with and without 1p/19q losses. On the other hand, different cells of origin with a varying susceptibility for 1p/19q losses might be the source for temporal and extratemporal oligodendroglial tumors.

Combined losses of 1p/19q are found in approximately 5% of GBM, suggesting an oligodendrogloma rather than an astrocytoma genotype and, therefore, a better prognosis than GBM without this alteration. There is an overlap between GBM with combined losses of 1p/19q and GBM with an oligodendroglial component (He et al. 2001). However, two studies imply that patients with GBM with combined losses of 1p/19q do not have a better prognosis than patients with normal GBM. In a series of 220 GBM, combined losses of 1p/19q were identified in 9% of cases. However, there was no difference in survival between patients with and without combined 1p/19q losses (Houillier et al. 2006). In a different study GBM long-time survivors were tested for 1p/19q losses. Only 2 of 32 tumors carried combined 1p/19q losses, thereby indicating that this genetic lesion is not a marker for longer survival (Krex et al. 2007).

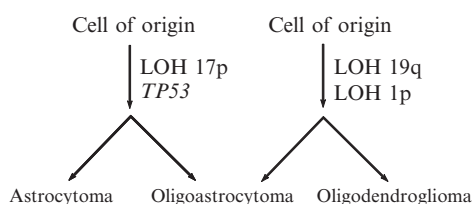


Fig. 2.2 Model for oligoastrocytomas. The major fraction of oligoastrocytomas exhibits either genetic alterations typical for astrocytoma or for oligodendrogloma

Combined 1p/19q losses were also observed in gliosarcomas. A recent study identified this lesion in five of seven recurrent gliosarcomas which were diagnosed as oligodendroglomas at first resection. Interestingly, the lesions were present in both the glial and sarcomatous component. The authors suggested the name “oligosarcoma” for this gliosarcoma variant (Rodriguez et al. 2007).

2.4.2

Isolated and Combined Losses of 1p and 19q Oligodendroglial and Astrocytic Tumors

While the combination of 1p/19q losses is typical for oligodendroglial tumors, a deletion of either chromosomal region is also seen in astrocytic tumors. In fact, 19q losses have been demonstrated to frequently occur in the progression of astrocytoma toward malignancy (von Deimling et al. 1994; Hartmann et al. 2002). Likewise, 1p deletions have been described in malignant astrocytic tumors. Therefore, coincidence of 1p and 19q deletions is also expected in some astrocytic tumors. However, the extent of deletions on the chromosomal arms 1p and 19q differ between oligodendroglial and astrocytic tumors. While the entire 1p and 19q arms are lost in oligodendroglial tumors, these deletions are much smaller in astrocytic tumors. Interestingly and in line with classical clinicopathological correlations, small 1p deletions in astrocytic tumors are associated with a poor prognosis contrasting the finding of favorable prognosis indicated by losses of the entire 1p and 19q arms in oligodendroglial tumors (Idbaih et al. 2005; Ichimura et al. 2008).

Due to the clinically important differences between the losses of the entire 1p and 19q arms versus losses involving only parts of chromosomal arms 1p and 19q, it has been suggested to analyze not only telomeric but also centromeric locations on 1p (Boulay et al. 2007).

2.4.3

Mechanism for Combined Losses of 1p and 19q

Recently, a centromeric or pericentromeric $t(1;19)(q10,p10)$ translocation was identified as the mechanism leading to the combined loss of the two chromosomal arms (Griffin et al. 2006; Jenkins et al. 2006). In fact, chromosome 1 and 19 translocation was already observed earlier in a single cell line, but has not been recognized as a general feature of these tumors (Magnani et al. 2005).

Optical fusion of signals from a chromosome 1 probe and a 19p12 probe using fluorescence in situ hybridization (FISH) was observed in 90% of the cases that showed combined losses of 1p and 19q. In total 55% of oligodendrogliomas, 47% of oligoastrocytomas, and 0% of astrocytomas demonstrated this $t(1;19)(q10,p10)$ translocation. Overall survival time was nearly similar for patients that were evaluated for 1p/19q losses or $t(1;19)(q10,p10)$ translocation (Jenkins et al. 2006).

The centromeric regions of chromosomes 1 and 19 (and interestingly chromosome 5 as well) show a high sequence homology. Presumably, the specific chromosomal karyo-architecture of the oligodendroglioma precursor cell results in centromeric co-localization of chromosome 1 and 19 that might promote centromeric instability in this cell type, thus promoting translocation events (Jenkins et al. 2006). Interestingly, in two cases a $t(1;19)(q10,p10)$ translocation but no 1p/19q losses were observed (Jenkins et al. 2006). This finding might indicate that there is a small portion of oligodendrogliomas with a reciprocal whole-arm exchange at the centromere. Further, it may suggest that the rate of oligodendrogliomas with chromosome 1 and 19 alterations is even higher than that detected by methods focusing on 1p/19q deletions only (Fig. 2.3). On the other hand, $t(1;19)(q10,p10)$ translocations were described in only 90% of the cases that demonstrated 1p/19q losses (Jenkins et al. 2006). This might be due to insufficient translocation

detection but could also be caused by losses without translocation.

Further confirmatory studies have not been reported yet. Recently, 1p/19q deletions without evidence of a $t(1;19)(q10,p10)$ translocation have been reported in short-term culture of oligodendroglioma (Gadji et al. 2008).

2.4.4

Methods for Detection of Allelic Losses on Chromosome 1p and 19q

Different methods for detection of 1p/19q losses are employed in routine diagnostics. PCR-based microsatellite analysis with several markers is still considered the most robust needing only a small amount of tumor DNA (Hartmann et al. 2005). However, this method is quite labor-intensive and also requires constitutional DNA, usually extracted from peripheral blood leukocytes. A novel technique, multiplex ligation-dependent probe amplification (MLPA), has the advantage of not requiring constitutional DNA (van Dijk et al. 2005). Furthermore, processing of MLPA PCR is faster and allows a higher resolution due to the simultaneous assessment of more than 40 markers (Fig. 2.4). Both methods cannot detect the $t(1;19)(q10,p10)$ translocation. The method most familiar to pathologists is FISH, which is rapid and is suitable for routine laboratories specialized in histology. A big advantage is that FISH is performed on paraffin-embedded material used for standard diagnostic protocols. In addition, FISH does not require control tissues such as peripheral leukocytes required for microsatellite analysis or MLPA. However, FISH usually covers only a single position on the chromosome thus not giving conclusive information on the extent of the potential deletion. This could be circumvented by demonstrating the translocation with FISH using centromeric probes (Griffin et al. 2006; Jenkins et al. 2006). However, the kits commercially available are not suitable for detecting the translocation. In addition FISH is at danger of being misinter-

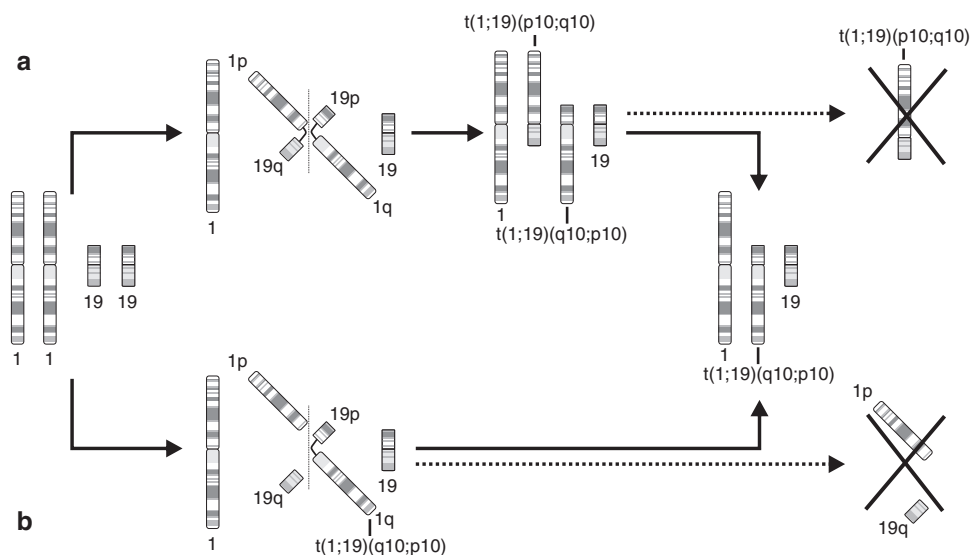


Fig. 2.3 Models for $t(1;19)(q10;p10)$ translocation mechanisms in oligodendroglial tumors based on data from Griffin et al. 2006 and Jenkins et al. 2006. **(a)** The centromeric or pericentromeric regions of one chromosome 1 and one chromosome 19 come close to each other, the repetitive DNA strains break and 19p recombines with 1q arm to $t(1;19)(q10;p10)$ and 1p recombines with 19q to $t(1;19)(p10;q10)$. In this intermediate phase, no losses of 1p/19 can be detected. In a second step the $t(1;19)(p10;q10)$ fusion chromosome is eliminated from the tumor cell and, therefore, a loss of 1p/19q occurs. This

translocation model would imply that there are oligodendrogliomas that do not show losses on 1p/19q but demonstrate a translocation. Interestingly, such tumors were identified in small numbers (Jenkins et al. 2006). **(b)** An alternative mechanism. After centromeric or pericentromeric fracture of one chromosome 1 and one chromosome 19, only the 19p and 1q arm fuse leading to a $t(1;19)(q10;p10)$. The remaining 1p/19q arms will be eliminated directly. In this model, the number of tumors that show losses of 1p/19q and a $t(1;19)(q10;p10)$ translocation should be nearly identical

interpreted because artifacts and signals tend to fade after long-term storage.

The most attractive method to separate oligodendroglial tumor with losses on 1p/19q from those without would be based on immunohistochemistry. However, no reliable immunohistochemical marker has been identified so far. Different microarray expression studies already have been performed on oligodendroglial tumors but no suitable markers were identified (Watson et al. 2001; Fuller et al. 2002; Kim et al. 2002; Mukasa et al. 2002; Nutt et al. 2003; Mukasa et al. 2004; Tews et al. 2006). Proteome analysis by two-dimensional protein gel electrophoresis might be a more successful approach. Indeed, differently

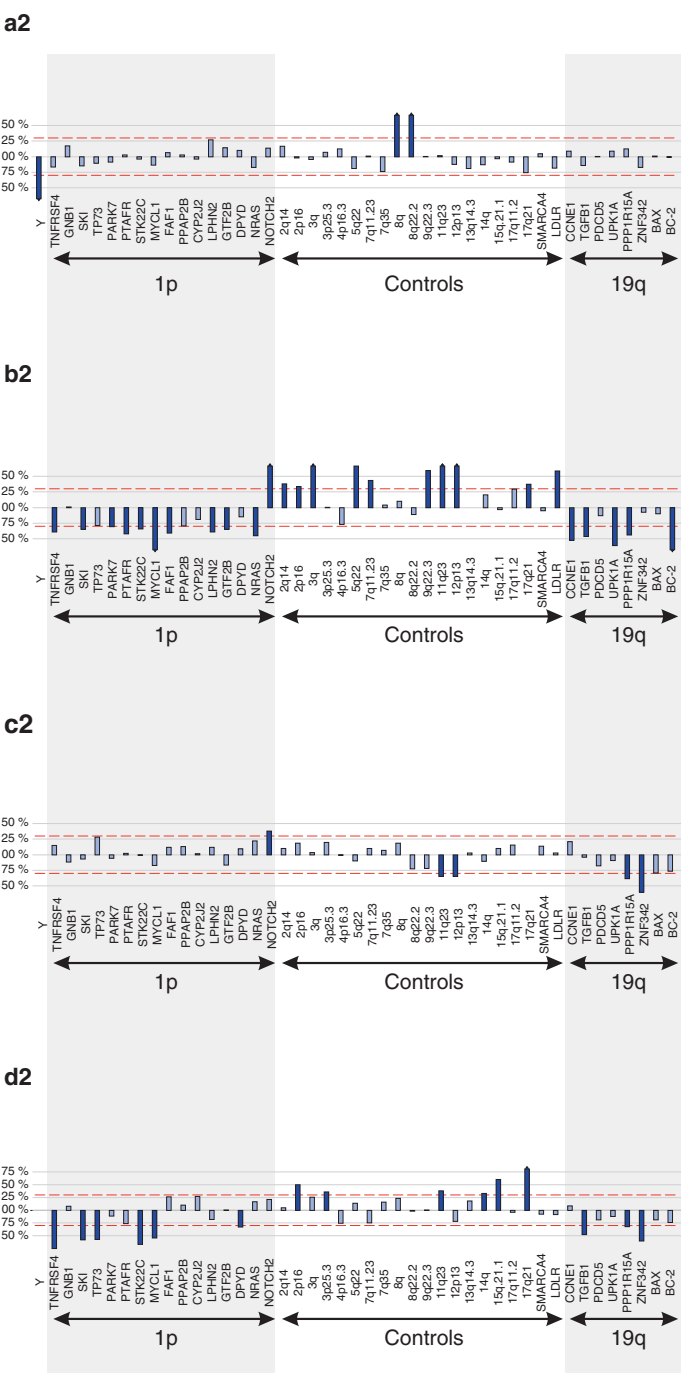
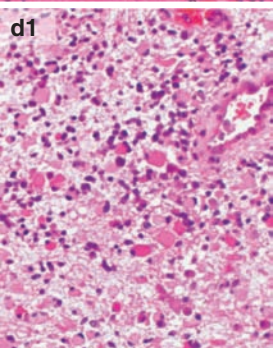
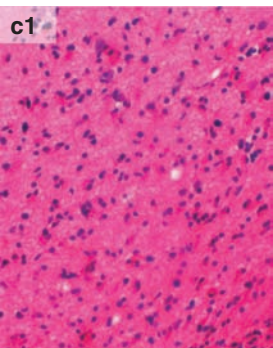
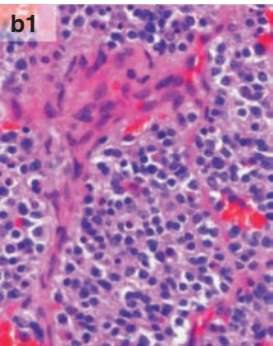
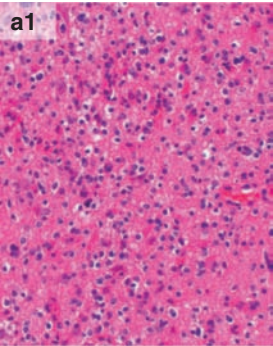
expressed proteins were identified between oligodendrogliomas with and without losses on 1p by this strategy (Okamoto et al. 2007), but it remains to be shown whether some of these proteins are useful immunohistochemical markers for 1p/19 loss.

2.4.5

Tumor Suppressor Gene Identification on 1p and 19q

The observation of a centromeric or pericentromeric $t(1;19)(q10;p10)$ translocation with a complete loss of 1p and 19q challenges the concept of the presence of at least one tumor suppressor gene (TSG) on 1p and 19q each with relevance

2



for oligodendroglial tumors (Griffin et al. 2006; Jenkins et al. 2006). In many tumors, reproducible chromosomal translocations join two genes to a fusion gene which acquires tumor-promoting properties. The t(1;19)(q10,p10) translocation might lead to such activation and all attempts to identify an altered TSG on the remaining copies of 1p and 19q may be fruitless. Nevertheless, to date no genes have been observed in the centromeric or pericentromeric regions of chromosomes 1 and 19 which may be candidates for a tumor-promoting fusion protein (Jenkins et al. 2006). The highly repetitive nature of centromeric DNA complicates sequencing but there is evidence that genes map within centromeric regions (Cooke 2004). The observation of oligodendrogliomas that show a t(1;19)(q10,p10) translocation but no losses of 1p/19q (Jenkins et al. 2006) may indicate an intermediate phase with the presence of a temporary t(1;19)(p10;q10) fusion chromosome (Fig. 2.3, model a). If the t(1;19)(q10,p10) translocation results in an oncogenic fusion gene, the tumor cells should have no additional benefit by removing the t(1;19)(p10;q10) fusion chromosome in a second step. However, if the primary benefit of the t(1;19)(q10,p10) translocation for tumor cells is the loss of 1p/19q, the elimination of the temporary t(1;19)(p10;q10) fusion chromosome in a second step may indicate that candidate TSGs on 1p/19q are important for induction of oligodendrogliomas.

2.4.6

Candidate Genes on 1p

Many candidate TSGs have been suggested but have not been confirmed in consecutive studies.

One of the interesting genes is *CDKN2C*, which carried point mutations (Husemann et al. 1999) or homozygous deletions (Pohl et al. 1999) in some oligodendrogliomas. Among recent candidates of interest is *CITED4*, which was found to be differentially expressed between oligodendroglial tumors with and without LOH 1p in an expression microarray (Tews et al. 2006). *CITED4* is not mutated, but carries a hypermethylated promoter in oligodendrogliomas with LOH 1p/19q, and hypermethylation was found to be a significant predictor of longer survival. *CITED4* is an attractive TSG candidate due to the fact that CITED4 protein binds CBP and EP300, is a co-activator of the transcription factor AP-2, blocks binding of HIF1 α to EP300, and inhibits HIF1 α transactivation as well as hypoxia-mediated reporter gene activation (Tews et al. 2007). Another TSG candidate on 1p31.3 is *DIRAS3* or *ARHI* encoding a RAS-related GTPase that confers growth suppression to breast and ovarian cancer cells (Yu et al. 1999). The promoter region of this gene is significantly hypermethylated in OII and OIII with losses on 1p compared to those tumors without losses. Furthermore, a correlation of *DIRAS3* inactivation with survival was reported (Riemenschneider et al. 2008). The most centromeric gene on 1p is *Notch2*. Mapping may indicate that the translocation breakpoint region maps within this gene (Boulay et al. 2007). Currently, functional data or information about potential translocation partner genes on chromosome 19 is not available. However, the observed translocation breakpoint region defines *Notch2* as the first attractive candidate gene that can be included in the concept of a t(1;19)(q10,p10) translocation.

Fig. 2.4 Typical deletions pattern of 1p and 19q in oligodendroglial and astrocytic tumors by multiplex ligation-dependent probe amplification (MLPA) PCR. The 100% line indicates the presence of two copies of the specific marker; values below the 75% line indicate a loss of one copy. **a1** – OIII, **a2** – corresponding MLPA

PCR data for this tumor showing no losses on 1p and 19q. **b1** – OIII, **b2** – nearly all markers on 1p and 19q are below the 75% line indicating a complete loss of both chromosomal arms. **c1** – AIII, **c2** – no losses on 1p and telomeric losses on 19q. **d1** – AIII I, **d2** – telomeric losses on 1p and loss of 19q

2.4.7

Candidate Genes on 19q

Due to the t(1;19)(q10,p10) translocation with a complete loss of 19q in oligodendrogliomas, the mapping studies for identification of the 19q candidate region are likely to have focused on astrocytic tumors with partial deletions. This implies that the suggested 19q13.3 TSG candidate region (Hartmann et al. 2002) is of interest for astrocytic but not for oligodendroglial tumors. Candidates looked at did not reveal mutations in significant numbers (Hartmann et al. 2004). Therefore, attention shifted towards epigenetic silencing of genes by promoter methylation. *PEG3* is imprinted in normal brain and only the paternal allele is expressed. The expression of *PEG* is reduced in some gliomas and glioma cell lines and can be re-expressed by 5-aza-2'-deoxycytidine treatment (Maegawa et al. 2001). However, a link between 19q losses and reduced expression was not shown. In addition, 19q losses exhibited no uniparental deletion pattern suggestive of inactivation of imprinted genes by loss of the active gene copy (Hartmann et al. 2003). These observations further reduce the likelihood of *PEG* being an oligodendroglioma-relevant TSG. *ZNF342* showed frequent promoter methylation in OII and OIII with losses on 19q, expression was reduced in cases with promoter methylation, and expression was restored in cell lines after treatment with a demethylating agent (Hong et al. 2003). However, it remains to be determined whether *ZNF342* promoter methylation did not occur in oligodendrogliomas without 19q losses. Recently, *EMP3* was found to be differentially expressed between low-grade gliomas with and without 19q losses by cDNA microarray expression profiling (Tews et al. 2006). Aberrant methylation in the 5'-region of *EMP3* was significantly associated with reduced mRNA expression and LOH 19q in a similar frequency in OII and OIII, thereby suggesting a role of *EMP3* in the initiation of

the majority of oligodendroglial tumors (Kunitz et al. 2007). However, another study did not find a link between *EMP3* promoter methylation and losses on 19q (Li et al. 2007).

2.4.8

IDH1 Mutations in Oligodendroglial Tumors

A whole-genome sequencing project recently identified mutations in the cytosolic NADP⁺ dependent isocitrate dehydrogenase gene (*IDH1*) in GBM. All mutations were heterozygous and exclusively affected arginine in amino acid position 132 (Parson et al., 2008). We identified *IDH1* mutations in approximately 75% of oligodendrogliomas, oligoastrocytomas and astrocytomas WHO grades II and III (Balss et al., 2008). While that study did not show significant associations between *IDH1* mutations and 1p/19q losses, we now have the impression of a significant association of these lesions (based on a larger series, unpublished data). The mutation frequencies in WHO grade II and anaplastic WHO grade III gliomas were similar, and therefore, *IDH1* mutations might constitute an early role in gliomagenesis.

Isocitrate dehydrogenase catalyzes the oxidative decarboxylation of isocitrate to α -ketoglutarate, thereby reducing NADP⁺ to NADPH. The subcellular localization of the isocitrate dehydrogenase protein is the cytoplasm and the peroxisome (Geisbrecht et al., 1999). In the cytoplasm, the role of the protein might be to provide NADPH under conditions not favorable for generation of NADPH by the hexose monophosphate shunt. In the peroxisome, *IDH1* protein is the only known source of NADPH that is required by several enzymes such as hydroxymethyl-CoA-, 2,4-dienoyl-CoS- and acyl-CoA-reductases. An important role of *IDH1* in protection from oxidative stress may be concluded from the observation of increased resistance of IDPc, the mouse homolog of *IDH1*, overexpressing and sensitivity of IDPc deficient

NIH3T3 cells to exposure of hydrogen peroxide (Lee et al., 2002). Further, IDPc negative HL-60 cells exhibited increased caspase-3 activation under oxidative stress, suggesting a role in apoptosis (Kim et al., 2007).

Mutations affected the amino acid arginine in position 132 of the amino acid sequence that belongs to an evolutionary conserved region locating to the binding site of isocitrate. In the vast majority of the cases wild type arginine in position 132 was replaced by histidine. The reported mutations always were heterozygous and alterations suggestive for protein inactivation such as splice site or non-sense mutations were not detected, thus prompting speculations on an activating nature of the mutation (Parson et al., 2008). However, site directed mutagenesis leading to a R132E exchange in rat IDP2 which is homologous to human IDH1 completely abrogated enzyme activity (Jennings et al, 1997). Further, a mutation in porcine NADP-isocitrate dehydrogenase at position 133 (R133Q) corresponding to human position 132, also resulted in downregulation of the enzyme activity (Sounda et al., 2000). Thus, the effect of the R132H mutation on enzyme activity currently is not resolved.

The very high *IDH1* mutation rate implies that besides 1p/19q losses this alteration plays a fundamental role in oligodendrogliomas, oligoastrocytomas and astrocytomas. The functional mechanism of the *IDH1* mutations needs to be clarified in further studies.

2.4.9

Progression-Associated Genetic Alterations

Deletions on the short arm of chromosome 9 occur more frequently in OIII than in OII and can be found in 22–50% of the cases (Reifenberger et al. 1994; Weber et al. 1996; Bigner et al. 1999; Kros et al. 1999; von Deimling et al. 2000; Kitange et al. 2005). *CDKN2A* encoding p16^{INK4a}

and *CDKN2B* encoding p15^{INK4b} were identified as major targets of homozygous deletions on 9p21 in OIII (Cairncross et al. 1998; Bigner et al. 1999; Bortolotto et al. 2000; Ino et al. 2001; Watanabe et al. 2001a). Alternatively, these genes are inactivated by promoter hypermethylation in oligodendroglioma (Watanabe et al. 2001a; Wolter et al. 2001). Other genes of the RB1 pathway like *CDK4* (amplification) or *RB1* (promoter hypermethylation) are altered in a lower frequency (Watanabe et al. 2001b).

Losses of chromosome 10 were found in 14–58% of OIII (Reifenberger et al. 1994; Jeuken et al. 1999; Kros et al. 1999; von Deimling et al. 2000; Sanson et al. 2002). Losses on chromosome 10 are inversely associated with losses on 1p/19q (Jeuken et al. 1999; Hoang-Xuan et al. 2001; Ino et al. 2001; Ueki et al. 2002; Thiessen et al. 2003). *PTEN* on 10q23.31 and *MGMT* on 10q26.3 are frequently discussed as target genes for chromosome 10 losses. However, *PTEN* mutations occur only in 3–10% of OIII (Duerr et al. 1998; Jeuken et al. 2000; Sasaki et al. 2001; Sanson et al. 2002). Promoter hypermethylation of *MGMT* was described in most oligodendrogliomas and shows an association with 1p/19q losses.

The inverse association between losses on chromosome 9p and 10 and losses on 1p/19q and the exclusive alteration pattern of *TP53* mutations and 1p/19q losses may suggest genetically different groups of oligodendroglial tumors. On the other hand, 9p and 10q deletions are typical for glioblastoma and anaplastic oligodendroglioma is difficult to distinguish from glioblastoma especially if relaxed criteria are applied for diagnosis.

Several studies have shown the activation of oncogenes in oligodendroglioma (Alonso et al. 2005; Kitange et al. 2005). In analogy to 9p and 10q losses, the activated oncogenes identified are frequently mutated in glioblastoma and, therefore, these findings may also reflect the morphological overlap between anaplastic oligodendroglial tumors with glioblastoma.

2.5

The Origin of Oligodendrogliomas

2.5.1

Phenotype and Genotype of Gliomas

In the rat an O2A precursor cell was identified with the capability to generate both oligodendroglial and astrocytic lineages (Raff et al., 1983). This observation prompted the speculation that oligodendrogliomas and diffuse astrocytomas evolve from the same precursor cell. On the other hand, the nearly mutually exclusive occurrence of 1p/19q losses and *TP53* mutations in oligodendroglial and astrocytic gliomas favoured the existence of different precursor cells for these tumors (Mueller et al., 2002).

However, the observation of *IDH1* mutations in the majority in both, oligodendrogliomas and diffuse astrocytomas may again support the concept of a common precursor cell (Balss et al., 2008). *IDH1* mutations may be a very early tumor-initiating event in the putative human equivalent of the O2A precursor cell. *TP53* mutations and 1p/19q losses may be subsequent lesions. Further studies are necessary to test this hypothesis.

In most cases, human oligoastrocytomas have either an oligodendroglioma genotype (losses on 1p/19q) or an astrocytoma genotype (*TP53* mutations) (Kraus et al. 1995). In only few cases different genetic alterations were observed in the oligodendroglial and astrocytic tumor component (Dong et al. 2002; Qu et al. 2007). If both genetic variants of oligoastrocytomas do have the potential to present an oligodendroglial and an astrocytic phenotype, this might indicate that the morphological appearance of diffuse gliomas is less related to a specific genotype and is more a consequence of local conditions. This concept is supported by a mouse model in which nestin-promoter-driven up-regulation of RCAS-Akt and RCAS-PDGF yielded tumors with features of oligoastrocytoma. In the astrocytic component both

pathways were active, in the oligodendroglial component only PDGF-expression was observed. The authors concluded that variant signaling can modify cellular morphology within a tumor (Dai et al. 2005). Both human tumors and murine tumor models demonstrate that molecular parameters more closely characterize oligoastrocytomas than morphology.

2.5.2

Progenitor Cells of Oligodendrocytes and Oligodendroglial Tumors

Recently, CD133⁺ glioma stem cells were identified in GBM. Another way of identifying stem cells is selection of clones with neurosphere-like growth in defined culture conditions. These cells have the ability of self-renewal and multi-lineage differentiation (Dirks 2008). To date, only limited data are available on glioma stem cells in oligodendrogliomas. In OAIII CD133⁺/Nestin⁺ cells were isolated showing neurosphere-like growth and exhibited the ability of self-renewal (Yi et al. 2007). In another study on malignant gliomas with oligodendroglial differentiation, CD133⁺ cells were identified and displayed neurosphere-like growth, multi-lineage differentiation capability, and tumorigenicity in nude mice. Patients with tumors harboring these CD133⁺ cells had a less favorable prognosis than patients with CD133⁻ tumors (Beier et al. 2008). However, it remains unclear if these glioma stem cells are the cells of origin for initiation and progression of glioma, or the results of such processes (Fan et al. 2007).

2.6

Prognosis

Differing values regarding the prognosis of patients with oligodendroglial tumors have been reported. The main reason for these differences is varying criteria for inclusion of patients. The median

postoperative survival time of OII ranged from 3.5 to 16.7 years (Shaw et al. 1992; Heegaard et al. 1995; Dehghani et al. 1998; Olson et al. 2000). The 5-year survival rate ranged from 38% to 83% (Sun et al. 1988; Shimizu et al. 1993; Gannett et al. 1994; Heegaard et al. 1995; Dehghani et al. 1998; Wharton et al. 1998; Yeh et al. 2002). Progression to anaplasia occurs in a lower frequency than in astrocytic tumors (Louis et al. 2007).

The median postoperative survival of OIII ranged from 0.9 to 7.3 years (Shaw et al. 1992; Shimizu et al. 1993; Cairncross et al. 1998; Dehghani et al. 1998; van den Bent et al. 1998; Puduvalli et al. 2003). The 5-year survival rate ranged from 23% to 66% (Cairncross et al. 1998; Davis et al. 1998; Dehghani et al. 1998; Puduvalli et al. 2003). Chemotherapy of OIII has prolonged the median time to progression to 25 months for responders (Cairncross et al. 1994; Cairncross et al. 1998). The largest series reported that 50 of 93 patients with OIII who were treated either with chemotherapy or radiation developed tumor progression after a median of 48 months (Puduvalli et al. 2003).

Only few reports exist for OAII. The median postoperative survival times ranged from 3.9 to 6.3 years (Jaskolsky et al. 1987; Shaw et al. 1992) with a 5-year survival rate of 58% (Shaw et al. 1992). One study reported a median duration of survival in OAIII similar to AIII and shorter than in OIII (Winger et al. 1989).

2.6.1

Clinical and Histological/Immunohistological Prognostic Factors

Clinical parameters have been identified for prediction of patient outcome. For example, age at surgery, extent of surgical resection, and postoperative Karnofsky score were associated with survival in both uni- and multivariate analysis. Tumor location and symptoms at presentation showed a significant correlation with survival in uni- but not in multivariate analysis (Schiffer et al. 1997).

The histological features which separate OII from OIII are based on their relevance for prognosis (Louis et al. 2007). For example, the proliferation index determined by Ki67-positive nuclei correlates with recurrence of oligodendrogliomas (Coleman et al. 2006). In contrast to astrocytic tumors there is no correlation between vascular proliferation or necrosis and clinical outcome in OIII (Schiffer et al. 1999; Smith et al. 2006). However, there seems to be a difference in clinical outcome between OAIII with and without necrosis (Miller et al. 2006; van den Bent et al. 2006). Due to this reason, the WHO 2007 brain tumor classification now separates OAIII from GBM with oligodendroglial features in cases of necrosis (Louis et al. 2007).

2.6.2

Losses on 1p and 19 as a Prognostic Factor

Oligodendrogliomas are the first CNS neoplasm in which a genetic signature was correlated with outcome in phase III trials (Cairncross et al. 2006; van den Bent et al. 2006). Initially, Cairncross et al. identified losses on 1p/19q in OIII to be predictive for chemosensitivity, longer recurrence-free survival after PCV chemotherapy, and longer overall survival (Cairncross et al. 1998). In the meantime multiple studies confirmed these findings (Smith et al. 2000; Van Den Bent et al. 2003; Walker et al. 2005). A correlation of losses on 1p/19q and chemosensitivity to temozolomide was also reported (Chahnavi et al. 2003; Hoang-Xuan et al. 2004; Triebels et al. 2004; Brandes et al. 2006; Kouwenhoven et al. 2006; Levin et al. 2006). Not only losses on 1p/19q correlated with a better outcome. Patients with a t(1;19)(q10,p10) translocation demonstrated a similar response to chemotherapy (Jenkins et al. 2006). An analysis of oligodendroglioma patients with combined losses on 1p/19 which have not been treated by chemotherapy or radiation therapy showed no difference in outcome compared to those without

losses. This suggests that combined 1p/19q losses are not prognostic but predictive (Weller et al. 2007).

2.6.3

MGMT as a Prognostic Factor

In GBM, promoter hypermethylation of the *MGMT* gene on chromosome 10q26.3 was identified as a predictor for response to temozolomide treatment (Hegi et al. 2005). Therefore, it appears likely that *MGMT* hypermethylation combined with reduced expression of O6-methylguanine DNA methyltransferase protein could also serve as a prognostic factor in oligodendrogliomas. In fact, one study reported an association between response to temozolomide treatment and *MGMT* protein expression in OII (Levin et al. 2006). However, in OIII treated by temozolomide, *MGMT* hypermethylation showed only a borderline correlation with overall survival. The authors conclude that further studies on *MGMT* hypermethylation should be performed in randomized trials to test its correlation with survival (Brandes et al. 2006). In OII that were not treated by chemotherapy *MGMT* hypermethylation was not identified as a prognostic marker (Watanabe et al. 2002).

2.6.4

Other Prognostic Molecular Factors

Different molecular markers were identified as prognostic markers for oligodendroglial tumors. Most of them resemble chromosomal areas or are genes that are frequently altered in astrocytic tumors. It should be kept in mind that these markers may indicate an “astrocytic genotype” and, therefore, do not delineate specific oligodendroglial subgroups.

TP53 mutations or LOH 17p13 are rarely found in tumors with an oligodendroglial phenotype and are usually inversely associated with losses on 1p/19q (Ohgaki et al. 1991; Burger et

al. 2001; Wolter et al. 2001; Mueller et al. 2002; Ueki et al. 2002). *TP53* mutations or LOH 17p13 were identified as prognostic markers that indicate a reduced progression-free survival (PFS) and total survival (*TP53*) (McLendon et al. 2005) or total survival (LOH 17p13) (Walker et al. 2005). However, in another study focusing on patients with OIII, neither *TP53* mutations nor p53 IHC results were associated with survival (Cairncross et al. 1998).

Losses of chromosome 10 are mostly observed in high-grade gliomas and inversely to losses on 1p/19q (Jeuken et al. 1999; Hoang-Xuan et al. 2001; Ino et al. 2001; Ueki et al. 2002; Thiessen et al. 2003). Different studies reported an association between losses of chromosome 10 and clinical outcome: either progression-free survival (Hoang-Xuan et al. 2001; Sanson et al. 2002) or total survival (Walker et al. 2005) was reduced in patients with oligodendroglial tumors with this chromosomal alteration. However, one study did not find an association between reduced survival and losses of chromosome 10 (Cairncross et al. 1998).

EGFR amplifications are rare events in oligodendroglial tumors inversely associated with losses on 1p/19q (Diedrich et al. 1991; Wong et al. 1994; Reifenberger et al. 1996; Bigner et al. 1999). However, one study identified a few patients with OIII with *EGFR* amplifications that had reduced progression-free survival (Hoang-Xuan et al. 2001).

Prognostic markers that are not inversely linked to 1p/19q losses may be more attractive for identifying specific oligodendroglial subgroups with differing clinical outcome. Homozygous deletions of *CDKN2A* on 9p21 are predominately found in anaplastic oligodendroglial tumors with and without losses on 1p/19q (Reifenberger et al. 1994; Weber et al. 1996; Bigner et al. 1999; Kros et al. 1999; von Deimling et al. 2000; Kitange et al. 2005). Reduced survival was found in patients with OIII with homozygous deletions of *CDKN2A* (Cairncross et al. 1998). Reduced progression-free survival was observed in patients with OIII with

homozygous deletions of 9p21 (McLendon et al. 2005). A trend toward an unfavorable outcome was seen in patients with OIII with homozygous deletions of *CDKN2A* (Hoang-Xuan et al. 2001). However, there is an older report that described losses on 9p to be inversely associated with losses on 1p/19q (Weber et al. 1996). In conclusion, deletions of *CDKN2A* on 9p21 may be a prognostic marker to separate different groups of OIII.

Gains on chromosome 8q were identified to be strongly associated with poor outcome in five patients with oligodendroglioma. Three of these patients demonstrated losses on 1p/19q as well. This finding indicates that there may be two subgroups of oligodendroglioma patients with 1p/19q losses that can be separated from each other by the presence or absence of gains on 8q (Kitange et al. 2005). However, these findings need to be confirmed by an independent study.

The fact that *IDH1* is the most frequently mutated gene in oligodendroglial tumors (Balss et al., 2008) raises the question of whether this alteration is of prognostic importance. However, currently no data is available.

2.7 Conclusions

In spite of impressive advances in the diagnostic approach to and therapy of oligodendroglial tumors, many aspects are not yet resolved. Morphological criteria need to be refined with emphasis on more committing guidelines for the diagnosis of oligoastrocytomas. Several aspects render the current concept of a mixed oligoastrocytomas questionable. Amongst them the genetic heterogeneity of this group with hallmarks either typical for astrocytomas or for oligodendrogliomas. Further, there is observation that there is little or no difference between the clinical course of oligodendroglioma and oligoastrocytomas both with combined losses of 1p/19q. We expect

molecular analysis to become the major criterion for diagnosis of these tumors in the near future. Whether these analyses will target the t(1;19) (q10,p10) translocation, a putative fusion protein, an associated surrogate marker such as allelic losses, or putative tumor suppressor genes not yet identified will need to be established. The high interobserver variation in the diagnosis of oligodendroglial tumors is also due to the lack of an antigenic profile that clearly distinguishes oligodendroglial from astrocytic tumor cells and that can be used to identify these cells by immunohistochemical analyses on paraffin-embedded tissues. The WHO guidelines for distinction of anaplastic oligoastrocytomas from glioblastoma with oligodendroglial component are controversially discussed among neuropathologists and ongoing studies are expected to alter the current definitions. Given the diagnostic and predictive importance of 1p/19q losses, noninvasive methods for identification of oligodendroglial tumors with 1p/19q losses need to be refined.

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