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Review

Low-grade gliomas: clinical and pathobiological aspects

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Summary. The optimal management of patients with low-grade gliomas remains a challenge for the treating physician. The natural history of the disease shows a large variety, and there is a substantial controversy about many of everyday treatment recommendations. However, new developments in clinical and basic research in neuro-oncology have occurred during the last years. In this review some of these new insights into clinical and biological aspects of low-grade gliomas are discussed, with focus on the translation of new knowledge from basic research into clinical practice. For example, molecular genetic profiling of tumour material has started to guide treatment recommendations and clinical management of some patients with oligodendrogliomas. Experimental studies of the different molecular pathways in tumour cells and in their normal counterparts involved in cell-cycle check-point control have elucidated some of the underlying mechanisms of resistance of gliomas to radiotherapy and chemotherapy. Finally, improved classification of the different subtypes of low-grade gliomas may be achieved in the near future by characterization of the genetic heterogeneity within the tumour and by identification of a putative stem cell as the origin of the tumour cells.

Key words: Low-grade gliomas, Prognostic factors, Tumour progression, Heterogeneity, Subclassification

Introduction

The optimal management of patients with low-grade gliomas is still a matter of debate. The controversies that have existed for so long regarding optimal therapeutic strategies are at least partly explained by the large clinical variety of the disease. It is well known that some patients show a complete indolent course of disease for many years, whereas others experience rapid tumour progression and a fast fatal disease. The knowledge concerning the biological mechanisms that underlie this clinical variety is still insufficient. Also, there has been a substantial lack of prospective clinical trials studying the effects of different therapeutic strategies on survival of the patients. Only recently evidence from large randomised studies has come forward concerning the effect of radiotherapy. This evidence is the first step on the way to a more general consensus on the optimal treatment strategy of patients with low-grade gliomas. The role of other therapies such as surgery and chemotherapy is still controversial. In this review, we discuss the clinical behaviour in correlation to the pathobiology of the most common types of low-grade gliomas.

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Classification and clinical behaviour

The most common tumours of glial origin in the central nervous sytem are astrocytomas, oligodendrogliomas and mixed gliomas, all of which are discussed separately in this section. According to the World Health Organization (WHO) classification of brain tumours, the adult low-grade gliomas correspond to astrocytomas, oligodendrogliomas and mixed gliomas grade II (Kleihues et al., 1993). More uncommon adult types are the pleomorphic xanthoastrocytomas, the ependymomas and subependymomomas. Adult low-grade gliomas are characteristically localized supratentorially and are well-differentiated tumours that lack histological signs of high malignancy such as mitoses, endothelial cell proliferation and necrosis (McLendon et al., 1998). Only moderate nuclear polymorphism is tolerated according to the histopathological criteria of the WHO for grade II gliomas. The low-grade gliomas that mainly affect children and young adults such as the pilocytic astrocytoma and the brain stem gliomas usually show a different clinical and biological behaviour and are not further discussed here.

Astrocytomas

The most common adult astrocytoma is the diffuse astrocytoma that typically occurs during the third or

fourth decade of life. The tumours are characteristically diffuse infiltrating lesions that are poorly defined and lack contrast enhancement on computed tomography (CT) or magnetic resonance imaging (MRI). They can sometimes be misinterpreted as ischaemic infarctions. Microscopically, the tumours are divided in three types based on the type of astrocyte that has given rise to the tumour cells: fibrillary, protoplasmic and gemistocytic astrocytomas. This subclassification of diffuse astrocytomas based on morphological criteria has some prognostic implications since it is generally accepted that gemistocytic astrocytomas have a higher tendency to undergo rapid malignant transformation (Shaw et al., 1997).

Patients with diffuse astrocytomas usually present with epileptic seizures and little or no other symptoms in spite of sometimes extensive tumour mass. Initially the tumours do not show any or very little mass effects, and occasionally they are discovered accidentally. However, most diffuse astrocytomas transform in high malignant gliomas and of all low-grade gliomas patients with astrocytomas grade II carry the highest risk for malignant transformation. Five-year survival for patients with diffuse astrocytomas has been estimated around 50% (Shaw et al., 1997). In some cases, tumour progression occurs by increased tumour mass without certain signs of malignant transformation of the cells.

Oligodendrogliomas

Like the low-grade astrocytomas, oligodendrogliomas occur usually in the third or fourth decade. The tumours are less common than diffuse astrocytomas, but the classification and thus the real incidence of pure oligodendrogliomas is not uncontroversial (Daumas-Duport et al., 1997). Microscopically neoplastic oligodendrocytes are recognized by the characteristic perinuclear haloes around the naked nuclei of the cells and by the absence of immunostaining for glial fibrillary acidic protein (GFAP). The tumours may infiltrate the brain similarly as diffuse astrocytomas, but also more circumscribed and well-defined tumours are found. In around 50% of all cases calcifications are found showing a rather typical radiological picture on CT or MRI (Cairncross, 1997).

Patients with oligodendrogliomas have a better prognosis than patients with astrocytomas and their five-year survival is around 70-80% (Cairncross, 1997). The tumours can be indolent for several years, and sporadic cases are described of patients having survived for 3 or 4 decades. However, a substantial number of patients develop a more aggressive tumour over the years with histological and clinical signs of anaplastic oligodendroglioma. Also, malignant transformation into a mixed glioma or into an anaplastic astrocytoma can occur, suggesting that the tumour cells with highest malignant potency are derived from a coexisting neoplastic lineage of GFAP-positive astrocytes or from a tumour stem cell with astrocytic characteristics.

Mixed gliomas

The occurrence of mixed gliomas exemplifies that a mixture of neoplastic cells with different glial phenotypes can exist within one tumour. Mixed gliomas show a mixture of neoplastic oligodendrocytes and astrocytes. Clinically the tumours behave often like diffuse astrocytomas with a higher risk for malignant transformation than pure oligodendrogliomas (Gutierrez, 1999). Radiologically the tumours cannot be distinguished from other low-grade gliomas, and the diagnosis is as for the other low-grade gliomas made on histopathological criteria. When the tumours progress into histologically high-grade gliomas, they are usually indistinguishable from anaplastic astrocytomas and finally glioblastomas, suggesting that malignant transformation is driven by the astrocytic component.

Other types

Ependymomas are uncommon low-grade gliomas that are derived from ependymal cells and develop close to the ventricles or the central canal. The incidence of ependymomas in the spinal cord is much higher than in the brain. Radiologically the tumours are often well-defined and circumscribed tumours and thus more suitable for complete excision, although their central localization in the brain may complicate surgery (Gutierrez, 1999). The pleomorphic xanthoastrocytoma (PXA) is another infrequent type of low-grade glioma, that may be misinterpreted as a high-grade tumour because of its microscopically pleomorphic appearance. The prognosis of PXA is favourable but malignant transformation into a high-grade glioma may occasionally occur (Gutierrez, 1999).

Therapeutic management

The absence of general consensus about the therapeutic management of low-grade gliomas that has existed so far is largely due to the lack of controlled and randomised prospective studies on the effect of different treatment strategies. There have been many reports of retrospective studies on the effect of radiotherapy and surgical resection, but the results have been inconsistent and difficult to interpret. However, recently large European and American randomised controlled trials have made new advances in understanding the potential of radiotherapy (Karim et al., 1998; Shaw et al., 1998). The results of some of these trials are discussed briefly, as well as the potential of other treatment modalities such as surgery and chemotherapy.

Radiotherapy

The European Organization for Research and Treatment of Cancer trial reported no difference in 5-year survival between patients who received radiotherapy postoperatively and those patients who did

not (Karim et al., 1998). However, a significant difference in progression-free survival was found between the two groups, in favour of the group that received radiotherapy postoperatively. Thus, immediate radiotherapy may control tumour growth initially but does not influence the overall survival of the patients. Taking into account the potential neurotoxicity of radiotherapy, a cautious approach towards patients with stable disease is defendable or even preferable (Surma-aho et al., 2001). Especially for patients with oligodendrogliomas that have a long estimated survival, withholding radiotherapy until necessary is justified (Olson et al., 2000). A number of questions still have to be answered. Results of the quality-of-life studies for patients with immediate radiotherapy and those with delayed radiotherapy are still to be analysed. Another point of debate is the right radiation dose, since no dose-related response was found between patients irradiated with high dose and those with sub-maximal dose (Karim et al., 1998; Shaw et al., 1998).

Surgery

In relieving neurological deficit or in obtaining a histological diagnosis, the role of surgery is well established. The effect of surgery on the overall survival of patients with low-grade gliomas is less certain (Bampoe and Bernstein, 1999). Well-designed studies of relatively large series of patients with similar histological tumour types addressing the issue of timing and extent of surgery are lacking. Clinical parameters such as age and preoperative status of the patient, size and localisation of the tumour are determinants of overall survival, but the timing and extent of surgery are still uncertain factors (Berger et al., 1994). It is probably a good strategy to confine early and more aggressive resection for those patients with unfavourable prognosis, especially patients >40 years old with large tumour mass causing mass effects (Berger and Rostomily, 1997; Bampoe and Bernstein, 1999). Younger patients with inoperable tumours but good clinical status may be selected for stereotactic biopsy and be followed clinically and radiologically and treated with either surgery and/or radiotherapy upon tumour progression.

Chemotherapy

In general, gliomas are not particularly sensitive to chemotherapy. In most clinics chemotherapy for low-grade gliomas is used as a salvage option in previously irradiated patients with recurrent or progressive disease (Lesser, 2001) Some specific subsets of high-grade gliomas such as the anaplastic oligodendroglioma may be responsive to chemotherapy, but there is yet no unequivocal evidence that the addition of chemotherapy to radiotherapy prolongs survival of patients with high-grade glioma (Mikkelsen, 1999). The introduction of new cytostatic drugs with relatively well tolerated safety profile such as the DNA alkylating agent Temozolomide has led to an increased interest in the use of chemotherapy for patients with gliomas (O'Reilly et al., 1993). A logical and soon to be expected step is the use of these cytostatic agents during earlier stages of disease, such as for patients with low-grade gliomas that show the first signs of tumour progression. However, since these patients are still likely to have a relatively long survival time it will take great effort to design the right experimental clinical set-up to evaluate the impact of these drugs on tumour control, patient survival and quality of life.

Prognostic factors

Despite their histological similarity, low-grade gliomas differ widely in their clinical behaviour. Over the past decade there have been several attempts to identify clinical and biological markers that reflect the aggressiveness of the tumour and the prognosis of the patient.

Established clinical prognostic factors

The most important prognostic factor for patients with low-grade gliomas is tumour histology. Patients with oligodendrogliomas have a favourable prognosis compared to the subgroups astrocytomas and mixed tumours. Indeed, many of the difficulties in evaluating the impact of different treatment modalities on the natural course of disease of patients with low-grade gliomas are caused by mixing the histological subgroups with different clinical behaviour.

Retrospective studies have indicated a number of favourable patient-related prognostic factors: young age, good clinical status and chronic epileptic seizures as only symptom. These parameters can be used to define subgroups of patients with divergent overall survival and consideration of these prognostic subgroups may be important in the stratification of patients for clinical trials and for defining therapeutic strategies (Bauman et al., 1999).

An important finding of the European Organization for Research and Treatment of Cancer (EORTC) concerns the correlation of tumour size and localisation with prognosis of the patient (Karim et al., 1996). Patients with best prognosis, after accounting for the effects of histology, were those with relatively small tumours (3-4 cm in diameter) located in cortical areas away from the midline causing no neurological deficits. This subgroup is also called the low-grade gliomas of chronic epilepsy, and is considered as a distinct clinical and pathological entity (Piepmeier et al., 1993; Bartolomei et al., 1997). The outcome for these patients is significantly better than for patients with tumours localised in the white matter and with more complex symptoms.

Molecular genetic prognostic factors

Some of the genetic alterations that occur in the stepwise development of glial tumours appear to be of

prognostic value (Smith and Jenkins, 2000). For oligodendrogliomas, alterations of the 1p and 19q chromosome arms have emerged as strong predictors of chemosensitivity and of overall survival (Cairncross et al., 1998). Mutations of p53, found in up to 67% of all low-grade astrocytomas, are among the earliest mutations that occur in low-grade gliomas and are thought to be of importance for malignant progression of the tumour (Ichimura et al., 2000). It is not clear whether p53 mutations are independent predictors of survival. The p53 mutation is considered as a marker for the astrocytic origin of the tumour and thus of use for the classification of mixed gliomas where the astrocytic component reflects a more unfavourable prognosis. Thus, in mixed gliomas at least two different genotypes are found, one with astrocytic alterations (p53 mutations) and one with oligodendrocytic alterations (1p and 19q). In a large series of gliomas including both high- and low-grade astrocytomas, mutations of PTEN, a recently identified tumour suppressor gene, were strong, independent predictors of shorter survival (Sano et al., 1999).

Other prognostic factors

Over the last decade many retrospective studies have been undertaken to identify factors and parameters that can be used to predict the prognosis of patients with low-grade gliomas, and which may aid in the clinical management of these patients. Many of these studies are difficult to interpret because patients from different prognostic subgroups (histological diagnosis, age, symptoms) have been combined. Some of the more recent studies have recognized this problem and have focused on patient groups of better homogeneity. In a retrospective study of 74 diffuse low-grade astrocytomas levels of Vascular Endothelial Growth Factor (VEGF), a powerful angiogenic factor, in the tumours were shown to be independent prognostic markers of survival (Abdulrauf et al., 1998).

The introduction of new imaging techniques and optimization of their clinical application has offered new ways to study prognosis and clinical out-come in series of patients (Fig. 1) (Roelcke and Leenders, 2000). We have recently shown that the ^{11}C-methionine uptake in the tumour of patients with low-grade gliomas measured by Positron Emission Tomography is of prognostic value (Ribom et al., 2001). Patients with low uptake of ^{11}C-methionine at presentation of their disease had a better outcome than those with high uptake independent of other established prognostic factors such as age and clinical status.

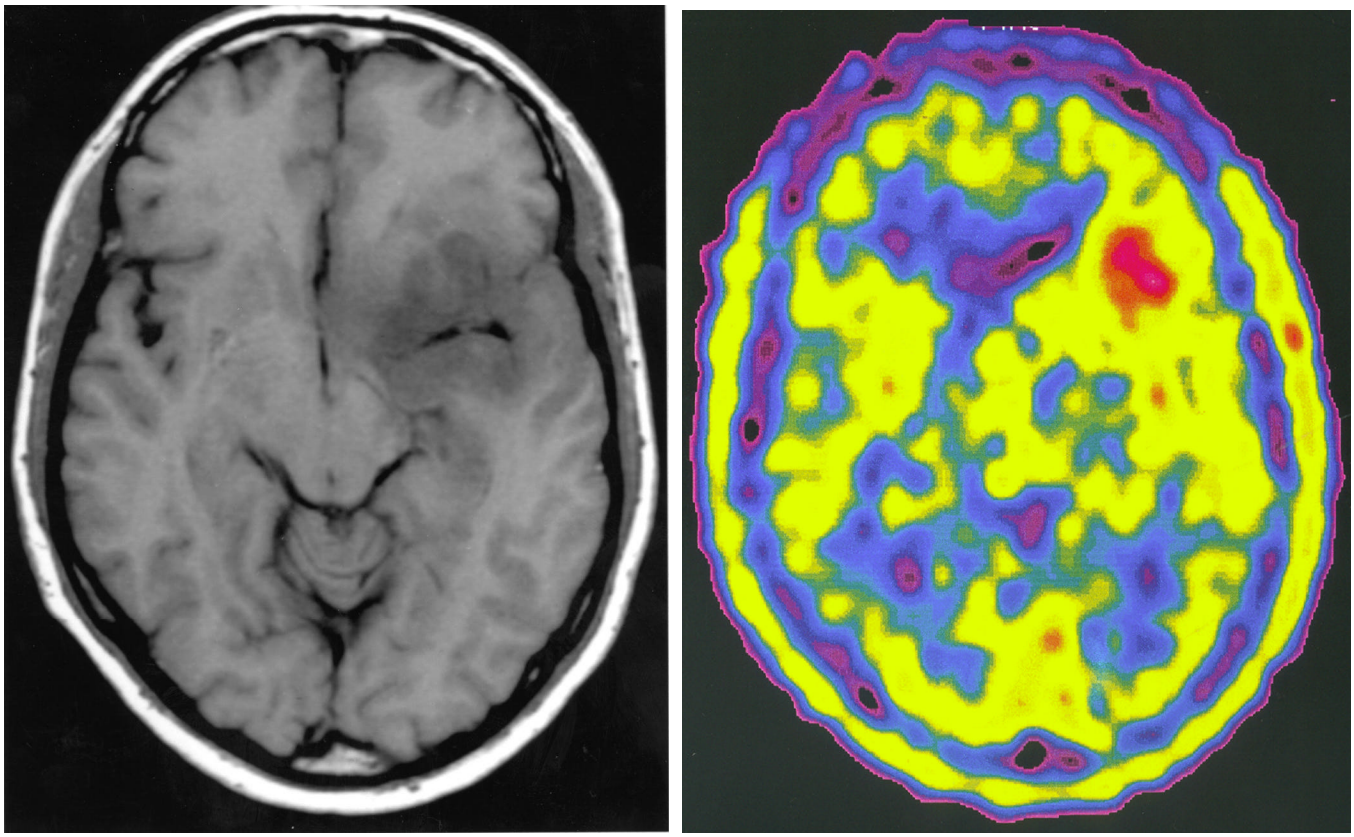

Fig. 1. T1-enhanced MR image **(left)** and L-^{11}C-methionine PET image **(right)** of a 40- year-old man with a diffuse astrocytoma in the left frontotemporal lobe presenting with partial complex epileptic seizures. Note the increased uptake of methionine (red colour) in the "hot-spot" of the

Developmental mechanisms

Identification of clinical and biological prognostic factors will enable us to subclassify patients with low-grade gliomas according to their prognosis. Such a subclassification will assist in the clinical management of these patients. However, for a more complete understanding of the clinical variety of the disease the basic mechanisms of tumour development and tumour progression must be elucidated.

The tumour stem cell concept

Human tumours are classified histogenetically, i.e. the classification is based on the tissue in which the tumour appears and on the morphological similarity between tumour cells and normal cell types of the developing and adult organism. Improved classification may result from a molecular genetic and functional analysis of tumour cells in comparison with normal stem cell populations. According to the theory of clonal evolution of tumour cells, a tumour is derived from one normal single cell that suffered a genetic alteration leading to a growth advantage compared to normal surrounding cells that do not carry the genetic alteration. The acquirement of genetic alterations provides an imbalance between growth inhibitory and growth stimulating signals and a genetic instability leading to further mutations and more advanced cancer growth (Nowell, 1976).

It is not known whether the original cell that develops into a cancer cell is an undifferentiated immature stem cell or a fully differentiated glial cell. It could be argued that high-malignant tumours originate from an immature stem cell with high proliferative potential (Fig. 2A). Low-grade gliomas may be derived from the same cell lineage, but may originate from a cell that has already started its differentiation programme. By some unknown external and/or internal mechanisms the cell aberrantly leaves the normal differentiation pathway and becomes a tumour cell (Fig. 2B).

An interesting theory is based on the assumption that glioblastomas derive from an O-2A progenitor cell lineage, a type of precursor cell that differentiates into oligodendrocytes and type II astrocytes (Raff, 1989) and of which a subset still exists although sparsely in the adult brain (Linskey, 1997). Others have also recognized the presence of multipotent precursor cells in the adult brain. Recently the presence of multipotent neural stem cells in the human adult brain has been demonstrated in the ependymal cell layer lining the wall of the ventricular system (Johansson et al., 1999). These stem cells can proliferate dramatically in response to injury to the central nervous system and give rise to astrocytes by asymmetric cell division. These cells are multipotent in a strict sense and may generate a broad variety of cell types depending on environmental circumstances (Clarke et al., 2000). These important findings within the field of neuroscience and neurodegenerative diseases may turn out to be also of great interest for understanding the origin of human gliomas.

Tumour progression

The step-wise developmental mechanism of high malignant cancer cells, originally described for colon cancer, seems to occur in the “secondary” glioblastomas (Sidransky et al., 1992). Some of the early genetic alterations that may contribute to the development of high-grade gliomas are p53 mutations and platelet-derived growth factor (PDGF) α-receptor over-expression. Evidence is now accumulating that these genetic alterations indeed are causally related to progression of the tumour into a more malignant phenotype (Ishii et al., 1999). Sometimes tumour progression occurs without signs of transformation into a higher malignancy grade. These tumours may expand by infiltration into surrounding brain tissue but without destroying the blood-brain barrier. This kind of tumour

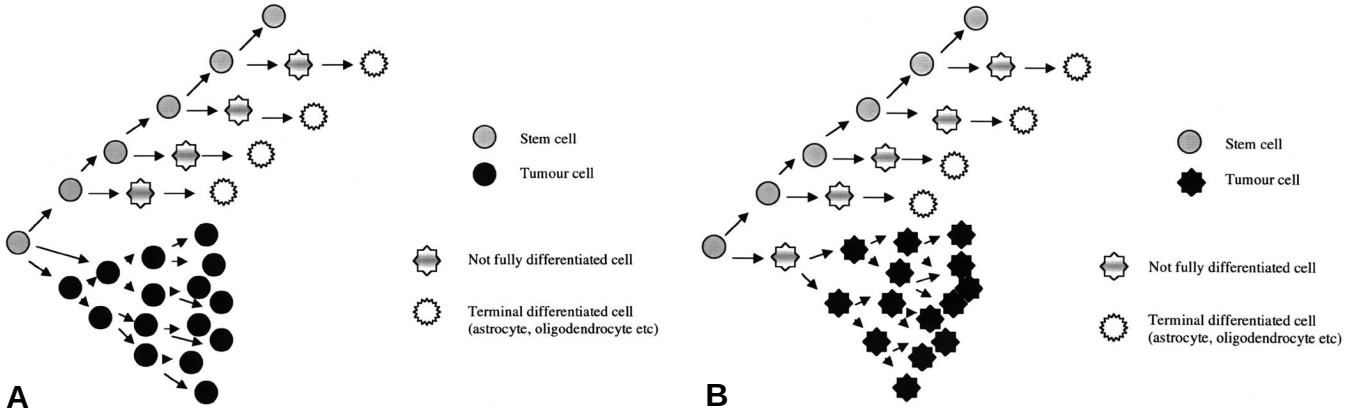

Fig. 2. Hypothetical model of the origin of a high grade glioma from an immature and undifferentiated stem cell **(A)**, and a low-grade glioma from the same cell lineage but in a further stage of differentiation **(B)**.

growth suggests that there are still relatively normal mechanisms of growth control present in these tumours. It is not known whether the genetic alterations in these tumours differ from those more common tumours that show progression by malignant transformation of the tumour cells. One can speculate, however, that mechanisms related to cell motility, adhesion and enzymatic degradation of the extracellular matrix are involved.

In "primary" or *de novo* glioblastomas no prior low-malignant lesion is found and this disease behaves differently both clinically and genetically to the secondary glioblastomas (Kleihues et al., 1995). Patients with *de novo* gliomas are usually older and the tumour has a rapid and fatal course. The rapid clinical course and the extreme derangement of the genome suggest a short "silent" time period in which the genetic alterations of the cancer cells have occurred and accumulated. The genetic alterations that are found are multiple and consist of defects such as EGF receptor amplification and loss of heterozygosity of chromosome 10 (Smith and Jenkins, 2000). Although the genetic anomalies in the *de novo* glioblastomas are different from those found in secondary glioblastomas, it is becoming more evident now that they represent different altered pathways of the same cellular control mechanisms (Collins, 1999). Probably other yet undefined types of glioblastomas exist that do not fit into either of these two broad categories.

Failure to therapy

In spite of the relatively intact mechanisms of growth control of the tumour cells, low-grade gliomas are generally resistant to therapy. The underlying causes of failure to radiotherapy and chemotherapy are not clear, but the biological basis for the radiation and chemotherapy resistance of gliomas is the focus of active research and interesting data are coming forward. Studies of the different molecular pathways that lead to cell cycle arrest versus apoptosis have revealed that genetic alterations of the factors involved in maintaining the genomic integrity can alter sensitivity to radiation of the tumour cells (Tada et al., 1998). Additional genetic changes that occur during tumour progression resulting in aberrant control of progression from G1- to the S-phase of the cell-cycle may augment radioresistance (Collins, 1999).

Another factor that is likely to contribute to the poor response to therapy is the heterogeneity of the tumour at the molecular genetic level, shown by recent studies (Coons et al., 1995). Also in low-grade gliomas that are histological homogeneous tumours, a large genetic heterogeneity may be found suggesting the existence of several subclones of tumour cells. It is likely that even aggressive therapy such as radiotherapy is not sufficient to extinguish these genetically different subclones of tumour cells. Theoretically, a multi-drug therapy utilizing several ways of attacking the tumour cells would be of value to overcome the problem of tumour heterogeneity (Linskey, 2000). One might speculate that certain therapeutic modalities may actually offer growth advantages for some specific subclones, a phenomenon that is clinically recognized as enhanced tumour progression for some patients after therapy (Haas-Kogan et al., 1999). These findings are consistent with the previously proposed "shifting of the cancer paradigm" suggesting that successful therapy is not likely to be achieved by complete extinction of the tumour but rather by re-imposing normal growth control on the tumour cells (Schipper et al., 1995).

Future aspects

Because of the low incidence rates for low-grade glioma and the relatively long natural history, careful follow-up of individual patients is needed to increase our knowledge of the clinical aspects of the disease. Evidence-based clinical trials will improve our ability to understand the clinical importance of various therapeutic modalities and of valuable prognostic factors. Analysis of genetic alterations in the tumours will help us in identifying subgroups of patients with different biological behaviour of the tumor and different clinical outcome. In addition, studies of altered gene expression by new techniques such as cDNA array technology will increase our insight in the transcriptional mechanisms of tumour growth and tumour progression (Caskey et al., 2000; Huang et al., 2000). This way, combined efforts of clinicians and basic scientists will lead to a better understanding of the pathogenesis and the mechanisms underlying the clinical variety of the disease. Also, these combined efforts will provide the basis for a new subclassification of patients. Such a subclassification founded on clinical, histopathological, biological and molecular genetic data will be one of the keys to a more differentiated and succesful management of the individual patient.

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