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Advances and Technical Standards in Neurosurgery

Volume 35

Low-Grade Gliomas

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Low-Grade Gliomas

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Preface

Advances and Technical Standards in Neurosurgery was conceived in 1972 by its founding fathers Jean Brihaye, Bernard Pertuiset, Fritz Loew and Hugo Krayenbühl at a combined meeting of the Italian and German Neurosurgical Societies in Taormina. It was designed to complement the European post-graduate training system for young neurosurgeons and was first published in 1974 initially through sponsorship by the European Association of Neurosurgical Societies. All contributions have been published in English to facilitate international understanding.

The ambition of all successive editorial boards has been to provide an opportunity for mature scholarship and reflection, not constrained by artificial limits on space. The series provides a remarkable account of progress over the past 35 years, both with regard to advances, detailed descriptions of standard operative procedures and in-depth reviews of established knowledge. The present volume is a new venture and is focussed on a single topic namely – low-grade gliomas. It incorporates a multidisciplinary approach that should appeal to both experienced neurosurgeons and young neurosurgeons in training alike.

The Editors

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Molecular neuropathology of low-grade gliomas and its clinical impact.
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Advances in imaging low-grade gliomas

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With 12 Figures and 1 Table

Contents

Abstract

Imaging plays a key role in the management of low-grade gliomas. The traditional view of these tumours as non-enhancing areas of increased signal on T_2-weighted imaging is now accepted as being incorrect. Using new MR and PET techniques that can probe the pathological changes with in these tumours by assessing vascularity (perfusion MR), cellularity and infiltration (diffusion weighted and diffusion tensor MR), metabolism (MR spectroscopy and FDG PET) and proliferation (MR spectroscopy, methionine PET and ^{18}F-fluorothymidine FLT PET). These tools will allow improvements in tumour grading, biopsy/therapy guidance and earlier assessment of the response to therapy.

Keywords: Magnetic resonance imaging; positron emission tomography; prognostic factors; perfusion imaging; diffusion imaging; MR spectroscopy; biopsy guidance; response to therapy.

Introduction

Advances in imaging have been central to advances in managing brain tumours. In low-grade gliomas, however, imaging is probably more important than other brain tumours. They are the major group of tumours where making a diagnosis and start a management plan of 'watch and wait' based purely on imaging [115]. It is essential, therefore, imaging is able to differentiate low-grade gliomas from other conditions, especially the high grade tumours, and that it can identify malignant transformation at an early stage.

The last few years have seen a change in imaging practice. Conventional imaging is excellent at providing information on anatomical location as well as providing valuable information to assist making a diagnosis. New techniques, however, probe pathophysiology by showing features like the tumour's vascularity (perfusion imaging), cellularity and infiltration (diffusion weighted and diffusion tensor imaging) and metabolism (MR spectroscopy and positron emission tomography – PET) [110]. In this review I plan to outline the limitations of conventional imaging techniques and will review the potential role the new MRI and PET imaging techniques may have in the diagnosis and man-

agement of low-grade gliomas (principally WHO Grade II diffuse astrocytomas, oligodendrogliomas and the mixed oligoastrocytomas).

Conventional imaging

Computed tomography (CT) imaging

Low grade gliomas can be difficult to detect on CT as they appear as regions of either low or similar density to normal brain. Calcification is seen in 20% of diffuse astrocytomas and 40% of oligodendrogliomas [74]. Contrast enhancement is not uncommon, and is seen in up to 20% of oligodendrogliomas [74]. This cannot be used to reliably grade these tumours as 31% of 'highly anaplastic' astrocytomas and 54% of 'moderately anaplastic' astrocytomas fail to enhance [17].

Magnetic resonance imaging

As MRI provides better soft tissue resolution, it should be considered the imaging modality of choice: CT should only be used to assess these tumours when MR is contraindicated. An example of the difference in appearances is shown in Fig. 1. On MRI, low-grade gliomas usually appear as well defined masses that are low signal on T_1- and high signal on T_2-weighted imaging and

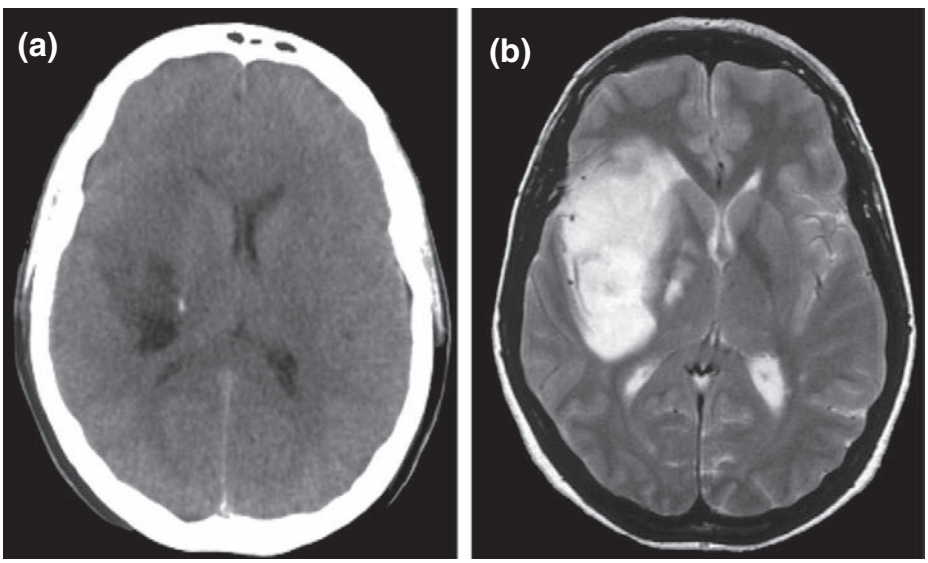

Fig. 1. An example of the difference in appearance between CT and MRI. This 35-year-old male presented with a seizure. The CT (a) shows low density mainly in the posterior part of the tumour. Only the T_2-weighted MRI image (b) shows the full extent of the tumour clearly

produce little mass effect with little oedema [28]. These appearances, however, should not be considered as diagnostic. In a study where patients with these criteria for low-grade glioma underwent a biopsy, the diagnosis was changed in half of cases, with most showing features of an anaplastic glioma, and one having a non-neoplastic condition (encephalitis) [63].

Contrast enhancement in low-grade gliomas

Although low-grade gliomas are considered as non-enhancing tumours, contrast enhancement cannot differentiate between high- and low-grade gliomas. Alokaili *et al.* found that 35% of low-grade gliomas enhanced, and 16% of high grades did not [1]. Other studies suggest that one third of non-enhancing tumours are in fact high grade [123]. For oligodendroglial tumours the situation is more confused with between 50 and 60% of WHO Grade II oligodendrogliomas enhancing [55, 148] while 38% of anaplastic oligodendrogliomas do not enhance [148]. An example of enhancement in a WHO Grade II oligodendrogliomas can be seen in Fig. 2.

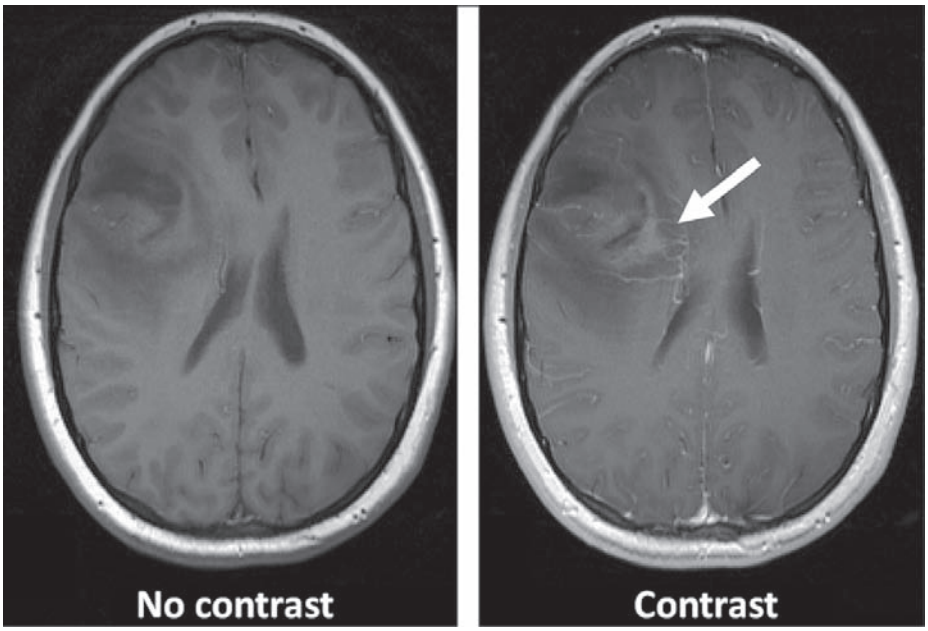

Fig. 2. An example of enhancement in a WHO Grade II oligodendroglioma. This 20-year-old female presented with seizures. Imaging showed a posterior frontal lobe tumour with areas of subtle enhancement mainly on the deep surface (arrowed). She underwent craniotomy and debulking of this lesion which exhibited no evidence of cellular or microvascular proliferation that would suggest it was a more aggressive tumour

Subtle enhancement can be demonstrated using quantitative methods [140]. By calculating the volume of a low-grade glioma that enhances more than 10% compared to the baseline, Tofts *et al.* could show that in some low-grade gliomas the volume of enhancement increased over a number of months before tumour transformation. In tumours that did not transform, the enhancing volume remained stable [140]. The volume of enhancing tissue had prognostic information; tumours with an enhancing volume greater than 4 mLs had a worse prognosis with only 28% of patients progression free at 5 years, compared to 80% of patients with an enhancing volume less than 4 mLs [140].

Assessment of tumour margins with conventional MR

Although low-grade gliomas can appear as distinct masses, it is well appreciated that they can spread beyond the abnormality seen on both T_2- and T_1-weighted imaging [113]. The margin of low grade tumours is usually very indistinct on T_1-weighted imaging and is better demonstrated on T_2-weighted imaging. The use of sequences such as fluid attenuated inversion recovery (FLAIR) – a sequence that typically produces a T_2-weighted image where the signal from CSF is nullified, shows the extent of these tumours very well and often will show subtle abnormalities not appreciated with conventional T_2-weighted images; this is particularly true in regions around the ventricles.

Table 1. *Summary of the differences between astrocytomas and oligodendrogliomas, and the 1p19q status of oligodendrogliomas*

Modality	Astrocytomas vs. oligodendrogliomas	1p19q status
Conventional MRI	Little to differentiate them. Contrast enhancement more common in oligodendrogliomas	LOH of 1p19q is associated with indistinct margin and heterogeneity on T_1 and T_2-weighted imaging
Perfusion MRI	Low rCBV in astrocytomas, increased in oligodendrogliomas	Higher rCBV with LOH 1p19q
Diffusion MRI	Lower ADC in oligodendrogliomas compared to astrocytomas	1p19q loss associated with even lower ADC values
MR Spectroscopy	Larger increase in Cho and Cr in oligodendrogliomas compared to astrocytomas	No difference found
FDG-PET	More marked hypometabolism with astrocytomas	Increased FDG uptake seen with 1p19q loss

rCBV Relative cerebral blood volume; *ADC* apparent diffusion coefficient; *LOH* loss of heterozygosity; *Cho* Choline; *Cr* Creatine; *FDG* fluorodeoxyglucose.

In oligodendrogliomas, studies assessing tumour margin have shown that tumours with indistinct tumour margins are more likely to have loss of heterozygosity at chromosomes 1p19q [55, 87] – an important genetic marker of chemosensitivity and prolonged survival [14]. This genotype of oligodendrogliomas also demonstrated heterogeneous T_1- and T_2-weighted appearances [55]. The suggestion was that the indistinct tumour margin is also a marker of tumour infiltration [87], but image guided biopsies in this group of patients has failed to show this [55]. There is some suggestion that the more indistinct tumour margin is associated with a shorter time to progression and overall survival [38]. These findings are summarised in Table 1.

Assessment of low-grade glioma growth

Changes in low-grade gliomas volume can be assessed by volumetric studies. Follow up of a cohort of oligodendrogliomas and oligoastrocytomas showed that these tumours have a mean growth rate of 4.1 mm/year [80]. Where the diameter grew faster than 8.1 mm/year, the median survival was 5.1 years, compared to more than 15 years where the growth rate was below this threshold [103].

Advanced MRI techniques

Conventional MR methods focus on structural changes within tumours. The last section showed that these are usually non-specific and therefore only provide limited information. Advances in MR technology have allowed faster imaging, at higher fields and create a more homogeneous magnetic field. This has allowed the development of new techniques that probe tumour pathology and are described in more detail in other reviews [110]. Since low grade tumours are classified by the WHO as tumours of increased cellularity without features of anaplasia (i.e. proliferation or disrupted cytoarchitecture), and no increase in vascularity or development of necrosis, imaging methods that can look at changes in cellularity, vascularity and metabolism may allow a better differentiation of low-grade gliomas from both higher grade tumours and more benign conditions. It may also provide prognostic information, identify early transformation and allow better direction of biopsies or other therapies.

Perfusion MRI

One of the key histological features of low-grade gliomas is their lack of microvascular proliferation [61]. The development of endothelial hyperplasia has been shown to be a poor prognostic marker in oligodendrogliomas [25]. Perfusion imaging provides additional information about tumour vascularity.

The relative cerebral blood volume (rCBV) of tumours correlates with tumour vascularity as assessed by non-quantitative scales of histological vascularity [4, 131], measures of microvascular density [5] and angiographic vascularity [131]. It also correlates with the expression of vascular endothelial growth factor (VEGF) within the tumour [77] and the presence of endothelial hyperplasia [15].

Differentiating high- from low-grade gliomas

Many studies have attempted to use perfusion MRI to provide a method to non-invasively grading gliomas [4, 5, 9, 62, 70, 126, 131, 133]; all these studies show that low-grade gliomas have a significantly lower rCBV than glioblastomas (an example in a WHO Grade II astrocytomas is shown in Fig. 3). Attempts to find a threshold that can differentiate between high- and low-grade gliomas have been hampered by the use of different acquisition techniques and methods of reporting the rCBV. Using a spin echo technique that is sensitive to the microvascular component tends to give a lower ratio than using a gradient echo technique [33, 133] that is sensitive to the 'total' CBV from all vessels [8]. Studies using SE sequences suggest that a rCBV threshold of 1.5 can differentiate between high- and low-grade gliomas [4, 75]. Published thresholds for GE sequences are more variable and depend on

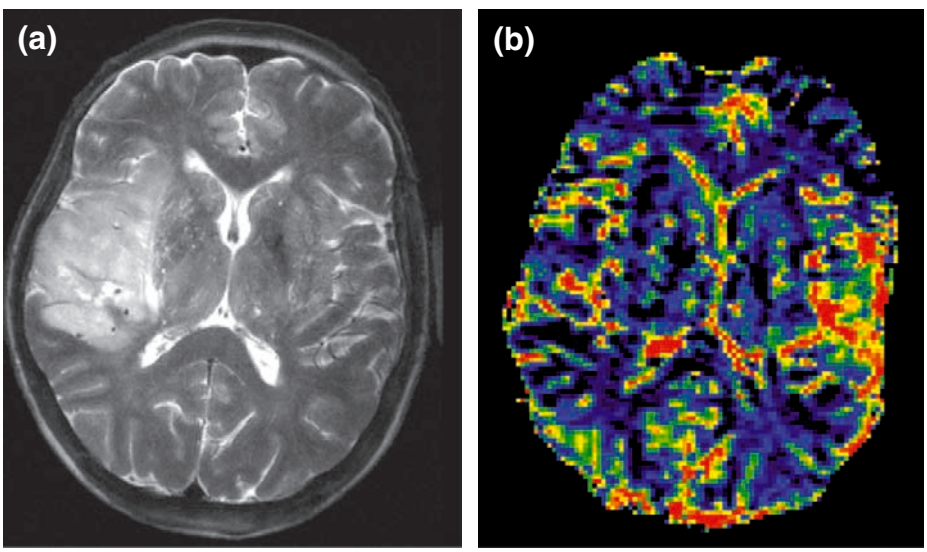

Fig. 3. This 61-year-old female presented with focal seizures affecting her left hand. Imaging (a) showed this to be a non-enhancing lesion in the right insular region. Perfusion imaging (b) showed low rCBV in the tumour (measured at 1.3). Biopsies revealed this to be a WHO Grade II astrocytomas. She remains progression free at 4 years

whether the aim is to increase specificity (rCBV 1.75–2.9) [71, 126] or increase sensitivity (rCBV 3.5) [71].

There are a number of problems using perfusion parameters to grade gliomas for an individual patient. The first is that all studies show marked overlap of rCBV values in different tumour grades [34, 62, 126, 131, 133], particularly differentiating WHO Grade III from either WHO Grade II or WHO Grade IV gliomas. Secondly, most measures are made by placing a region of interest onto the brightest 'hot spot'. This is dependent on the location the region is placed – more reproducible results can be obtained using measures from histogram analysis of the whole tumour [36, 72]. Finally, oligodendrogliomas have higher rCBV values than astrocytic tumours [16, 75] – a finding related to their dense network of branching capillaries that resembles the pattern of 'chicken-wire' (an example is shown in Fig. 4). As a result, low grade oligodendrogliomas could be falsely graded as a higher grade tumour in unselected groups of low-grade gliomas. Studies that only include oligodendrogliomas show a significantly higher rCBV in WHO Grade III anaplastic oligodendrogliomas compared to WHO Grade II oligodendrogliomas [129]. Although this study had small numbers of patients (7 per group) it concluded

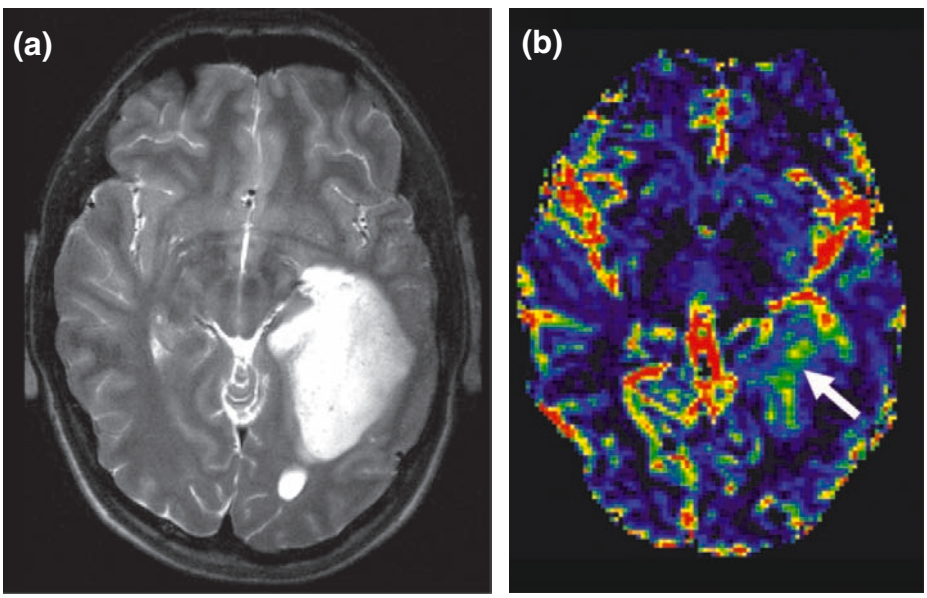

Fig. 4. An example of the increased rCBV seen with oligodendrogliomas. This 18-year-old male presented with a seizure. (a) Conventional imaging showed a large, non enhancing mass adjacent to the atrium of the ventricle. (b) Perfusion imaging showed increased rCBV within part of the tumour (arrowed). This was biopsied and confirmed to be a WHO Grade II oligodendroglioma without any anaplastic features. The patient remains progression free after 3 years

that an rCBV threshold of 2.16 could differentiate between the grades with 100% specificity and 86% sensitivity. The rCBV in oligodendroglial tumours is further complicated by the fact that tumours with chromosomes 1p19q deletion have an even higher rCBV [58, 68] (cf. Table 1).

Perfusion imaging as a prognostic marker in low-grade gliomas

Since perfusion MR can identify areas of microvascular proliferation, a known histological feature of poor prognosis, attempts have been used to use perfusion MRI to assess prognosis. Law *et al.* have shown that an rCBV threshold of 1.75 could differentiate between a prolonged survival group (median time to progression approx. 10 years) with a poor prognosis group (median time to progression less than one year) [69, 73]. An example of this is shown in Fig. 5. A recent follow up study has shown that there is a significant increase in rCBV that can be detected up to one year before there was evidence of tumour transformation [24].

Perfusion MR has also been used to guide biopsies of non-enhancing tumours [78]. Where perfusion MR demonstrated heterogeneous rCBV, the

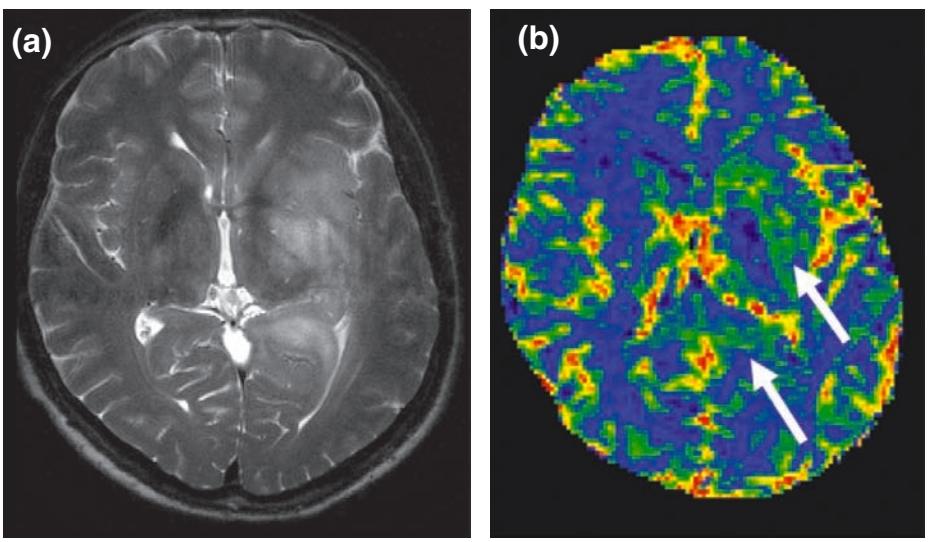

Fig. 5. This 45-year-old male who presented with seizures and headache was shown to have a non-enhancing tumour in the left insular region extending along the temporal lobe to the atrium of the lateral ventricle (a). Biopsies confirmed it to be a WHO Grade II astrocytoma. In contrast to the patient presented in Fig. 3, perfusion imaging (b) shows areas of increased rCBV (measured at 2.8 – arrowed). Post-biopsy he had radiotherapy (54 Gy in 30 fractions). Within one year he clinically deteriorated and had evidence of tumour progression and the development of enhancement on imaging. He died of progressive disease despite chemotherapy 18 months after initial presentation

target for biopsies was taken as the region with the highest rCBV. Biopsies of these regions demonstrated oligodendroglial differentiation or anaplastic regions whereas tumours with uniformly low rCBV were more likely to be WHO Grade II diffuse astrocytomas.

Perfusion imaging at recurrence: differentiating radiation necrosis from recurrent tumour

One major difficulty in the management of all patients with brain tumours treated with radiotherapy is differentiating changes that occur following treatment. Tumour recurrence and radiation necrosis can appear similar and both can have a very variable appearance on conventional MRI [18]. Radiation necrosis can be identified by areas of reduced rCBV. Studies in patients with radiation necrosis in the temporal lobes following radiotherapy of nasopharyngeal carcinomas (where there is no confusion with recurrent tumour) showed reduced rCBV in these regions [143]. Subsequent studies have suggested that rCBV values below 0.6 are predictive of radiation necrosis, and values above 2.6 are predictive of tumour; the difficulty lies with the mixed cases with values between 0.6 and 2.6 [134].

Diffusion-weighted and diffusion tensor MRI

The appearance of low-grade gliomas on diffusion-weighted (DWI) imaging is variable. The high signal on DWI images is largely a result of T_2-weighted 'shine through' effects and is more dependent on the T_2-weighted appearance [91]. The increase in the apparent diffusion coefficient (ADC) is therefore used as a better, quantitative marker of diffusion in brain neoplasms.

ADC values are determined by a combination of processes. Firstly, it is increased by the increased volume of water in the tumour tissue due to vasogenic oedema. The ADC value correlates with both oedema (using T_2-weighted signal intensity) and blood brain barrier permeability (using the percentage enhancement seen on T_1-weighted imaging following a dose of gadolinium contrast) [95]. In addition, the ADC is dependent on cellularity – the more cells present, the less the distance that the water molecules can diffuse. Studies have indeed confirmed that there is an inverse correlation between ADC and tumour cellularity [40, 65, 132].

Grading gliomas using diffusion-weighted imaging

As low-grade gliomas tend to be less cellular than their high grade counterparts, attempts have been used to grade gliomas using ADC values. Studies suggest low-grade gliomas have a significantly increased ADC compared to high grade tumours [65, 132].

The problems of using ADC values to grade these tumours are similar to the use of perfusion MRI. There is marked overlap in individual values making grading of individual patients impossible. In addition, it is not possible to differentiate between low-grade gliomas and other benign problems [12], and some studies that have largely used WHO Grade III tumours as their high grade tumours could not differentiate between high- and low-grade gliomas at all [67]. In addition, just like using rCBV measures, ADC is significantly lower in oligodendrogliomas [141], and within the oligodendrogliomas the tumours that have lost chromosome 1p19q have lower ADC values [56]. These changes, however, are much less marked than the changes seen in rCBV values (cf. Table 1).

Some studies have used diffusion-weighted imaging to differentiate radiation necrosis from tumour recurrence following therapy. Areas of tumour recurrence showed higher mean ADC values compared to radiation necrosis [48, 135]. Unfortunately the values for necrosis and recurrence overlap making it of little value for the individual patient. Compared to other modalities, diffusion imaging does not appear to add much in this setting [120].

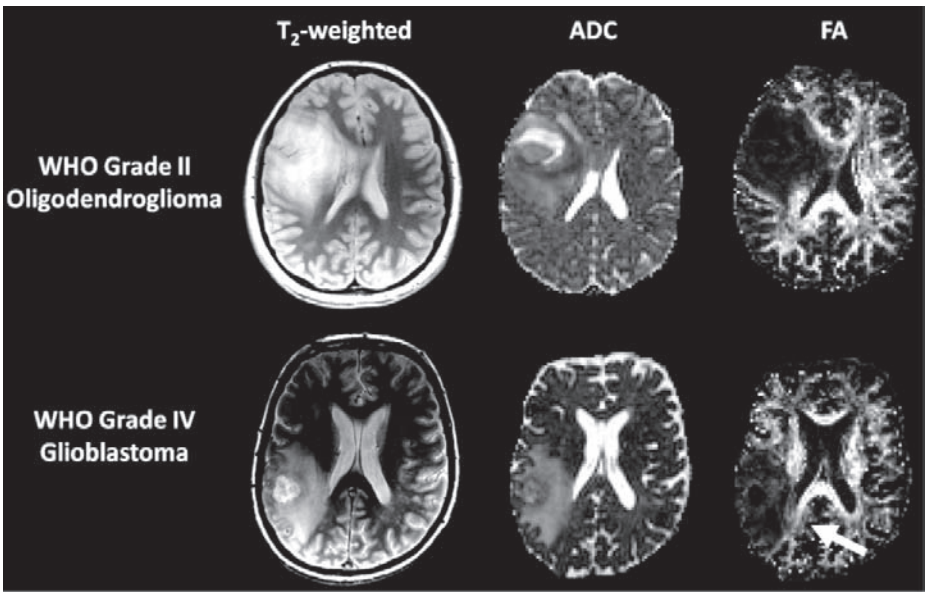

Fig. 6. Diffusion weighted (ADC) and diffusion tensor (FA) in a patient with a WHO Grade II oligodendrogliomas (top row) and WHO Grade IV glioblastoma (bottom row). The lower grade tumour shows regions of much higher ADC and generally lower FA compared to the glioblastoma. In the glioblastoma patient there is infiltration of the adjacent white matter tracts which is seen as gradual reduction in FA values in these regions (arrowed). This is not seen in the low grade patient

Diffusion tensor imaging in low-grade gliomas

Diffusion tensor imaging (DTI) is a modification of DWI that is sensitive to the directional diffusion of water (anisotropy). It provides more information on tissue architecture that is not available on DWI as reduced anisotropy can occur with loss of tissue organisation (e.g. as seen with demyelination), destruction of axonal processes, widening of extracellular spaces (e.g. as seen with tumour infiltration) and changes in cell size. The most commonly used parameter of DTI imaging is *fractional anisotropy* (FA) – a rotationally invariant measure of anisotropy.

Studies in tumours show that the FA values correlate with tumour cellularity and vascularity [7] as a result low-grade gliomas tend to have lower FA values. Using a threshold of 0.188, Inoue *et al.* could differentiate between high- and low-grade gliomas [52]. Studies looking at the periphery around the tumour have shown there is no reduction in FA in the white matter tracts adjacent to low-grade gliomas, compared to the reduction in normal appearing tracts adjacent to high-grade gliomas [43, 111] (Fig. 6). This difference has been suggested as due to tumour infiltration – but since low-grade gliomas infiltrate, especially oligodendrogliomas, it probably relates to white matter destruction from tumours and the lack of sensitivity of these DTI measures. Recent biopsy studies using novel tissue signature methods [106, 114] have shown that DTI can identify this occult infiltration, even in low-grade gliomas [113].

Magnetic resonance spectroscopy

Unlike the other imaging methods, MR spectroscopy (MRS) allows the non-invasive study of metabolism from either a single, small region of interest (single voxel spectroscopy) or multiple regions (multivoxel or chemical shift imaging). Virtually all clinical spectroscopy studies focus on the ^{1}H nucleus (which is essentially a proton) due to its abundance, its strong magnetic signal and the fact it can be detected using standard MR equipment. Although up to 30 peaks can be identified in the ^{1}H spectrum, fewer peaks are commonly studied in clinical practice.

MR spectroscopy to differentiate high- and low-grade gliomas

All gliomas show a spectrum with an increased choline (a marker of membrane turnover) and reduced N-acetyl aspartate (NAA – a neuronal marker) (Fig. 7). Peaks of lipid (a marker of necrosis) and lactate (a marker of tumour hypoxia) are rarely elevated in low-grade gliomas, but are elevated in higher grade gliomas [84, 90, 93, 97, 98] (Fig. 8). Their presence in low-grade gliomas appears to mirror the proliferative index; when the Ki67 labelling index is <4% no lipid or lactate is detectable, when it is 4–8% lactate can be detected without lipids and

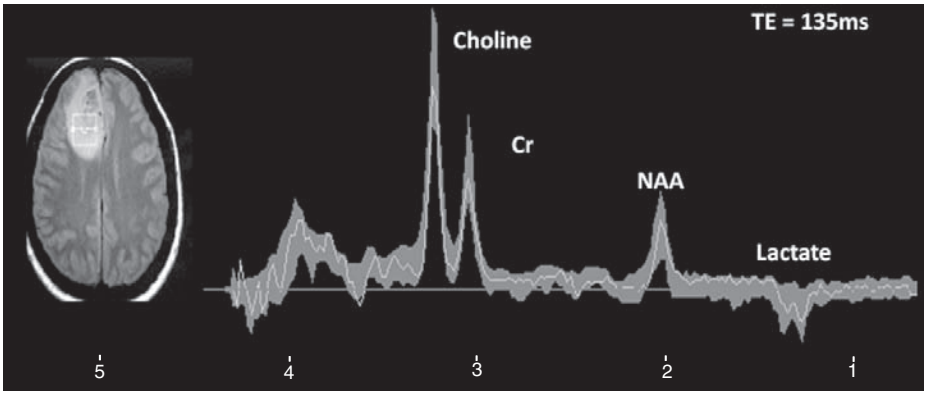

Fig. 7. Single-voxel, proton spectra from 20 patients with WHO Grade II astrocytomas (solid line is mean, grey area is standard deviation). There is an increase in choline peak with reduction of NAA (which still can be seen). Lactate, with this long echo time ($TE = 135$ ms) is frequently seen in these patients as an inverted peak

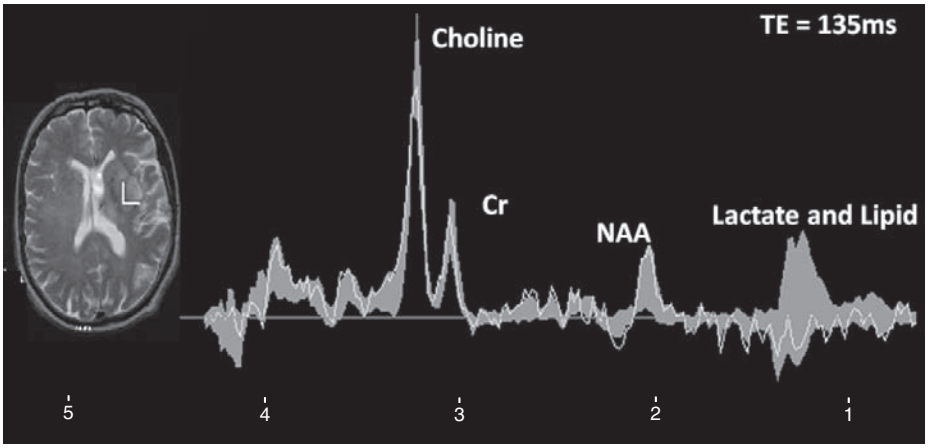

Fig. 8. Mean spectra (with standard deviation) for five patients with WHO Grade III anaplastic astrocytomas. Compared to Fig. 7 there is a higher choline peak with more reduced NAA. Lipids and lactate can now be seen regularly

above 8% there is an increase in lipids [46]. Although creatine (Cr – a marker of energy metabolism) is often used as a reference signal to express the other peaks as a ratio to the creatine peak, it is actually decreased in brain tumours [88, 90]. The reduction is, however, small and does not appear to be related to the grade of tumour [90].

One problem with MRS is that tumours are heterogeneous. Single voxel techniques have the same problems with sampling error that is seen with biopsies. Multivoxel techniques can over come this, and 3D techniques are

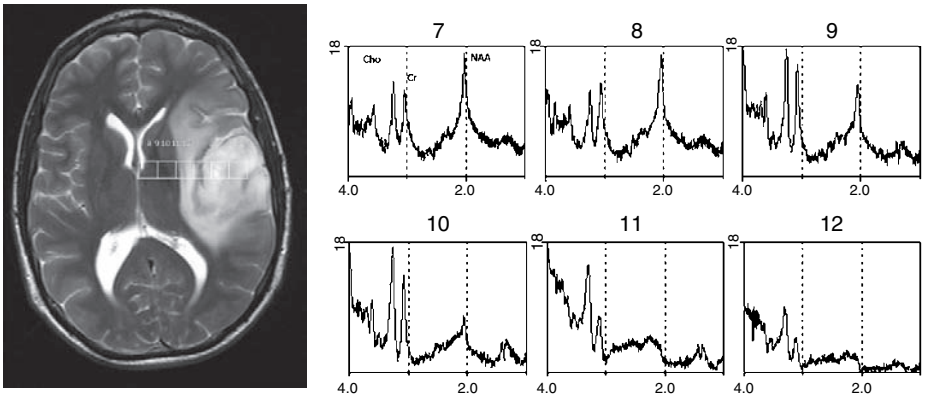

Fig. 9. Multivoxel spectra from a 16×16 grid at TE 30 showing variation in NAA, creatine and choline going from normal brain (in voxel 7) to pure tumour (in voxels 11 and 12).

becoming more widespread. An example of the heterogeneity of spectra across a low-grade glioma is seen in Fig. 9.

Various studies have tried to understand what the MRS findings tell us of the tumour biology. McKnight *et al.* have shown that the Choline/NAA ratio correlates with cell density, proliferative index and the ratio of proliferation to cell death [86]. Other groups have also shown that the Choline/NAA and Choline/Cr correlate with the proliferation index and that the normalised values of Choline correlate with both proliferation index and cell density. In a cohort of low-grade gliomas Guillevin *et al.* showed that cellular atypia correlated with increased Choline/NAA ratio, a lower NAA/Cr ratio and the lipid peak [46].

Using this information it can be shown that low-grade gliomas have a significantly lower Choline/Cr ratio [71, 84, 93, 97, 98, 128], and an increase in NAA [71, 85, 93, 97, 98, 128]. It is possible to differentiate between high- and low-grade gliomas with sensitivity of 73–92% and specificity of 63–100% [6, 37, 51, 71, 124]. Studies comparing the performance of MR spectroscopy and perfusion imaging to correctly grade tumours provide mixed results. One study suggested spectroscopy was superior to perfusion [37], while another showed rCBV measurements were better, and the addition of metabolic information did not improve the diagnostic yield [71].

Differentiating low-grade gliomas from other conditions

MRS has a role in differentiating low-grade gliomas from other conditions that can present with similar clinical symptoms and appearances on conventional imaging. Focal cortical developmental malformations (e.g. cortical dysplasias and dysembryoplastic neuroepithelial tumours) certainly have very similar con-

ventional imaging findings. Vuori *et al.* showed that low-grade gliomas had a more marked reduction in NAA and increase in Choline, while the focal cortical developmental malformations exhibited less change (< 30% difference to normal brain) [146]. The NAA/Cr ratio, in particular, was markedly lower in low-grade gliomas than in the focal cortical developmental malformations. Tumefactive demyelinating plaques, however, have similar MRS appearances to low-grade gliomas with increase in choline, reduced NAA and can contain lactate. Repeat imaging after an interval shows the spectra returns to a more normal appearance in MS, but remains abnormal in low-grade gliomas [13].

Most of the studies discussed so far have concentrated on peak height of a very limited number of metabolites. A recent multicentre study – the INTERPRET study (International Network for Pattern Recognition of Tumours Using Magnetic Resonance – *http://azizu.uab.es/INTERPRET/index.html*) developed a computer-based decision support system that analysed the whole spectrum as a tool to assist with diagnosis. Their database could correctly classify brain lesions in 89% of cases and has provided an infrastructure for other multicentre studies [137]. The eTUMOUR project (www.etumour.net) aims to further develop the database to provide more information to improve differentiation of tumours that may appear similar on conventional imaging.

Identification of low-grade glioma subtypes with MR spectroscopy

Just like diffusion and perfusion MR, there are differences in the MRS spectrum that can differentiate low-grade astrocytomas from oligodendroglial tumours. Oligodendrogliomas exhibited a more marked increase in choline and an increase in creatine. This is in contrast to astrocytomas where there is a more modest increase in choline and a decrease in creatine [146]. Analysis of the whole spectrum could also differentiate between these types of tumours [137]. Unlike perfusion and diffusion imaging, however, spectroscopy cannot differentiate between tumours with or without loss of chromosomes 1p19q [57] (cf. Table 1).

MRS to detect low-grade glioma transformation

Since high-grade gliomas can be differentiated from lower grade tumours by their larger increase in Choline and decrease in NAA and the presence of lactate and lipid, attempts have been made to use these features to identify transformation in low-grade gliomas. One of the difficulties in using MR spectroscopy for follow up studies is the small region that is imaged in single voxel spectroscopy – it is very possible the voxel is not located in the region of the tumour where transformation occurs. Attempts to monitor tumours using this method had a specificity of only 57.1% [3]. Even using multivoxel imaging

techniques appears to have limited uses. Tedeschi *et al.* showed that progressive tumours had a markedly increased (>45%) Choline compared to stable tumours, but it did not appear before they could identify progression on conventional imaging [138]. Reijneveld *et al.* found that in their seven progressive patients, MRS could only detect a difference before conventional MR in 2 cases, and in 2 patients they failed to show any progression on MRS [116]. More worryingly, four of their seven patients with stable disease showed progression on MRS.

Using MRS to assess response to therapy in low-grade gliomas

As a tumour responds to chemotherapy changes in cell numbers/density can occur before there is obvious change in tumour volume. As most studies report little change in tumour volume, there is great interest in using advanced imaging methods to detect early response to therapy. Murphy *et al.* showed in a group of 12 patients with low-grade gliomas treated with temozolomide the decrease in the choline peak correlated with a reduction in tumour volume [94]. They suggested this was due to reduced cell density. They found some increase in NAA, but this was only seen in 3 patients. A further case study that combined MRS with DTI also reported a decrease in choline and an increase in NAA [127]. The decrease in choline correlated with increases in ADC – further evidence that it is due to reduced cellularity. The increase in NAA also correlated with increases in FA suggesting improvement in axonal structures. Further studies are needed to monitor treatment response in individual patients.

One of the major uses of MRS in a clinical setting is the differentiation of radiation necrosis from tumour recurrence. Regions of radiation necrosis exhibit lower NAA/Cr and NAA/Cho ratios and higher Cho/Cr ratios than tumour progression [19, 119]. The presence of lactate can be seen with either pathology and suggests that ischaemia is the underlying mechanism of radiation injury [19]. Like the other modalities, although MRS can identify pure tumour and pure radiation necrosis, it is not able to differentiate the mix picture, which is probably the most common setting [119].

^{31}P-Phosphate MR spectroscopy in low-grade gliomas

Although ^{1}H-proton spectroscopy is the most used clinically, ^{31}P-phosphate spectroscopy can also be performed, with the appropriate equipment. It can provide information on both phosphate metabolites (especially ATP and energy metabolites) and pH. Studies with low-grade gliomas show that they have a similar phosphorus spectrum to normal brain, with essentially normal pH values [49, 79]. The development of anaplastic changes results in a decrease in both phosphocreatine and phosphodiesters peak, with pH showing increas-

ingly alkaline values [49, 79]. With treatment there is a trend to increasingly alkaline pH values, but studies have been done on limited patient numbers and it is difficult to define a relationship with prognosis [79].

Positron emission tomography (PET) imaging

Over the last decade PET imaging has developed with our improved knowledge of cellular biochemistry and the development of new radiotracers that can probe these biological processes. The multiple pathways involved in tumour development can now be studied by these processes. Although a number of PET tracers have been developed for cancer imaging, only three groups are in routine clinical usage. These study glycolytic metabolism, protein synthesis and nucleotide uptake as markers of tumour proliferation. Newer tracers that study membrane turnover have been developed but their use has yet to be determined.

Imaging glycolytic metabolism: 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) PET

It has long been recognised that tumour cells have an increase in glucose utilisation and glycolytic metabolism. Otto Warburg first noticed the relationship between aggressive tumour behaviour and increased glycolysis [147]. It is due to an increase in the expression of numerous genes and is regulated by the hypoxia inducing factor HIF-1. In many tumours there is induction of HIF-1 due to disruption of its normal control that can occur in the absence of hypoxia. The hyperglycolysis seen in tumours is due to increases in glucose transport across the blood brain barrier and cell membranes (e.g. the glucose uptake transporters GLUT-1 and GLUT-3) and increases in the principal enzymes of glucose metabolism (e.g. hexokinase, phosphofructokinase, lactate dehydrogenase and pyruvate dehydrogenase).

The fluorinated glucose analogue 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) has high sensitivity (although poor specificity) for identifying areas of increased tumour metabolism. FDG uptake and metabolism in normal and tumour cells are shown in Fig. 10.

Low-grade gliomas tend to have the same or lower uptake to normal grey and white matter, whereas high-grade gliomas tend to exhibit increased uptake of FDG [31, 136]. Using a tumour-to-white matter ratio >1.5, and tumour-to-grey matter ratio >0.6 it is possible to differentiate high and low grade tumours with a sensitivity of 94% and specificity of 77% [29]. FDG uptake appears to predict grade better than appearances on contrast enhanced CT [104]. In low-grade gliomas areas of increased FDG uptake correlate with tumour anaplasia [44]. Levivier *et al.* found that FDG PET could identify targets for stereotactic

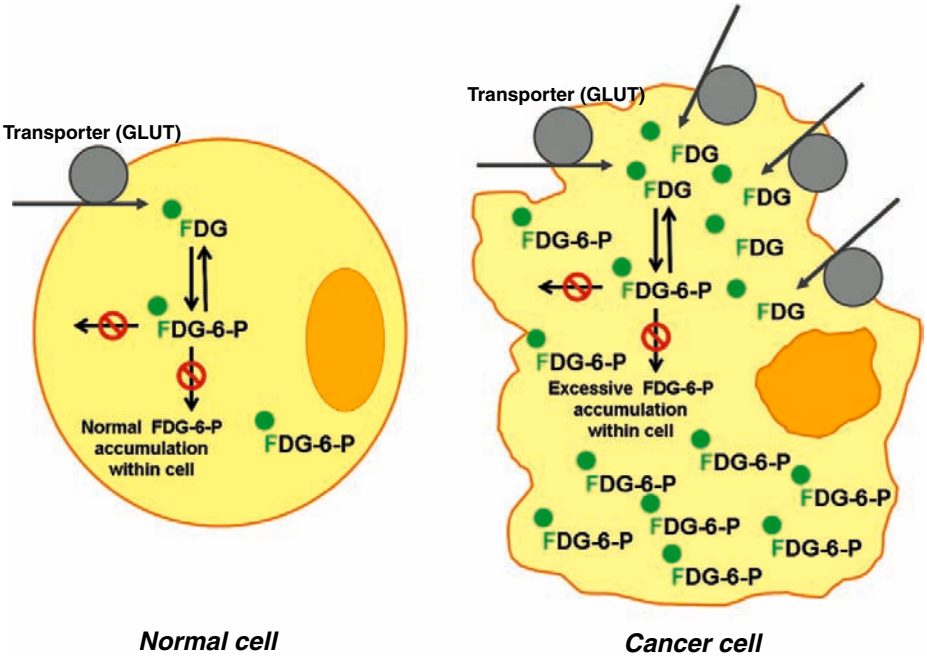

Fig. 10. FDG metabolism in normal and cancer cells. FDG is taken up into cells due to the upregulated glucose transporters (e.g. GLUT-1 and GLUT-3) and is then phosphorylated by hexokinase to FDG-6-phosphate. This does not undergo further enzymatic reactions and, because of its negative charge, it accumulates within the cell

biopsies far better than contrast enhanced CT [76]. They found that 6/35 targets selected by CT were non-diagnostic, whereas 0/55 targets selected by FDG PET were non-diagnostic. Follow up studies suggest that it might be possible to detect the transformation of low-grade gliomas to a higher grade with FDG PET before anatomical changes appear on CT [89, 121].

Studies that have looked at differences in FDG uptake in different histological subtypes of low-grade gliomas suggest that low grade astrocytomas have a lower glucose metabolism than oligodendrogliomas [31]. In series that just look at oligodendrogliomas, FDG uptake is significantly lower in WHO Grade II oligodendrogliomas than anaplastic oligodendrogliomas [30]. Increased glucose metabolism was also seen in low grade oligodendrogliomas with loss of 1p19q heterogeneity [130]. Those with intact chromosomes 1p19q all had reduced FDG uptake (cf. Table 1).

Since increased glycolytic metabolism appears to be a marker for and promoter of a more aggressive phenotype, FDG PET has been investigated as a prognostic marker. The survival of patients with hypermetabolic tumours is worse than those with hypometabolic tumours [2, 27, 105]. Follow up studies suggest increased glucose metabolism may predict tumour transformation [89].

Currently, one of the main uses of FDG PET is the differentiation of recurrent tumour from radiation necrosis. As both will enhance with contrast, standard MR techniques cannot differentiate between these two problems. Recurrent tumours have increased metabolic activity whereas areas of radiation necrosis are hypometabolic [32]. FDG can differentiate between these two with a sensitivity of 75% and specificity of 81% [20]. MR coregistration improves the sensitivity of FDG as it can distinguish recurrence uptake in the normal adjacent cortex. It can be misleading, however, as increased activity can be due to accumulation of activated macrophages.

The real limitation using FDG to assess brain tumours is that the uptake is non-specific and can occur in any region with an increase in metabolic activity. In the normal brain the cortex, basal ganglia, thalami, cerebellum and brainstem have increased uptake, whilst white matter and CSF have low uptake. The uptake is also non-specific since other inflammatory diseases can exhibit increased FDG uptake. In addition, FDG PET is a marker of glycolytic metabolism and not cellular proliferation. Studies have confirmed that the correlation between FDG uptake and Ki-67 expression of tumours is poor [21, 59]. FDG uptake does, however, show a regionally specific correlation with tumour vascularity [5]. The information it provides is therefore complementary to other imaging techniques.

Imaging protein synthesis: amino acid PET studies

In all cancer cells there is an increase in amino acid uptake due to both an increased demand for amino acids due to increased protein synthesis, and an increase in the transport of amino acid as a result of the malignant transformation [53].

Most amino acid labelling studies have used ^{11}C since it does not change the chemistry of the molecule. ^{11}C-methionine (L-[methyl-^{11}C]-methionine) or ^{11}C-tyrosine (L-1-[^{11}C]-tyrosine) are the most commonly used amino acids. The major draw back of using ^{11}C, however, is its short half life of only 20.4 min which means production has to be made when it is required, in a unit with an on site cyclotron. This is in contrast to ^{18}F compounds that have a half life of 109 min that can be produced in a central cyclotron and transported to a number of units for use later in the day. Currently there is much interest in the use of *O*-2-[^{18}F]fluoroethyl-L-tyrosine (FET) as a PET tracer.

In vitro studies have shown good correlation between methionine uptake and cellular proliferation markers [66], a finding confirmed in a cohort of patients who underwent glioma resection [60]. In comparison to FDG PET, methionine PET appears to provide better delineation of tumours [100, 145]. In tumours that are iso-/hypometabolic to glucose, 90% have increased methionine uptake [23]. Low-grade gliomas commonly show methionine accumu-

lation [101], although quantitative values are usually similar to that of normal brain [31]. The uptake in low grade oligodendrogliomas, however, appears to be greater than that of low grade astrocytomas [30, 31]. As the tumour grade increases methionine uptake increases in a more heterogeneous pattern [30, 101]. Methionine PET has a 97% sensitivity for detecting high grade and a 61% sensitivity for detecting low-grade gliomas [101], and it appears to be a more sensitive marker than FDG [30, 41]. Overall, Herholz *et al.* found that in a series of 196 patients, ^{11}C-methionine PET could differentiate low-grade gliomas from non-neoplastic problems in 79% of cases [50]. As there is little uptake into inflammatory cells, methionine appears to be particularly sensitive in differentiating radiation necrosis from recurrent tumour [139], and tumours from inflammatory lesions.

As a prognostic marker, WHO Grade II and Grade III gliomas have a shorter survival time if they exhibit increased methionine uptake [26]. Similar results have been reported using FET [38] This survival prediction is true for both low grade astrocytomas [99] and oligodendrogliomas [117, 118]. Follow up studies show that low-grade gliomas undergoing malignant transformation show increased methionine uptake [121]. Tumours that show stable or reduced methionine following radiotherapy have a more favourable outcome [99].

Since methionine uptake appears to correlate with proliferation and is increased in the higher grade areas, various groups have used it to guide image-guided brain biopsies. Go *et al.* described cases where biopsies taken from areas of increased uptake of L-[1-^{11}C]Tyrosine provided better diagnostic yield than conventional MRI in lesions that did not enhance with gadolinium [42]. Goldman *et al.* compared targets determined from FDG PET with methionine PET and found that methionine could differentiate active tumour from necrosis better than FDG. This group has subsequently shown that combining MRI and PET for biopsy targeting improves the diagnostic yield in brainstem tumours [81], paediatric brain tumours [109] and in tumours with little uptake of FDG [108]. They have also suggested that PET-guided resections could remove the part of the tumour with the largest potential for transforming into a more malignant form, although they have not presented any data that this affects clinical outcome [107].

Imaging DNA synthesis with labelled pyrimidine analogues

Since thymidine is only incorporated into DNA and not RNA it has long been used as a measure of DNA synthesis and is an obvious target for labelling for PET studies. Cells obtain thymidine from both a *de novo pathway* that synthesises thymidine from glutamine and a *salvage pathway* where exogenous thymidine is transported to the cells and is then phosphorylated by

thymidine kinase to thymidine monophosphate. In all cells the de novo pathway provides most of the thymidine used in cells, although there is some evidence, however, that the brain may be deficient in the de novo pathway [39]. Since the ratio of both pathways is relatively constant, there is a constant fraction of thymidine derived from the salvage pathway.

Initial attempts at pyrimidine imaging used ^{11}C-thymidine. This is challenging to produce, involves the short lived ^{11}C isotope and is broken down into metabolically active metabolites. Initial studies in gliomas showed that in half of patients studied the information derived was significantly different in some way from either FDG PET or conventionally MRI [35]. Active tumour could be identified in areas demonstrating little FDG uptake, and within the non-specific area of enhancement on MRI within the tumour bed.

3′-deoxy-3′-fluorothymidine (FLT) was initially developed as an antiretroviral drug. In vitro studies of FLT metabolism have shown that it enters cells using the nucleoside transporters but at half the rate of thymidine [64]. FLT is a selective substrate for TK-1 and it is phosphorylated by TK-1 to FLT monophosphate (FLTMP), again at a rate slower than thymidine [92]. The metabolism of FLT is shown in Fig. 11. As the rate of TMPK is 23-times slower than TK-1 [45] FLT accumulates greater than thymidine in proliferating cells [125]. The small amount of FLTTP produced is not incorporated into DNA due to the modification at the 3′ site.

Clinical validation studies of this model have been performed in patients with lung tumours and has shown that FLT uptake values obtained from compartmental analysis correlate with Ki67 expression in resected tumour specimens [96]. More detailed kinetic analyses in gliomas suggest that although the trapping of FLT-MP by *thymidine kinase*-1 is involve, the most important factor determining FLT accumulation was the rate of transport into the cell [54].

For gliomas a few studies have been recently reported. FLT uptake is markedly increased in high-grade gliomas [21, 22, 54, 112]. Low grade gliomas frequently show no FLT uptake [112] (see Fig. 12). For patients where

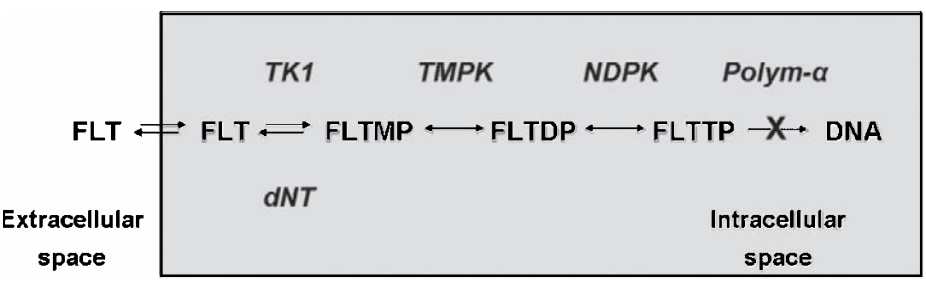

Fig. 11. FLT metabolism in cells. In dividing cells the uptake of FLT is increased. The main metabolism of FLT involves phosphorylation to FLT-MP which is only slowly metabolised further. As a result it accumulates in dividing cells

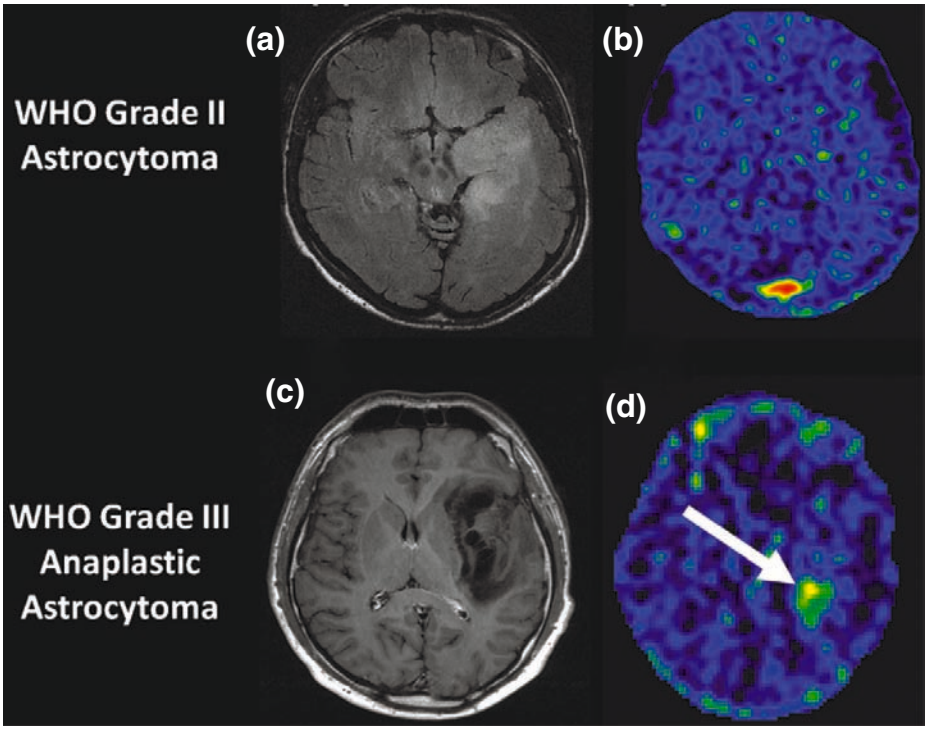

Fig. 12. FLT images in two patients. The upper row shows the FLT in a patient with a WHO Grade II astrocytoma (a). The FLT image (b) shows some uptake in the skull bones and within the sagittal sinus posteriorly. There is no obvious uptake into the tumour. In the lower row this tumour did not enhance with contrast (c). FLT, however, shows a region in the posterior aspect of the tumour that has increased FLT uptake (d). Biopsies were taken from this region which showed anaplastic features sufficient for a diagnosis of WHO Grade III anaplastic astrocytomas

histological material was available, the maximal FLT uptake correlates with the highest MIB-1 labelling index in the tumour [21, 22, 54]. Uptake appears to be a good predictor of tumour progression and overall survival [21]. Compared to FDG PET, FLT is more a sensitive in detecting tumour due to the improved contrast-to-background ratio [21, 22]. False positive results, however, can occur as increased uptake can occur in regions of blood brain barrier disruption – this especially occurs in recurrent low grade tumours following radiotherapy [122].

Imaging hypoxia

One of the main drivers of a 'high-grade' phenotype is hypoxia. A number of markers have been developed for this purpose. Most work has used ^{18}F-fluor-

omisonidazole (^{18}F-FMISO), a nitroimidazole derivative whose metabolites accumulate in hypoxic cells. PET studies have shown that it accumulates in high grade tumours [10, 144] and can differentiate it from other tumours where hypoxia is less of a problem [11]. Studies are needed in low-grade gliomas.

One problem with ^{18}F-MISO is that it is only taken up into viable cells – it will not identify necrotic areas. A promising new marker ^{60}Cu-diacetyl-bis(N^4-methylthiosemicarbazone) (^{60}Cu-ATSM) overcomes this issue. Although studies have been done in man, no studies have yet reported on its use in brain tumours [102].

Imaging membrane turnover

As we have previously seen with MR spectroscopy, imaging membrane turnover correlates with cellular proliferation. Two different PET approaches have been used for this. The first, like proton spectroscopy, uses choline. Although both ^{11}C and ^{18}F based tracers have produced, the fluorinated version has a higher tumour-to-normal ratio [47]. In low-grade gliomas the uptake is low – similar to normal brain. More aggressive/more anaplastic areas within a glioma show increased uptake and, as a result, may guide biopsies [47].

The second method uses 1-^{11}C-acetate. This tracer was originally used for measuring oxidative metabolism in the myocardium. In the brain acetate is preferentially taken up into and metabolised by glial cells. In tumour cells acetate can be transformed into acetyl-CoA, or used as a precursor of membrane fatty acids [151]. In low-grade gliomas there is little uptake of acetate; the uptake is significantly increased in high-grade gliomas, even in tumours with little FDG uptake [142, 150].

The future: imaging molecular expression

Compared to our increased understanding of the molecular biology of low grade tumours, the imaging modalities that are currently available could be considered as relatively crude. There is a lot of largely preclinical work that is trying to develop imaging methods to image gene expression. These techniques, extensively reviewed elsewhere [82, 83], mostly use reporter genes that are inserted into tumours using either cells or via viral vectors. Most studies identify gene expression using optical imaging. A recent PET study showed that it is possible to detect expression of the *Herpes simplex* thymidine kinase gene (HSV1 tk) in a patient with a glioblastoma undergoing immunotherapy using CD8$^+$ T-cell engineered to express IL-13 and the HSV1 tk gene with a ^{18}F-radiolabelled 9-[4-fluoro-3-(hydroxymethyl)butyl]guanine (^{18}F-FHBG) [149]. There is a great need for improvements in detection technology and

the development of more sensitive and specific reporters before these techniques are used in the routine clinical management of patients with low-grade gliomas.

Conclusions

Application of these new MR and PET techniques can help greatly in confirming a diagnosis, providing prognostic information, guiding biopsies and treatment. Perfusion and diffusion MR can be performed on all modern MR machines – most will also do proton spectroscopy. These are becoming standard methods of assessing low-grade gliomas in a clinical setting. The availability of PET is more limited, but the development of PET/CT and the increasing utility of this in cancer treatment will ensure that they will be available in most cancer centres and will be come in increasingly important tool in the management of these difficult tumours.

As we now begin to understand what information these imaging techniques tell us, the next stage is to use these methods to individualise treatment. Such starting points may be differentiating those tumours that are likely to progress rapidly from those that have a more indolent course. The former group may be suitable for more aggressive therapy at diagnosis. In addition, markers that provide warning of likely transformation may allow early intervention. Clinical trials are needed to determine the utility of these imaging biomarkers in a clinical setting.

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Molecular neuropathology of low-grade gliomas and its clinical impact

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With 5 Figures and 1 Table

Contents

Abstract

The term "low-grade glioma" refers to a heterogeneous group of slowly growing glial tumors corresponding histologically to World Health Organization (WHO) grade I or II. This group includes astrocytic, oligodendroglial, oligoastrocytic and ependymal tumor entities, most of which preferentially manifest in children and young adults. Depending on histological type and WHO grade, growth patterns of low-grade gliomas are quite variable, with some tumors diffusely infiltrating the surrounding central nervous system tissue and others showing well demarcated growth. Furthermore, some entities tend to recur and show spontaneous malignant progression while others remain stable for many years. This review provides a condensed overview concerning the molecular genetics of different glioma entities subsumed under the umbrella of low-grade glioma. For a better understanding the cardinal epidemiological, histological and immunohistochemical features of each entity are shortly outlined. Multiple cytogenetic, chromosomal and genetic alterations have been identified in low-grade gliomas to date, with distinct genetic patterns being associated with the individual tumor subtypes. Some of these molecular alterations may serve as a diagnostic adjunct for tumor classification in cases with ambiguous histological features. However, to date only few molecular changes have been associated with clinical outcome, such as the combined losses of chromosome arms 1p and 19q as a favorable prognostic marker in patients with oligodendroglial tumors.

Keywords: Astrocytoma; oligodendroglioma; ependymoma; 1p/19q; molecular genetics.

Abbreviations

WHO	World Health Organization
CBTRUS	Central Brain Tumor Registry of the United States
GFAP	glial fibrillary acid protein

MAP2	microtubule-associated protein 2
EGFR	epidermal growth factor receptor
LOH	loss of heterozygosity
PDGFRA	platelet-derived growth factor receptor alpha
PXA	pleomorphic xanthoastrocytoma
NF1	neurofibromatosis type 1
SEGA	subependymal giant cell astrocytoma
EMA	epithelial membrane antigen
CGH	comparative genomic hybridization

WHO classification and grading of low-grade gliomas

Gliomas are classified according to the WHO classification of tumors of the central nervous system [57]. In addition to tumor typing, the WHO classification includes a histological grading according to a four-tiered grading scale. WHO grade I lesions include tumors that have low proliferative potential and can be potentially cured following surgical resection alone. WHO grade II lesions are also characterized by a low proliferative activity, but are often infiltrative in nature and thus bear the tendency to recur. In addition, WHO grade II tumors often have the intrinsic ability to progress to higher grades of malignancy, with diffuse astrocytoma transforming to anaplastic astrocytoma and eventually secondary glioblastoma as a classic example. Nevertheless, owing to their shared low proliferative activity and the lack of histological signs of malignancy, WHO grade I and II gliomas are frequently subsumed under the category of "low-grade glioma". In contrast, glial tumors of WHO grades III and IV are referred to as "high-grade gliomas". It should be clear, however, that the dichotomy of "low-grade glioma" versus "high-grade gliomas", albeit common for clinical practice, is an oversimplification that carries potential pitfalls as heterogeneous tumor entities with different biological and clinical behavior are grouped together. For example, studies on "low-grade gliomas" often include both pilocytic and diffuse astrocytomas, which show quite distinct growth patterns and clinical outcome. Nevertheless, we stick here to the commonly used term of "low-grade glioma" and use it as a kind of umbrella to cover the different glioma entities and variants histologically corresponding to WHO grade I or II tumors. As stated previously, the low-grade glioma category includes a quite heterogeneous group of neoplasms that greatly differ in their clinical and histological appearances (Table 1). All these tumors are characterized by unique histological and immunohistochemical features. In addition, molecular studies during recent years have uncovered that they are also associated with distinct patterns of defined genetic changes, which may actually serve to supplement histopathological classification, especially in cases with borderline histological features.

Table 1. Classification of low-grade gliomas

Tumor type	WHO grade
Diffusely infiltrating astrocytic gliomas	
Diffuse astrocytoma	II
Fibrillary astrocytoma	II
Protoplasmic astrocytoma	II
Gemistocytic astrocytoma	II
Astrocytic gliomas with more circumscribed growth	
Pilocytic astrocytoma	I
Pilomyxoid astrocytoma	II
Pleomorphic xanthoastrocytoma	II
Subependymal giant cell astrocytoma	I
Oligodendrogliomas and mixed gliomas	
Oligodendroglioma	II
Oligoastrocytoma	II
Gliomas with ependymal differentiation	
Ependymoma	II
Myxopapillary ependymoma	I
Subependymoma	I
Other rare glial tumor types	
Chordoid glioma of the third ventricle	II
Astroblastoma	not determined
Angiocentric glioma	I

In this chapter we will provide an overview on the molecular aberrations typically associated with the individual entities of low-grade glioma. Each entity will be introduced with a brief paragraph on the characteristic epidemiological, histological and immunohistochemical features, followed by a review of the associated molecular characteristics.

Diffuse astrocytoma (WHO grade II)

Epidemiological, histological and immunohistochemical features

According to the Central Brain Tumor Registry of the United States (CBTRUS 2005), diffuse astrocytoma of WHO grade II has an annual incidence rate of 1.3/1 million population. Mean age of diagnosis is 46 years and the 5-year survival rate is about 45%. Histologically, the most common subtype is *fibrillary astrocytoma*, followed by *gemistocytic astrocytoma*, i.e. a diffuse astrocytoma consisting of more than 20% of gemistocytic astrocytes. Several reports indicate that

gemistocytic tumor cell differentiation is a prognostically unfavorable feature as these tumors tend to undergo more rapid malignant progression [72, 91]. A rare astrocytoma variant is *protoplasmatic astrocytoma*. In these cases, neoplastic astrocytes exhibit a small cell body with few, flaccid cell processes and only weak GFAP expression. Although diffuse astrocytomas are considered low-grade gliomas, they bear an inevitable tendency for recurrence and malignant progression to anaplastic astrocytoma and secondary glioblastoma.

Immunohistochemically, diffuse astrocytomas stain generally positive for glial fibrillary acid protein (GFAP), vimentin, protein S-100 and microtubule-associated protein 2 (MAP2). Nuclear accumulation of the tumor suppressor protein p53 is present in about 60% of diffuse astrocytomas, while immunoreactivitity for the epidermal growth factor receptor (EGFR) is rather a feature of high-grade gliomas. Labeling indices for the proliferation-associated antigen Ki-67 (MIB-1), while exhibiting considerable inter- and intratumoral variability, usually do not surpass a value of 5% positive tumor cells.

Molecular genetics

The most common genetic alteration in diffuse astrocytomas is mutation of the *TP53* tumor suppressor gene at 17p13.1 in approximately 60% of cases [36] (Fig. 1). In the gemistocytic variant *TP53* mutations are found in up to 80% of the cases [105]. Not only are *TP53* mutations already present in the first biopsy, but their frequency does not increase in recurrences, suggesting that those mutations are among the earliest events in astrocytoma development. This hypothesis is supported by the fact that brain tumors in patients harboring a *TP53* germline mutation predominantly correspond to astrocytic tumors (usually anaplastic astrocytoma or glioblastoma). In line with Knudson's double hit hypothesis, *TP53* mutations in diffuse astrocytomas are commonly associated with loss of heterozygosity (LOH) at polymorphic loci on 17p resulting in complete loss of wild-type p53 in the tumor cells. Diffuse astrocytomas with-

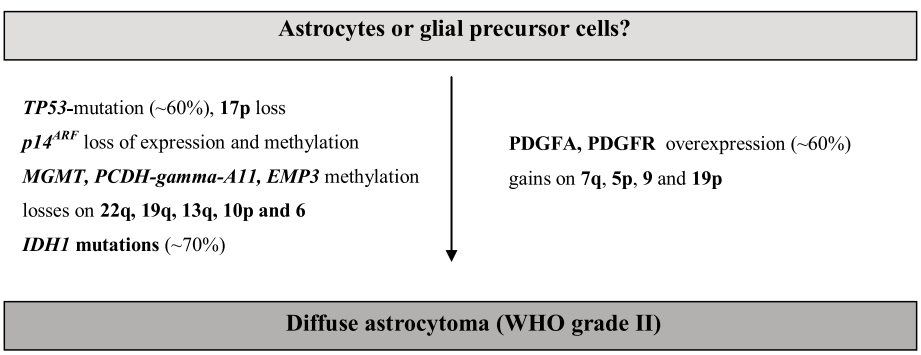

Fig. 1. Schematic representation of the molecular pathogenesis of diffuse astrocytoma

out *TP53* alterations frequently exhibit promoter methylation and loss of expression of the $p14^{ARF}$ gene at 9p21, the gene product of which regulates MDM2-mediated degradation of p53 [106]. Other frequent, just recently identified molecular alterations in diffuse astrocytomas are codon 132 mutations of the isocitrate dehydrogenase 1 (*IDH1*) gene, originally described preferentially in glioblastomas [71] and later shown to occur in also about 70% of diffuse astrocytomas [3]. Genes that have been reported to be epigenetically silenced in more than 50% of diffuse astrocytomas include the *MGMT* gene at 10q26 [106], the protocadherin-gamma subfamily A11 (*PCDH-gamma-A11*) gene at 5q31 [103], and the *EMP3* gene at 19q13 [50]. Interestingly, *MGMT* hypermethylation was found to be associated with *TP53* mutation but is mutually exclusive to $p14^{ARF}$ hypermethylation [106].

Another common alteration in diffuse astrocytomas is overexpression of the platelet-derived growth factor receptor alpha (PDGFRA) and its ligand PDGFalpha, thereby enabling an autocrine growth stimulation of the tumor cells [31]. *PDGFRA* amplification, however, is restricted to a small subset of high-grade gliomas, in particular glioblastomas [23].

Karyotyping and comparative genomic hybridization analyses revealed trisomy 7 or gains of chromosome 7q as a common genomic imbalance, which is detectable in up to 50% of diffuse astrocytomas. Further chromosomal aberrations comprise losses on 22q, 19q, 13q, 10p, 6 and the sex chromosomes as well as gains on 5p, 9 and 19p [79]. In contrast to oligodendrogliomas (see below), combined losses on 1p and 19q are rare in diffuse astrocytomas.

Pleomorphic xantoastrocytoma (WHO grade II)

Epidemiological, histological and immunohistochemical features

Pleomorphic xanthoastrocytoma (PXA) accounts for less than 1% of all astrocytic neoplasms. The tumor usually manifests within the first two decades of life; however, older patients are also affected on occasion. PXA is typically located superficially in the cerebral hemispheres, most often the temporal lobe, with frequent involvement of the leptomeninges. Therefore, patients often present with a long-standing history of seizures.

Histologically, PXA is a relatively compact and well circumscribed tumor growing in the cerebral cortex and invading the meninges. It is composed of pleomorphic astrocytic tumor cells, including bipolar spindle cells growing in fascicles, epitheloid cells, as well as multinucleated giant cells, with variable subsets of the neoplastic cells displaying cytoplasmatic lipidization. Further characteristic features include a pericellular or perilobular reticulin network, eosinophilic protein droplets and prominent lymphocytic infiltrates. The vast majority of PXAs correspond to WHO grade II. The rare cases that exhibit

anaplastic changes, such as increased mitotic count and necroses, are referred to as *pleomorphic xanthoastrocytoma with anaplastic features* [26].

Immunohistochemically, PXAs stain positively for GFAP and protein S-100. Nuclear immunoreactivity for the p53 tumor suppressor protein and expression of the epidermal growth factor receptor (EGFR) is usually absent. Instead, expression of the CD34 antigen is often found not only in vascular endothelial cells but also in tumor cells [80]. The Ki-67 (MIB-1) labeling index usually does not exceed 5% (with exception of the rare PXA with anaplastic features).

Molecular genetics

Loss on chromosome 9 is the most common genomic imbalance in pleomorphic xanthoastrocytoma, which is detectable by CGH analysis in 50% of cases [108]. Other losses affect chromosomes 17 (10%), 8, 18 and 22 (4% each). Chromosomal gains could be identified on chromosomes X (16%), 7, 9q, 20 (8% each), 4, 5 and 19 (4% each) [108]. *TP53* mutations are seen in a small fraction of tumors (<10 of cases), while 1p/19q losses as well as amplification of *EGFR*, *CDK4* and *MDM2* are absent [25, 44]. In contrast, homozygous deletion of the tumor suppressor genes *CDKN2A*, $p14^{ARF}$ and *CDKN2B* on 9p21.3 is common in PXA [108]. Interestingly, transcript levels of the *TSC1* gene on 9q were found to be consistently low in PXA; however, the causative mechanism still remains unclear, as there was no evidence for *TSC1* mutations or promoter methylation [108].

Pilocytic astrocytoma (WHO grade I)

Epidemiological, histological and immunohistochemical features

Pilocytic astrocytomas comprise approximately 5–6% of all gliomas. They are the most frequent primary brain tumors in children and most commonly develop during the first two decades of life. The majority of pilocytic astrocytomas develop in the cerebellum. Other typical sites include midline structures, such as the optic nerve and optic chiasm, hypothalamus, thalamus, basal ganglia, and brain stem, but also the cerebral hemispheres or the spinal cord may be affected.

Pilocytic astrocytomas belong to the group of astrocytic tumors that exhibit a more circumscribed growth pattern and thus can be cured following surgical resection alone. Histologically, they are tumors of low to moderate cellularity characterized by a biphasic growth pattern with areas of compacted bipolar (piloid) cells and loose-textured microcystic areas with multipolar cells. Rosenthal fibers and eosinophilic granular bodies are a common though not

specific diagnostic feature. The majority of pilocytic astrocytomas correspond to WHO grade I. Rare cases with anaplastic features have been described.

Recently, the pilomyxoid astrocytoma has been recognized as a histologically and clinically distinct variant of pilocytic astrocytoma with a less favorable prognosis [98]. Local recurrences as well as cerebrospinal spread occur more often in pilomyxoid tumors than in pilocytic astrocytomas. The WHO classification thus assigns these tumors to WHO grade II. Histologically, pilomyxoid astrocytomas are characterized by a monomorphic population of bipolar neoplastic astrocytes in a myxoid matrix. Pseudorosette-like angiocentric architectures are typical. Rosenthal fibers are often missing. Immunohistochemically, both pilocytic and pilomyxoid astrocytomas stain positively for GFAP, S-100 and vimentin. Ki-67 labeling indices are of minor diagnostic importance as they considerably overlap between both tumors and may vary substantially.

Molecular genetics

In comparison to diffuse astrocytic gliomas, far less is known about the chromosomal and genetic aberrations in pilocytic astrocytomas (Fig. 2). Molecular cytogenetic investigation of 48 pilocytic astrocytomas using comparative genomic hybridization revealed chromosomal imbalances only in a small subgroup of 7 neoplasms [88]. Gain of 9q34.1-qter in three cases was the most common abnormality. Another study reports on recurrent trisomies of chromosomes 5 and chromosome 7 in a series of 53 pilocytic astrocytomas [74].

Pilocytic astrocytomas are the most common gliomas in patients with neurofibromatosis type 1 (NF1). In this setting, pilocytic astrocytomas are typically located in the optic nerve, often bilaterally, and carry allelic losses at the *NF1* tumor suppressor gene locus at 17q11.2 [45]. Sporadic pilocytic astrocytomas, in contrast, rarely demonstrate allelic loss at the *NF1* locus [45]. Also, neither *NF1* mutations nor loss of *NF1* mRNA expression were found in sporadic pilocytic astrocytomas [110]. Pilocytic astrocytomas do not

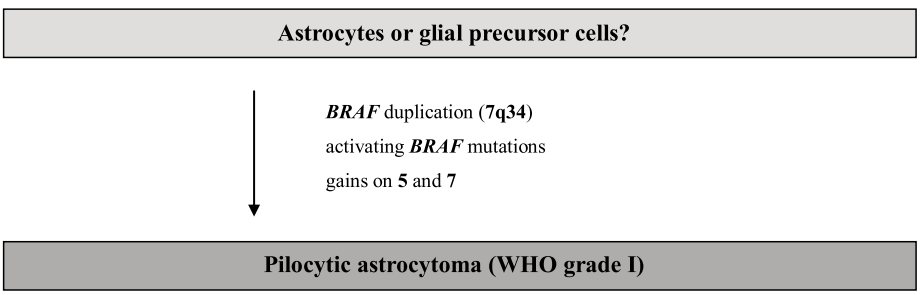

Fig. 2. Schematic representation of the molecular pathogenesis of pilocytic astrocytomas

share the high rate of allelic losses on 17p and mutations in the *TP53* tumor suppressor genes that are observed in diffuse astrocytomas [45, 52, 68]. However, circumscribed duplication of the *BRAF* gene at 7q34 resulting in increased BRAF expression has been identified as a common aberration in pilocytic astrocytomas [74]. A small subset of tumors alternatively carries activating *BRAF* mutations, thus implicating this gene as an important proto-oncogene in these tumors. Microarray-based expression profiling of pilocytic astrocytomas did not discriminate clinically aggressive or recurrent tumors from more indolent cases [93]. Similarly, expression profiles did not significantly differ between sporadic and NF1-associated pilocytic astrocytomas. However, supratentorial versus infratentorial tumors showed distinct gene expression signatures, suggesting that pilocytic astrocytomas, similar to findings in ependymomas, are characterized by lineage-specific molecular signatures that reflect the brain region in which they originate [93].

Subependymal giant cell astrocytoma (WHO grade I)

Epidemiological, histological and immunohistochemical features

Subependymal giant cell astrocytoma (SEGA) is closely associated with tuberous sclerosis, with an estimated 6% to 16% of tuberous sclerosis patients developing one or more of these tumors. As an intraventricular lesion, most often located in the region of the foramen of Monro, the tumor commonly manifests with symptoms of obstructive hydrocephalus and increased intracranial pressure. All SEGA patients should be clinically checked for the presence of other manifestations of tuberous sclerosis.

Histologically, the circumscribed, moderately cellular tumor is composed of large pleomorphic cells with abundant glassy eosinophilic cytoplasm, round ganglioid nuclei and distinct nucleoli. Intermixed smaller spindle cells as well as calcifications may be encountered. Mitoses are usually absent or rare. Immunohistochemically, SEGAs show variable expression of GFAP and S-100. In addition, immunoreactivity for neuronal markers such as synaptophysin or neurofilaments may be detectable. The Ki-67 (MIB-1) labeling index usually does not exceed 5%.

Molecular genetics

Biallelic inactivation of either the *TSC1* or the *TSC2* tumor suppressor gene is typical for these tumors [13]. Since the corresponding gene products have an inhibitory function on the mTOR pathway, their mutational inactivation leads to aberrant activation of mTOR signaling, which in turn represents an interesting novel target for specific pharmacologic inhibition. A comparative geno-

mic hybridization study on subependymal giant cell astrocytomas indicated that chromosomal imbalances are rare or absent [84].

Oligodendroglioma (WHO grade II)

Epidemiological, histological and immunohistochemical features

Oligodendroglioma accounts for approximately 2.5% of all primary brain tumors and 5–6% of all gliomas. Estimated annual incidence rates range from 0.27 to 0.35 per 100,000 persons. Oligodendrogliomas can develop at any age, but the majority of tumors arise in adults with an incidence peak between 40 and 45 years of age. In children younger than 14 years of age, oligodendroglial tumors account for only 2% of all brain tumors (CBTRUS 2005) [53, 70].

Oligodendrogliomas are monomorphous, moderately cellular, slowly growing, but diffusely infiltrating gliomas corresponding to WHO grade II. Histologically, the isomorphic tumor cells often display a characteristic "honeycomb" or "fried-egg" appearance on routine formalin-fixed paraffin sections, with uniform round to slightly oval nuclei and perinuclear halos due to cellular swelling and retraction of cytoplasmic processes. Microcalcifications, mucoid/cystic degeneration as well as a delicate, branching, so-called "chicken wire" vascular pattern are additional characteristic features in this entity. Prominent microvascular proliferation, necrosis and significantly increased mitotic or proliferative activity are absent in low-grade oligodendrogliomas. The infiltration patterns of oligodendrogliomas parallel those of other diffuse gliomas with more common involvement of cortical structures.

To date, the classification of oligodendrogliomas is still mainly based on the recognition of the histomorphological features described above, due to the fact that no specific oligodendroglial tumor markers have yet been identified. Oligodendrocyte lineage-specific transcription factors, such as OLIG-1 and OLIG-2, which originally appeared to be promising diagnostic markers for oligodendrogliomas [58, 61], have all been shown to be detectable not only in oligodendrogliomas but also in the vast majority of other gliomas [56, 85]. Oligodendrogliomas in general exhibit invariable and strong expression of the microtubule-associated protein 2 (MAP2) [5] as well as frequent overexpression of the epidermal growth factor receptor (EGFR). Immunoreactivity for protein S-100 is also common. In contrast to astrocytomas, GFAP immunoreactivity is either absent or scarce in oligodendrogliomas and generally restricted to special cell types, refered to as gliofibrillary oligodendrocytes and minigemistocytes. The tumors usually lack nuclear p53 staining, which may be due to the fact that *TP53* mutations and p53 protein accumulation are mutually exclusive to 1p/19q deletions (see below).

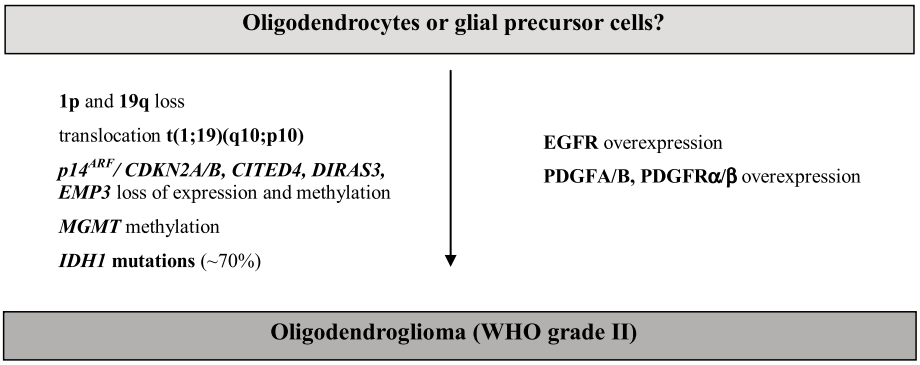

Fig. 3. Schematic representation of the molecular pathogenesis of oligodendrogliomas

Molecular genetics

The most common genetic alterations in oligodendrogliomas are combined deletions of chromosomal arms 1p and 19q as well as *IDH1* mutations. While oligodendrogliomas share the high frequency of *IDH1* mutations (~70%) with astrocytic gliomas [3], combined 1p/19q deletions are considered the hallmark genetic aberration in oligodendrogliomas and are found in up to 80% of the cases [83] (Fig. 3). Two recent studies reported that an unbalanced t(1;19)(q10;p10) translocation, with the chromosomal breakpoints located close to the centromers of both chromosomes, serves as the cytogenetic mechanism responsible for the frequent co-deletions of both chromosome arms in oligodendrogliomas [28, 39]. It is still unclear, however, which genes are the relevant targets on 1p and 19q. A number of candidate tumor suppressor genes from different regions on 1p have been proposed, including *TP73* (1p36.3), the calmodulin-binding transcription activator 1 gene (*CAMTA1*, 1p36), the DNA fragmentation factor subunit *β* gene (*DFFB*, 1p36), *SHREW1* (1p36.32), *CITED4* (1p34.2), *RAD54* (1p32), *CDKN2C* (1p32), and *DIRAS3* (1p31) [4, 16, 62, 63, 81, 86, 96]. In addition, the *NOTCH2* gene, which maps closest to the breakpoint region on 1p13-p11, has been reported as a putative oligodendroglioma-associated tumor suppressor gene, with intragenic homozygous deletions found in two tumors [7]. Candidate tumor suppressor genes on 19q include the *p190RhoGAP* gene at 19q13.3 [111], the myelin-related epithelial membrane protein gene 3 (*EMP3*) at 19q13.3 [1], *ZNF342*, a zinc-finger transcription factor gene at 19q13 [35], and the maternally imprinted *PEG3* gene at 19q13.4 [100]. However, none of these genes has been definitely proven to be directly involved in the tumorigenesis of oligodendrogliomas. Thus, the question remains as to whether two or more specific "1p/19q genes" exist in oligodendrogliomas.

Clinically, combined deletion on 1p and 19q has become of paramount importance as it was shown to be a powerful molecular marker for response

to chemotherapy and prolonged survival, in particular in patients with high-grade oligodendroglial tumors [10, 11, 102]. The prognostic role of 1p/19q deletion in low-grade oligodendroglioma patients is less clear. Several retrospective studies on small numbers of patients independently reported that 1p deletion or 1p/19q co-deletion were also associated with a trend towards longer survival [22, 89, 94]. More recent studies including larger numbers of low-grade oligodendroglioma patients indeed indicated a prognostic significance [43, 49]. In addition, clinical trials on low-grade oligodendroglioma patients treated with temozolomide revealed that 1p loss was associated with objective response to treatment [33, 55]. On the other hand, a study on low-grade oligodendroglioma patients treated by surgical resection alone did not reveal significantly longer survival of patients with 1p/19q deletion, suggesting that the prognostic significance of this genetic feature is linked to cytotoxic treatments, such as radio- and chemotherapy [109]. Concerning tumor location, it has been reported that allelic losses on 1p are common in oligodendroglial tumors of the frontal, parietal and occipital lobes but rare in tumors of the temporal lobe, insula and diencephalon [113].

While 1p/19q deletions are by far the most frequent alterations in oligodendrogliomas, several other genetic and epigenetic alterations have been described. Cytogenetic alterations that are less frequent than 1p/19q losses but occur at more than random frequency in oligodendrogliomas are gains on chromosomes 7 and 19p as well as losses on chromosomes 4, 6, 9p, 10q, 11p, 14, 18q, and 22q [41, 81]. Interestingly, several of these chromosomal imbalances have been suggested as being linked to poor outcome, including gain of 7p and 8q as well as losses on 9p and 18q [99]. Allelic losses on 17p and *TP53* gene mutations are rare in low-grade oligodendrogliomas and mutually exclusive to 1p/19q losses. Nevertheless, inactivation of the p53 pathway in 1p/19q-deleted tumors may be mediated by alterations of other members of the p53 pathway, such as epigenetic silencing of the $p14^{ARF}$ gene. $p14^{ARF}$ encodes a negative regulator of p53 activity that binds to Mdm2 and in this way inhibits the Mdm2-mediated degradation of p53 [107, 112]. Additional hypermethylated genes in subsets of oligodendrogliomas include the tumor suppressors *CDKN2A*, *CDKN2B* and *RB1*, as well as *DAPK1* (death-associated protein kinase 1), *ESR1* (estrogen receptor 1), *THBS* (thrombospondin 1) and *TIMP3* (tissue inhibitor of metalloproteinase 3) [2, 17, 112]. Frequent promoter hypermethylation and reduced expression of the *MGMT* gene in oligodendrogliomas and consecutive impairment of MGMT-mediated DNA-repair might in part contribute to the chemosensitivity of these neoplasms [64, 66].

Finally, low-grade oligodendrogliomas frequently demonstrate increased expression of growth factor receptors, such as EGFR, PDGFR and VEGF [15, 81]. While the mechanisms causing upregulation of EGFR expression in

these tumors are widely unknown, and *EGFR* amplification is restricted to rare cases of anaplastic tumors [24, 34, 37], PDGFR and its ligand PDGF are frequently co-expressed in oligodendroglial tumors, suggesting auto- and/or paracrine growth stimulatory activities of this signaling pathway [15].

Oligoastrocytoma (WHO grade II)

Epidemiological, histological and immunohistochemical features

Oligoastrocytoma is defined as a diffusely infiltrating glioma composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling the tumor cells in oligodendroglioma and diffuse astrocytoma of WHO grade II. The oligodendroglial and astroglial components may either be diffusely intermingled or separated into distinct, biphasic areas. Oligoastrocytomas are diffusely infiltrating gliomas of moderate cellularity and low mitotic activity.

The role of a quantitative assessment of the astrocytic and oligodendroglial tumor components in oligoastrocytomas is disputed. In particular, the WHO classification does not define a diagnostic threshold that is minimally required for the minor tumor component. Owing to these loosely defined classification criteria, the fraction of oligoastrocytomas among all low-grade diffuse gliomas varies considerably between different studies, with values ranging from 13% up to 27% in larger series. Estimated annual incidence rates range between 0.10 and 0.16 per 100,000 population (CBTRUS 2005) [49, 70, 101].

Molecular genetics

In contrast to the phenotypic heterogeneity at the histological level, molecular analysis of microdissected oligodendroglial and astrocytic tumor parts in individual tumors revealed uniform genetic changes, indicating a monoclonal origin of both components [48]. Oligoastrocytomas share the high frequency of *IDH1* point mutations with diffuse astrocytomas and oligodendrogliomas [3]. Approximately 30–50% of the oligoastrocytomas show allelic losses on 1p and 19q [20, 70, 81]. Loss of heterozygosity on 17p and/or *TP53* mutation have been detected in approximately 30–40% of the cases, with the *TP53* mutation being mutually exclusive to 1p/19q deletion [60, 67, 70, 112]. Histologically, oligoastrocytomas with 1p/19q loss are frequently oligodendroglioma-predominant, whereas oligoastrocytomas with *TP53* mutations are more often astrocytoma-predominant [60]. Furthermore, oligoastrocytomas of the temporal lobe demonstrate less frequent 1p and 19q losses when compared to oligoastrocytomas in other tumor locations [67]. On the contrary,

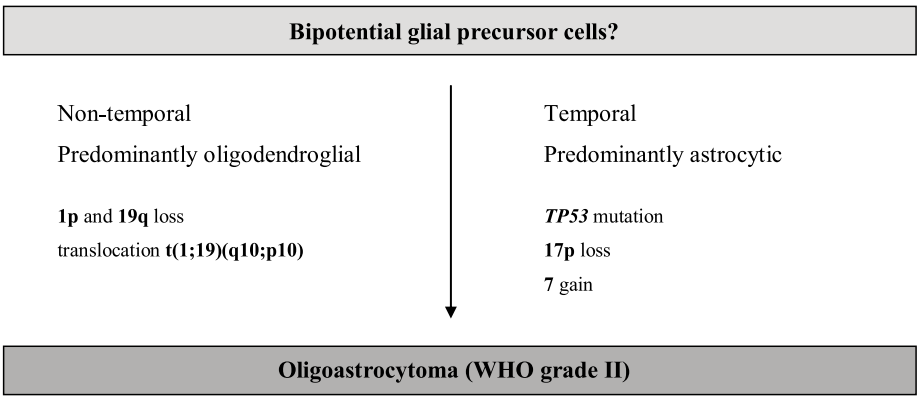

Fig. 4. Schematic representation of the molecular pathogenesis of oligoastrocytomas

TP53 mutations were significantly more common in temporal oligoastrocytomas than in oligoastrocytomas affecting other cerebral lobes (Fig. 4).

To date, no specific genetic abnormalities have been identified that genetically may separate oligoastrocytomas from oligodendrogliomas on the one side and diffuse astrocytomas on the other. Thus, in times of modern tumor biology and evolving molecular diagnostics, the nosological position of oligoastrocytomas is debatable. In support of this notion, oligoastrocytomas with 1p and 19q deletion behave clinically like oligodendrogliomas, while oligoastrocytomas without these deletions show a clinical course similar to diffuse astrocytomas [20]. Thus, the combination of morphological and molecular parameters may likely reshape the definition of oligoastrocytoma in the future.

Ependymoma (WHO grade II)

Epidemiological, histological and immunohistochemical features

Ependymal tumors account for approximately 2.3% of all primary brain tumors and 5.6% of all gliomas. The adjusted annual incidence rate is 0.33 per 100,000 population (CBTRUS 2005). There are two distinct incidence peaks: one in adults between 35 and 45 years of age, and one in children below 14 years of age.

Histologically, ependymomas are moderately cellular, slowly growing tumors that typically originate from the walls of the cerebral ventricles or the spinal cord. The tumor cells are uniform in shape and size, and usually have monomorphic round or oval nuclei with abundant, clumped chromatin. Hallmark histological features are perivascular pseudorosettes and true ependymal rosettes. In contrast to the diffusely infiltrating astrocytic and oligoden-

droglial tumors, ependymomas are characterized by a usually sharp interface with the surrounding CNS parenchyma.

Immunohistochemically, the majority of ependymomas stains with antibodies against the epithelial membrane antigen (EMA). Characteristic is a dot- or ring-like staining pattern or a linear labeling of luminal surfaces [30]. Expression of glial markers, such as GFAP, vimentin and protein S-100 is also commonly observed. The Ki-67 (MIB-1) index is generally low (< 5%).

Molecular genetics

Recent studies using comparative genomic hybridization (CGH) analysis reported on distinct patterns of chromosomal aberrations being linked to certain clinical and pathological features of ependymomas, such as patient age, tumor location, and histological subtype or WHO grade [12, 18, 40, 65, 95]. Overall, the most common copy number changes were losses of chromosomes 6q, 10, 13, 14, and 22q, as well as gains of chromosomes 1q, 7, 9, 12q, 15q, and 18. While spinal intramedullary ependymomas preferentially demonstrated losses of chromosomes 22q and 14q as well as gains on chromosomes 7q, 9p and 16, intracranial ependymomas frequently carried gains of 1q and losses on 6q (Fig. 5). Losses on 22q and gains of chromosome 4 were more common in adult tumors [65]. Gains on 1q correlated with the presence of structural chromosomal aberrations, pediatric age, high-grade histology and aggressive clinical behavior [12, 18, 65]. The distinct genetic profiles associated with tumor location were also reflected in regionally different mRNA expression signatures. Supratentorial ependymomas, for example, expressed elevated levels of members of the EPHB-EPHRIN and NOTCH families, whereas spinal ependymomas showed up-regulated expression of multiple HOX gene family members [95].

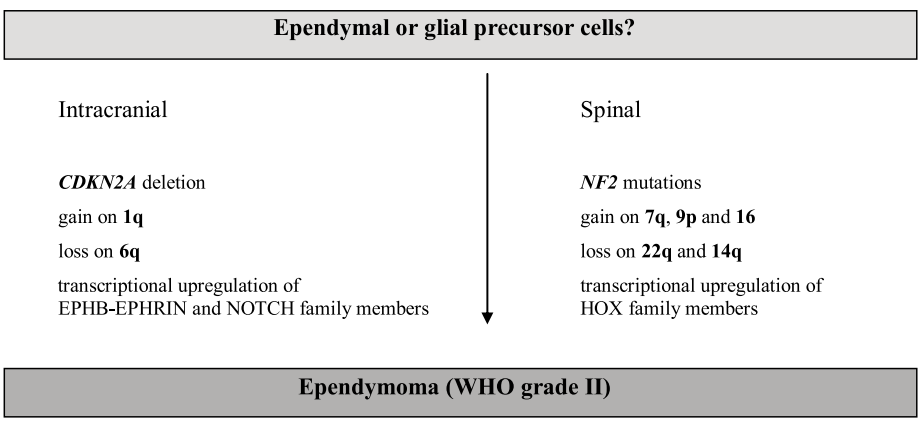

Fig. 5. Schematic representation of the molecular pathogenesis of ependymal gliomas

Molecular genetic studies on selected candidate genes revealed frequent *NF2* gene mutations in intramedullary spinal ependymomas, while deletions of the *CDKN2A* gene were frequent in intracranial supratentorial ependymomas but rare in ependymomas from other locations [95]. Mutations in the *TP53*, *PTEN* and *INI1* tumor suppressor genes are rare or absent in ependymomas [19, 47, 69]. Epigenetic silencing by aberrant promoter methylation has been described in ependymomas, affecting the known tumor suppressor genes *RASSF1*, *CDKN2A*, *CDKN2B*, $p14^{ARF}$ and *TP73*, as well as other genes potentially involved in the tumorigenesis of ependymomas, such as *CASP1*, *MGMT*, *TIMP3* and *THBS1* [29, 87]. As in other gliomas, growth factor receptors, such as EGFR and the related ERBB2 and ERBB4 receptors, are commonly upregulated in ependymal tumors and have been linked to faster tumor growth and shorter survival [27, 65]. Amplification of the respective genes, however, does not occur in low-grade ependymomas [65].

Myxopapillary ependymoma (WHO grade I)

Epidemiological, histological and immunohistochemical features

Myxopapillary ependymoma constitutes a distinct type of a benign ependymal neoplasm that typically arises in the conus-cauda-filum terminale region of the spinal cord. Corresponding to WHO grade I, this slowly growing tumor follows a favorable benign course. Anaplastic variants are virtually unknown. The frequency of myxopapillary ependymomas among all ependymomas is about 10% [51, 92]. In the conus-cauda region myxopapillary ependymomas are the most common intramedullary neoplasms with incidence rates of about 0.05 to 0.08 per 100,000 persons per year (CBTRUS 2005).

Histologically, myxopapillary ependymomas are characterized by tumor cells forming papillary structures around vascularized mucoid stroma cores. An alcian-blue positive, myxoid and often microcystic matrix is abundant between tumor cells and blood vessels. Immunohistochemistry is positive for GFAP, S-100 and vimentin. Punctate or ring-like EMA-staining may also be observed. Mitotic activity and MIB-1 labeling indices are generally low.

Molecular genetics

In spite of their benign clinical behavior, myxopapillary ependymomas are often aneuploid or tetraploid and carry numerous chromosomal imbalances as determined by CGH analysis. In fact, the average number of chromosomal aberrations per tumor is considerably higher than that in ependymomas

and anaplastic ependymomas [90]. The most common imbalances are concurrent gains of chromosomes 9 and 18 [59]. Additional recurrent alterations include gains of chromosomes 3, 4, 7, 8, 11, 13, 17q, 20 and X, as well as losses of chromosomes 10 and 22. Also, cDNA profiles with high expression levels of HOXB5, PLA2G5 and ITH2 in myxopapillary ependymomas clearly differed from those in intracranial ependymomas [46], thus indicating that myxopapillary ependymomas are molecularly distinct from other ependymal tumors.

Subependymoma (WHO grade I)

Epidemiological, histological and immunohistochemical features

Subependymoma is a slowly growing, benign glioma corresponding to WHO grade I. It is typically attached to a ventricular wall, and arises most frequently in the fourth ventricle, followed by the lateral ventricles. As subependymomas often remain asymptomatic, precise estimation of their incidence is difficult. In a retrospective series of 298 ependymal tumors, subependymoma accounted for 8.3% of the cases [92].

Histologically, subependymomas are paucicellular lesions composed of clusters of uniform, cytologically bland cells embedded in a densely fibrillar glial matrix. Many tumors exhibit microcystic degeneration. Formation of perivascular pseudorosettes is indistinct and true ependymal rosettes are usually absent. Immunohistochemically, subependymomas are positive for GFAP, protein S-100 and vimentin. Focal dot-like EMA staining may be seen. MIB-1 positivity is low, with reported mean labeling indices of less than 1% [76].

Molecular genetics

Molecular genetic data on subependymomas are scarce. Cytogenetic investigation of two tumors revealed no structural or numerical abnormalities [14]. Individual cases studied for allelic losses on chromosome arms 10q and 22q, as well as for mutations in the *hSNF5/INI1*, *NF2* and *PTEN* genes did not show any aberrations [14].

Other rare low-grade gliomas

Chordoid glioma of the third ventricle (WHO grade II)

Chordoid glioma of the third ventricle is a rare, slowly growing, non-invasive glioma located in the anterior parts of the third ventricle and histologically

corresponds to WHO grade II. Chordoid gliomas preferentially manifest in adults with a wide age range from 25 to 75 years [9, 78, 82]. The histogenesis of third ventricular chordoid gliomas is unknown, with proposed origins either from specialized ependymal cells in the subcommissural organ or from so-called tanycytes.

Histologically, chordoid gliomas are solid tumors of moderate cellularity characterized by clusters, ribbons and cords of epitheloid tumor cells with prominent eosinophilic cytoplasm and relatively uniform nuclei that are embedded in an alcianophilic, mucinous and sometimes vacuolated matrix. The tumors are sharply demarcated from the surrounding brain tissue, mitotic activity is low and histological signs of anaplasia are absent. Immunohistochemically, chordoid gliomas strongly express GFAP, vimentin and CD34. EGF receptors and merlin/schwannomin may also be expressed [82]. The MIB-1 labeling index is generally low.

To date, only a few cases have been subjected to molecular analyses. A comparative genomic hybridization study of four tumors did not identify any chromosomal imbalances [82]. Hallmark alterations of other common central nervous system tumors like deletions on chromosome 22 in meningiomas or genetic alterations of the *TP53, CDKN2A, EGFR, CDK4* and *MDM2* genes were all absent, reinforcing the notion that chordoid gliomas of the third ventricle must be regarded as a distinct glioma entity.

Astroblastoma

Astroblastoma is a rare glial neoplasm that mainly affects children, adolescents and young adults. In a study of 20 patients, the average age at diagnosis was 14 years (range: 3–46 years; [8]. Individual cases of congenital astroblastoma as well as astroblastomas in patients over 50 years of age have also been reported [32, 75, 97].

Astroblastoma is a usually well-circumscribed glioma. Its histological hallmark is the formation of distinctive perivascular pseudorosettes (so-called "astroblastic pseudorosettes"). These pseudorosettes are characterized by a single layer of epitheloid tumor cells sending broad, non-tapering processes towards a central blood vessel. Vascular thickening and hyalinization are further characteristic histological features. Astroblastoma is not assigned to a distinct WHO grade because exact grading is still an undefined issue. However, histological subdivision into low-grade (well-differentiated) and high-grade (anaplastic) lesions has been suggested and is of prognostic significance [6, 8, 97]. Astroblastomas show immunoreactivity for GFAP, S-100 protein, vimentin and Leu-7/HNK-1 [6, 8, 38]. A mean MIB-1 index of 3.2% has been reported in well-differentiated tumors as compared to 15.5% in anaplastic variants [8].

Knowledge about the chromosomal and genetic alterations in astroblastomas is limited and restricted to small series of tumors or single reported cases. Cytogenetic analysis of an astroblastoma from a 15-year-old girl showed an abnormal hypodiploid karyotype with 45 chromosomes, monosomies of chromosomes 10, 21, and 22 and two marker chromosomes [38]. Studies employing comparative genomic hybridization analysis revealed gains of chromosome arm 20q and chromosome 19 as the most frequent genomic alterations [8]. Recurrent losses were found on 9q, 10 and the X-chromosome. These results suggest a distinct pattern of genetic aberrations in astroblastomas as compared to other glioma entities.

Angiocentric glioma (WHO grade I)

Angiocentric glioma is a rare, stable or slowly growing cerebral tumor that histologically corresponds to WHO grade I and is often associated with chronic epilepsy. Angiocentric glioma has only recently been defined as a distinct entity and was newly introduced in the 2007 WHO classification [57]. To date, less than 30 patients have been reported, with a mean age at diagnosis of 17 years (range 2.3–70 years) [54, 77, 104].

Histologically, the tumor is characterized by remarkably monomorphic, bipolar spindle cells with an angiocentric growth pattern. The cells form mono- or multi-layered sleeves that extend lengthwise along vascular axes or may appear as radial pseudorosettes of ependymomatous nature. Immunohistochemically, tumor cells label for GFAP, S-100 and vimentin and also exhibit frequent dot-like cytoplasmatic labelling for EMA, as commonly observed in ependymomas. MIB-1 labelling indexes are usually below 5%.

Due to the limited number of reported cases, little is known about the underlying cytogenetic, chromosomal or genetic alterations. Chromosomal comparative genomic hybridization (CGH) revealed a loss of the chromosomal region 6q24-q25 in one out of eight cases. High-resolution array CGH suggested the *PTPRJ* (protein-tyrosine phosphatise receptor type J) gene as a possible target of copy number gain at 11p11.2 in one out of three cases investigated [77].

Clinical significance of molecular genetic alterations

The classification of low-grade gliomas is still mainly based on histological findings. Immunohistochemistry serves as a valuable adjunct, especially in cases with inconclusive or borderline histological features. As outlined above, a considerable amount of knowledge concerning the molecular alterations involved in the initiation or progression of distinct glioma entities has

been accumulated over the past years. Several of the identified molecular alterations have been investigated in regard to diagnostic and/or prognostic implications, but so far only few aberrations qualified as clinically relevant markers.

In this regard, combined deletion of chromosome arm 1p and 19q is undisputably the most important alteration. Initially reported by Cairncross and colleagues in 1998 [11], several retrospective studies have confirmed combined deletions of 1p and 19q as an independent marker of favorable response to radio- and chemotherapy as well as longer survival [21, 22, 34, 94]. The considerable prognostic value of 1p/19q deletion in patients with anaplastic oligodendroglial tumors has been corroborated in two recently published prospective and randomized phase III trials involving 368 patients and 289 patients, respectively [10, 102]. As a consequence of the major prognostic significance of the 1p/19q status in patients with anaplastic gliomas treated with radio- and/or chemotherapy, ongoing prospective trials are no longer stratifying anaplastic glioma patients according to histological type but according to the 1p/19q deletion status. Thus, it is likely that molecular testing for 1p/19q deletion will become a routine adjunct to histology in the diagnostic assessment of anaplastic gliomas.

As outlined above (see paragraph on oligodendroglioma), the role of 1p/19q testing in patients with low-grade oligodendroglial tumors is less clear. This is due to the fact that the clinical implications of 1p/19q loss in WHO grade II oligodendrogliomas are still based on only a few retrospective studies, most of which suggested that low-grade oligodendrogliomas with 1p/19q loss are also associated with longer survival times and greater likelihood of response to chemotherapy at the time of recurrence. Thus, 1p/19q testing in WHO grade II oligodendrogliomas is being requested by more and more clinicians and patients. For example, the demonstration of 1p/19q loss may provide additional reassurance that a particular tumor can be closely followed, rather than aggressively treated up-front with either chemotherapy or radiation. In addition, knowledge of the 1p/19q status may be helpful to make therapeutic decisions at tumor progression.

The diagnostic significance of the 1p/19q status is still debated. Although 1p/19q deletion is closely associated with oligodendrogliomas showing classic histological features, 1p/19q loss should not be used as a decisive diagnostic criterion for the diagnosis of oligodendroglioma. In other words, 1p/19q testing is not be recommended to "rule in" or "rule out" a diagnosis of oligodendroglioma [81]. In line with this statement, the definition of oligodendroglioma in the latest WHO classification recognizes the frequent presence of 1p/19q deletions in these tumors but does not require this genetic alteration as an obligatory feature for making the diagnosis of oligodendroglioma. In fact, there are rare cases of histologically classic oligodendroglioma that lack detectable

1p/19q deletions, possibly due to small alterations that escape current detection methods.

For as much is known about 1p/19q as a prognostic marker, so little is known about the molecular mechanisms underlying its prognostic significance. As outlined above, the relevant target genes on 1p and 19q are still unidentified. Thus, it is unclear whether alterations in one or more genes on these chromosome arms, or rather completely different molecular changes may account for the clinically less aggressive behavior of 1p/19q-deleted tumors. It might also be conceivable that 1p/19q status is simply a surrogate marker for genetic or epigenetic alterations that influence treatment response and survival and are located on other chromosome arms. The observation that *MGMT* promoter hypermethylation is common in oligodendrogliomas with losses on 1p and 19q may point to at least one possible mechanism contributing to the chemosensitivity of these tumors [66]. Furthermore, one may speculate that not primarily the presence of 1p/19q loss but rather the absence of other prognostically unfavorable genetic alterations in 1p/19q-deleted tumors, e.g. losses of chromosome arms 9p, 10 and 18q or gains of chromosomes 7, 8q, 19q and 20, are responsible for the distinct clinical behavior [99]. All these issues remain to be investigated in future molecular and translational studies.

In contrast to oligodendrogliomas, mutations of the *TP53* gene and loss of heterozygosity are hallmark genetic changes in diffuse astrocytomas. Thus, the demonstration of a *TP53* mutation or the immunohistochemical detection of a nuclear accumulation of the p53 protein argues in favor of a diffuse astrocytoma as compared to oligodendroglioma. However, the sensitivity of *TP53* mutations and nuclear p53 accumulation as diagnostic markers for diffuse astrocytomas is not very high, as indicated by the fact that approximately 40% of diffuse astrocytoma lack these aberrations. In terms of prognosis, it has been suggested that diffuse astrocytomas with *TP53* mutation progress more frequently and earlier than diffuse astrocytomas without mutation. On univariate analysis, *TP53* mutation was a significant predictor of shorter time to progression [73]. However, this effect was largely due to a higher frequency of *TP53* mutation in gemistocytic astrocytomas, which tend to undergo malignant progression more rapidly than fibrillary astrocytomas. Thus, only the gemistocytic subtype but not *TP53* mutation remained as an unfavorable prognostic marker on multivariate analysis [73].

A diagnostic issue that may prospectively be facilitated by help of molecular markers is the differential diagnosis between diffuse and pilocytic astrocytomas. In addition to frequent *TP53* mutations, a recent integrated genomic analysis identified the isocitrate dehydrogenase 1 (*IDH1*) gene as frequently mutated in diffusely infiltrating astrocytic gliomas. In the initial study on 22 glioblastoma patients, mutations in the active site of *IDH1* occurred in a large fraction of young patients and were associated with an increased overall survival in

secondary glioblastoma patients [71]. A follow-up study analyzed *IDH1* codon 132 mutations in a larger series of 685 brain tumors comprising all major glioma subtypes and reported *IDH1* mutation frequencies of up to 70% in diffuse astrocytomas, while virtually no mutations were detected in pilocytic astrocytomas [3]. Pilocytic astrocytomas, in contrast, have been recently indicated to be molecularly characterized by gene duplication/fusion or mutation of the *BRAF* gene on 7q34. These *BRAF* gene alterations occur in about 60–80% of pilocytic astrocytomas but are infrequent in diffusely infiltrating low-grade astrocytomas [42, 74].

BRAF gene aberrations in pilocytic astrocytomas may not only be of diagnostic but also of potential clinical relevance with respect to a targeted therapy [74]. Tumors with duplications or activating mutations of the *BRAF* oncogene showed significantly increased mRNA levels of *BRAF* and its downstream target, *CCND1*, as compared to tumors without these molecular alterations. In subsequent functional analyses both the stable silencing of *BRAF* through shRNA lentiviral transduction and pharmacological inhibition of MEK1/2, the immediate downstream phosphorylation target of *BRAF*, blocked the proliferation and arrested the growth of cultured tumor cells derived from low-grade gliomas [74]. These findings suggest that pharmacological inhibition of the MAPK pathway may serve as a novel potential treatment option in pilocytic astrocytoma patients.

Conclusions

Low-grade gliomas are classified into distinct entities and variants on the basis of histological and immunohistochemical features as defined in the 2007 WHO classification of tumors of the central nervous system. Molecular studies during recent years have provided fresh insights into the pathogenesis of different low-grade glioma subtypes. The increasing knowledge about key molecular alterations may be helpful in the prognostic assessment of certain glioma entities, as exemplified by the 1p/19q deletion status in oligodendrogliomas and oligoastrocytomas. The impact of genetic alterations as diagnostic markers to facilitate the differential diagnosis between different types of gliomas is still limited but may become of future relevance. As such the differential diagnosis between pilocytic and diffuse astrocytomas can be facilitated using molecular analyses for *BRAF* alterations and *IDH1* mutations, respectively. A better understanding of aberrant molecular pathways in the tumors may guide the way towards innovative targeted therapies, which need to be evaluated further in preclinical and early clinical studies. Taken together, we are optimistic that intensified research efforts involving modern genome- and proteome-wide profiling techniques will reveal powerful diagnostic, prognostic and predictive biomarkers as well as novel targets for individualized and pathogenesis-based therapies.

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What is the place of conservative management for adult supratentorial low-grade glioma?

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With 2 Figures and 1 Table

Contents

Abstract

Adult supratentorial low-grade gliomas (LGG) cover a spectrum of neuropathologies that invariably present with seizure disorders. Following neuroradiological diagnosis management strategy will be determined by prognostic indicators such as patient age, lesion size, lesion location, clinical performance status and radiological differential diagnosis. Conservative management, characterised by a "watch and wait" policy, with serial neuroimaging and clinical observation, may form an integral part of overall Multi-Disciplinary Team management strategy in many patients. Conservative management may include

the periods following radiological diagnosis to primary surgery, and from the time of surgery to timing of radiotherapy or chemotherapy. Results from randomised controlled clinical trials in LGG, recent findings following microsurgical excision, findings from serial observations using volumetric MRI, and recent findings following chemotherapy and tumour genotyping have helped in defining the place of conservative management in individual cases. These recent findings have moved conservative management from a 'controversial' legacy of a bygone era to a more objectively based coherent management component that is understood by both medical and surgical neuro-oncologists. However there is still no evidence from randomised controlled trials to either support or indict the role of conservative management, prior to primary intervention, in LGG. Informing patients of the uncertainties in both interventional strategies and the place of conservative management in LGG is essential in optimising patient outcomes and satisfaction.

Keywords: Low-grade glioma; astrocytoma; oligodendroglioma; MRI; clinical trials watch and wait.

Introduction

There have been many reviews on the management aspects of adult supratentorial low-grade gliomas (LGG), and several of these have either focussed upon or discussed the role of conservative management and the dilemmas in managing this eclectic condition [1, 3, 5, 7, 10, 11, 17, 18, 26, 31, 40–43]. Historically there has been a surgical neurological approach to these lesions and a non-operative medical neurological approach that was well summarised in the editorial by Cairncross and Laperierre [3]. The medical approach was attributable to the facts that most of these patients presented to physicians with seizure disorders, the patients had no interictal neurological deficits and were, in the majority of cases, well controlled with anticonvulsants [28]. Anectdotal evidence with serial neuroimaging also suggested that most of these patients had variably slow growth of the lesions over many years. During this time they had normal quality of life. Eventually the lesion would either transform radiologically, enlarge and or cause problems with development of either focal deficit or symptoms of raised ICP. At this stage the conservative policy would be abandoned in favour of either biopsy of resection of the lesion, often followed by radiotherapy [9].

Neurophysicians were reluctant to refer such patients for early surgery because of the potential morbidity and belief that surgery had no significant impact on the natural course of the disease [40, 41]. Conversely many neurosurgeons would be concerned that delayed surgical management has compromised the long term outcome of the patient as well as making the surgery more technically difficult [2, 9, 14]. Both groups of specialists would cite anecdotes to

support their management strategy and opinions. Reference to the literature was in general not particularly helpful since few publications addressed the topic in a rigorous fashion and until relatively recently there had been no randomized controlled clinical trials in LGG management. Additionally the relatively uncommon nature of LGGs meant that no single surgeon or neurologist acquired a large population based series, and the published surgical series suffered from inherent forms of bias [2, 14, 40].

In the last decade there have been *inter alia*; several randomized clinical trials reported in aspects of LGG management [16, 26, 29], an analysis from three databases of pretreatment factors that predict outcome in LGG [1], the results of findings from serial MRI studies in patients with LGG [6, 21–23, 32, 35], a study evaluating the importance of genotype in LGG outcome [19], two studies evaluating the prognostic role of MRS in LGG [12, 33], literature reviews of both surgical and radiotherapeutic management [17, 18] and two comparative surgical series defining the impact of changes in microsurgical management in LGG [9, 38]. These eclectic studies have helped to define the role and limitations of conservative management as a component of modern management of adult supratentorial LGG. As a result nowadays there is much more of a collegiate, interdisciplinary approach to the management of intracranial gliomas that is not only manifest by the formation of Multidisciplinary Neurooncology Teams but by some consensus in formulating management. The patient is now likely to benefit from the considered opinion of neurologists, neurosurgeons, neuroradiologists, radiation and medical oncologists.

However there remains no evidence from randomized clinical trials about either the role of conservative management in LGG, and/or the timing of primary surgical intervention. A single centre case series has evaluated prognostic factors in the preoperative management of patients with later histologiocally proven low-grade gliomas [5] with findings similar to those from some RCTs. In an attempt to address this question several European units are collaborating to perform a prospective study of cases entered into a database. Such an approach should provide a better understanding and acceptance of the role of conservative management in LGGs. Since patients also now have greater access to information about the management of LGGs through the internet and various patient advocacy sites on the www, such an approach is important.

This article will therefore examine the factors that must be considered for prudent and pragmatic use of conservative management, and will re-evaluate the benefits and shortcomings of the contribution of conservative management for adult supratentorial LGGs. For the purposes of this article conservative management is defined as the planned delay of potentially useful therapies in the treatment of adult supratentorial LGGs. It therefore can be

suddivided into the period preceding any surgical histological confirmation of the neuroradiological 'LGG', a second period following biopsy or resection but before any radiotherapeutic intervention, and a more nebulous third period after radiotherapy that precedes transformation of the LGG to a high-grade glioma (HGG). Traditionally the first period, which is most commonly the longest time period, has provided the greatest controversy and debate, and this remains the case despite the advent of some good quality evidence that helps address some questions about its risks and benefits. The second period has been addressed in a randomised controlled trial [16]. The third period is becoming the domain of medical oncologists interested in the role of chemotherapy in LGGs [19, 30]. Aspects of each of these periods will be reviewed.

The role of conservative management in an initial "wait and watch" strategy

Here it is assumed that a neuroradiologist has made a confident diagnosis of LGG following discovery of a focal high intensity cerebral lesion on T2 imaging, a low intensity lesion on T1 imaging and minimal if any enhancement after contrast enhancement. There may be calcification of the lesion. The patient has no clinical deficit and has presented with either a seizure disorder or the lesion was discovered incidentally following investigations for other disorders for which a brain MRI or CT scan may be performed.

The patient needs to be informed of the diagnosis of a brain lesion that is probably a LGG. Ideally the patient should be shown their scans, and given information about the probable and differential diagnosis. Uncertainties in both diagnosis and natural progression of the disorder should be discussed [37]. The differential diagnosis of a lesion causing epilepsy or a solitary seizure is wide, and related to specific neuroradiological features, location of the lesion and importantly, age of the patient. The younger the adult patient the more likely the lesion is to be a WHO I tumour such as a pilocytic astrocytoma, ganglioglioma, gangliocytoma, DNET or neurocytoma.

My own practice is then to provide a copy of a paper entitled 'Dilemmas in the management of low-grade gliomas' [43] and arrange to see the patient and family a week or two later. The case is also discussed at a specialist Multi-Disciplinary Team Meeting of neuro-oncolgy providers so that there is either a consensus or majority favouring the option of delayed intervention. At this second patient consultation the impact of the diagnosis has usually been assimilated and the patient can then have a role in formulating a coherent and logical management plan, as well as understanding the inherent uncertainties of the disorder. If a 'watch and wait' policy is decided upon a subsequent MRI is performed 3 months later another 6 months later, and

Table 1. *Tumour and patient factors associated with relatively earlier progression or transformation of low-grade gliomas into anaplastic gliomas. These factors need to be considered if embarking on a conservative 'watch and wait' management strategy. Some referred papers cite the EORTC 22845 and 22844 trials*

Factors	References
Age at diagnosis	
>35 years	[9, 35, 36]
>40 years	[1, 23, 25, 35]
>50 years	[5]
Seizures	
None at presentation	[1, 35]
Functional status	
KPS<70	[1, 35]
KPS<80	[38]
Neurological deficit	[25, 35]
Tumour MRI/CT	
Enhancement after contrast agent	[1, 4, 27]
Increasing size	[2, 38]
Size>4 cm	[5]
Size>5 cm	[9]
Size>6 cm	[23, 25]
Midline shift	[23, 25]
RCBV>1.75	[6, 19]
Growth rate	
>8 mm/year	[24]
>20% volume increase/year	[28]
Histology	
Astrocytoma not oligodendroglioma	[23, 25, 35]

rCBV Relative cerebral blood volume.

then yearly unless signs or symptoms warrant earlier scanning. I also organise a neurophsychological review for baseline purposes [24]. Subsequent changes in this data before onset of surgery or radiotherapy may provide useful insights into disease progression [34].

Many patients will elect to have surgery undertaken early because they wish to know the diagnosis, or feel concerned by a conservative approach. Indeed using modern surgical techniques, preoperative fMRI and DT-MRI tractography, awake craniotomy with cortical and subcortical electrical mapping, with or without intraoperative MRI the vast majority of LGGs can now be safely resected to some degree [8, 20, 25, 36, 38, 44, 45]. Since I believe in many of these cases there is no absolute 'right' or 'wrong' approach I remain

flexible with regard to advocating surgery. In my view specific contraindications to conservative management would be if the lesion is >6 cm, there is midline shift, the patient has a poorer Karnofsky status, there is intractable epilepsy despite adequate anti-convulsants and the patient is aged >40–45 years. These features are all associated with a worse prognosis from RCTs and database reviews [1, 29, 5] and intervention should not be unnecessarily prolonged. However as has been pointed out [39] there is no evidence from RCTs that these patients will do better with earlier intervention. What we know is that these clinical and radiological features are prognostic indicators of a worse outcome (Table 1).

What contribution have serial MRIs shown in patients with suspected LGG undergoing a watch and wait policy?

Invariably in many patients 'eyeballing' the serial MRI scans of patients undergoing a watch and wait policy shows little change in consecutive images with respect to either size or pattern of contrast enhancement. However comparison of images over years usually reveals definite lesion enlargement, and serial change in volume of the lesion can be documented more easily if quantitative imaging techniques or automated software is used [21, 22, 28, 32]. However even with automated imaging software there can be considerable differences in volumes between two observers or even one observer analysing the same scan on separate occasions depending on threshold setting for the lesion. Several important papers have addressed the question of serial growth of LGGs and have unequivocally shown progressive increase in their size [21, 22, 28, 32].

In a recent seminal paper Rees and colleagues [32] have followed 27 patients with suspected LGG at 6 monthly intervals. Over a 3 year period some of these patients transformed to a more aggressive radiological phenotype and some remained stable. However all the tumours grew. Those patients in the non-transformers group had smaller tumours at entry (57 ml, 95% CI 35–80 ml) compared to transformers (83 ml; 95% CI 70–96 ml). The growth rates in non-transformers were lower (16% per annum, 95% CI 9–23%) compared to the transformers (26% per annum, 95% CI 20–31%). Those patients who transformed also had a more rapid rate of growth in the 6 months prior to transformation. Mandonnet and colleagues [22] in a similar MRI study, but using different measuring techniques (cube root of the product of [AP size$\times$mediolateral size$\times$infero-superior size]), again showed that all of 27 patients with subsequently confirmed WHO II oligodendrogliomas grew sequentially at a rate of 4.1 mm/year.

In a subsequent study of 143 patients with histologically proven WHO II tumours from the same eminent French group [28] it was shown, that

there was an inverse correlation between tumour growth and survival. Patients with growth rates of >8 mm/year had median survival of 5.2 years whilst those with growth <8 mm/year (which comprised 85% of the series) had >15 years of survival [28]. Another study evaluating the same cohort showed that Individual tumour Growth Rates were slower in tumours with LOH of 1p and 19q and tumours that did not overexpress p53 [35]. Individual tumour growth rates are therefore important and may provide biological information as well.

Perhaps more interestingly from the surgical perspective, and in view of the Rees' [32] and Berger's [2, 38] findings about importance of volume at initial study and surgery, Mandonnet [22] showed that after eliminating lead-time bias many tumours grew at comparable rates. This suggests that variation in time to progression of a patient on a 'watch and wait' policy will inversely relate to how long the tumour has been present. This finding fits well with the observation from surgical series where time to progression after surgery, was longer the smaller the tumour size at operation [2, 38]. Tumours less than 10 ml did not recur, and those between 10 and 30 ml had a longer time to recurrence than those >30 ml.

The role of measuring relative cerebral blood volume (rCBV) using dynamic weighted susceptibility contrast enhanced MRI has also been addressed in attempting to define transformers from nontransformers and prognosis in two studies [6, 21]. Although the designs of the studies were different Law and colleagues [21] found that with rCBV <1.75 prognosis was much better than those with rCBV >1.75. Rees' group [6] also found that a higher rCBV was associated with a poorer prognosis, with nontransformers having a stable rCBV of mean 1.52, whilst transformers continually increased their rCBV from a mean 1.92 at point of entry to the study. The changes in rCBV preceded by 12 months changes in T1 weighted contrast enhancement. These finding suggest that some useful information can be obtained by routine MRI scanning, and in future it may be useful to include rCBV measurements if the facility exists. Such information may give guidance about time to abandon a watch and wait policy or whether it is prudent to began it initially.

The other major neuroradiolocal concern is whether the CT and MRI diagnosed LGG is indeed a LGG (Fig. 1). Many (around 30%) radiologically diagnosed LGGs are anaplastic, and even a few turn out to be glioblastoma [37]. Some LGGs have patchy contrast enhancement and a recent single centre case series has suggested worse 5 year survival, and shorter time to recurrence [4], whilst another much larger study suggested patchy enhancement had no prognostic implication but nodular enhancement did [27]. The role of MRS in LGG has also been evaluated but the findings are variable, some papers suggesting it has a role in relation to tumour anaplasia [12] whilst others have not found it useful [33].

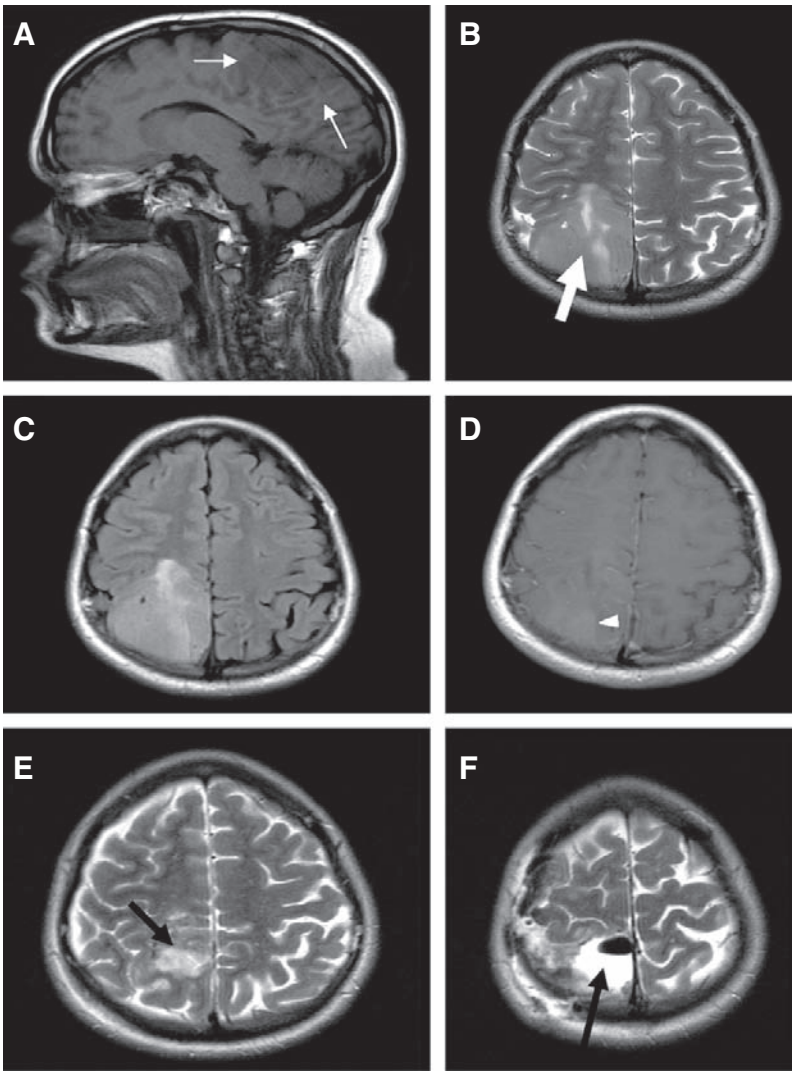

Fig. 1. Sometimes the neuradiological diagnosis of a low-grade glioma will be proven incorrect. These are selected brain images of a 25-year-old female who presented with several focal seizures. She was otherwise entirely asymptomatic and had no clinical deficit. The lesion was thought to be a low-grade glioma. She elected for early surgery which was performed with the patient awake. A near complete resection was obtained with no clinical deficit. My operative impression was of an oligodendroglioma since it was a soft tumour. The histology revealed a supratentorial PNET WHO IV. A) T1W sagittal pre contrast with arrows showing tumour. B) T2W axial imaging. C) FLAIR axial. D) T1W post gadolinium with faint diffuse enhancement (arrowhead). E) T2W 48 h post resection with minimal residual white matter signal change inferior to cavity (arrow). F) T2W also 48 h post resection showing surgical cavity with fluid and gas (arrow). Images courtesy of Dr. David Summers

Is patient outcome compromised by a watch and wait policy?

There is no good quality evidence to answer this question. The AANS reviewed this issue in a guidelines document published in 1998. Median survival following diagnosis of a LGG-like lesion on MRI is 5 years with a wide range [11]. Subsequently the importance of an oligoid component to the tumour, and molecular cytogenetic changes (e.g., Loss of Heterozygocity of 1p 19q, and p53 overexpression) have become important [15, 29, 35]. Age is also a key prognostic indicator with those <40 years generally doing better than older patients (Fig. 2). Other key prognostic indicators are the size of the lesion and presence of midline shift [1, 11, 17, 29]. From the practical surgical perspective tumour location and size are also important [9, 14, 18, 20, 38, 44].

Given all these clinicopatholoical variables, even without reference to MRI findings of variable contrast enhancement, rCBV value, whether an oligodendroglioma and its chromosomal status can be diagnosed without tissue on MRI scanning [15], and initial tumour volume it is easy to see why attempting a

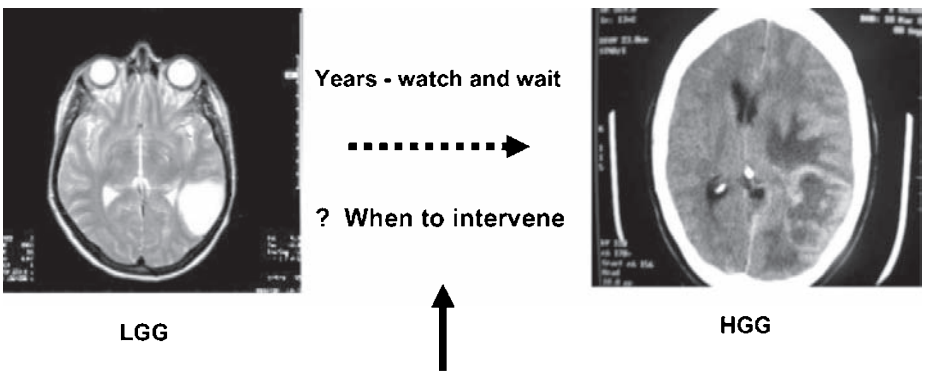

Fig. 2. The basic principles and considerations when undertaking a conservative strategy as part of the overall management in a patient with a suspected low-grade glioma. It is highly likely that the radiologically diagnosed low-grade glioma (LGG) will transform into a High-Grade Glioma (HGG). Time to transformation will depend on many clinical and tumour related variables. Both the treating neuro-oncology team and patient must be satisfied that a 'watch and wait' policy is the best initial management policy

randomised trial of conservative management versus early surgery would require both a large cohort, and a long time [17, 41]. Bauman and colleagues [1] in their analysis of 401 histologically proven LGGs from 3 centres, were with multivariate analysis, able to define four prognostic groups with Recursive Partitioning Analysis that had median survival ranging from 12 months for the worst group to 128 months for the best group. Therefore the most likely way of obtaining relatively quick advances in the field is by collaborative contributions to LGG databases, on a pan-European basis, similar to those pioneered by the Salpetriere group of Laurent Capelle, Hugues Duffau and Emmanuel Mandonnet.

There are four published studies evaluating cohorts of patients with LGGs undergoing early or delayed intervention. One retrospective hospital cohort was reported in which 26 patients undergoing a watch and wait policy were compared to those undergoing early surgery [31]. There was no difference in outcome between the two cohorts (median survival 7 years), and the median time to operation in those watched was 2 years. Another study evaluated the effects of a mean 'delay' of 4 years in the interventional management of patients with oligodendrogliomas, and concluded that the patients did not suffer [10]. A Dutch study from Utrecht comparing neuropsychological findings in 24 biopsy proven LGGs, 24 patients on a 'watch and wait' policy and healthy controls matched for educational level found no negative effects on cognitive performance in those with delayed intervention [34]. Another Dutch study from Rotterdam compared outcome in 30 patients who presented with epilepsy [40]. Thirteen were treated immediately and 17 had delayed surgery. At 5 years 63% of both cohorts were still alive. Obviously however such anectdotal findings cause consternation to some surgeons since Berger's observation that the smaller the tumour at time of operation the better the prognosis it could be argued that all patients should have early resection [38]. In view of the serial MRI findings however it may be that differences in outcome related to tumour size can be accounted for by differences in diagnostic lead-time, and hence bias between groups.

Perhaps surgeons' concerns about a watch and wait policy may be assuaged to some extent by the findings of two surgical series from Paris that examined the extent of LGG excision in two epochs [9]. The later cohort (1996–2003) had the benefit of awake craniotomy techniques with cortical and subcortical mapping ($n = 122$, median tumour volume 55 ml) than an earlier cohort ($n = 100$, 1985–96, median tumour volume 69 ml) that had very limited use of awake craniotomy with no cortical mapping. Despite advantages in technology only 25% of patients had a total tumour resection in the later study. Even though this was significantly higher than the 6% in the earlier series it demonstrates that even the best surgeons with the latest technology, but without access to intraoperative MRI [36] will have difficulty in excising all these lesions.

Conservative management of LGGs after surgery but before radiotherapy and/or chemotherapy

This previously highly controversial topic has been addressed by the EORTC in their 22845 RCT [16]. Patients with surgically confirmed LGG having delayed radiotherapy had the same median survival as those having earlier radiotherapy (66 vs. 63 months). However time to progression (37 vs. 44 months) was shorter. This suggests that overall patients will not be harmed in the long term by deferred treatment. Additionally, this trial clearly identified patients at higher risk of early recurrence and earlier death [29]. Our practice therefore is to irradiate such patients (i.e. age >40 years, tumour >6 cm, tumour crossing the midline, neurological deficit before surgery). The arguments for radiotherapy in patients without these features have been reviewed recently [18].

The role of conservative management versus intervention with chemotherapy in low-grade glioma is also becoming another focus of discussion [18]. The answer to this dilemma may become clearer once Phase II and case series of MRI response in LGGs is obtained in cohorts of patients given chemotherapy when there is evidence of radiological progression after radiotherapy [13, 30]. As mentioned before however patients cohorts in such studies are going to be extremely variable (i.e. age, tumour size, tumour histology, extent of resection, patient functional status, time since surgical and radiological diagnosis etc) and the values of such therapies are therefore going to be difficult to ascertain.

Conclusion

The role of conservative management in patients with LGGs will depend on multiple variables. Some of these are patient and tumour specific (e.g. age, size of lesion, location of lesion, clinical performance status). Some of these are neuroradiological (certainty of diagnosis of WHO II glioma, serial increase in tumour size, change in rCBV of tumour on MR). Some are related to the attitudes and bias of the treating surgeon and or Multidisciplinary Team. What literature there is has not demonstrated that patients are harmed by considered delays in primary intervention. Finally and perhaps most importantly nowadays the patients must be comfortable with the management strategy undertaken in his or her case. A wide-ranging discussion covering the uncertainties in natural history and progression of these lesions and the variable impact of interventions is fundamental. Because of the multiple factors involved, and the lengthy natural history of the disease, it is unlikely that an adequately powered Phase III randomised controlled clinical trial evaluating the role of conservative management in LGGS will ever be performed. Management will therefore be made on an individual basis [7], it

should be based on flexibility not dogma [26]. It is likely that further advances in this field will come from collaborative efforts of interested neuroradiologists, neurologists and neurosurgeons sharing and contributing to databases of patients. This is an area of much recent interest and people interested in finding out more about the European Low-Grade Glioma Consortium should email Prof Hugues Duffau (h-duffau@chu-montpellier.fr), Dr. Laurent Capelle (laurent.capelle@psl.aphp.fr) or Emmanuel Mandonnet (mandonnet@mac.com)

Potential conflicts of interest

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Seizures in patients with low-grade gliomas – incidence, pathogenesis, surgical management, and pharmacotherapy

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With 3 Figures and 1 Table

Contents

Abstract

Seizures complicate the clinical course of >80% of patients with low-grade gliomas. Patients with some tumor variants almost always have epilepsy. Diffuse low-grade gliomas (LGG) are believed to cause epilepsy through partial deafferentiation of nearby brain cortex (denervation hypersensitivity). Glioneural tumors may interfere with local neurotransmitter levels and are sometimes associated with structural abnormalities of the brain which may produce seizures. The severity of tumor associated epilepsy varies considerably between patients. Some cases may present with a first seizure. Others suffer from long-standing pharmacoresistant epilepsy.

Seizure control rates of >70–80% can be expected after complete tumor resections. Patients with drug-resistant epilepsy require a comprehensive preoperative epileptological work-up which may include the placement of subdural (and intraparenchymal) electrodes or intraoperative electrocorticography (ECoG) for the delineation of extratumoral seizure foci. Partial and subtotal tumor resections are helpful in selected cases, i.e. for gliomas involving the insula.

In one series, 40% of patients presented for surgery with uncontrolled seizures, i.e. medical therapy alone often fails to control tumor-related epilepsy. Use of the newer (second generation) non-enzyme inducing antiepileptic drugs (non-EIAED) is encouraged since they seem to have lesser interactions with other medications (e.g. chemotherapy). Chemotherapy and irradiation may have some minor beneficial effects on the patients' seizure disorder.

Overall 60–70% of patients may experience recurrent epilepsy during long-term follow-up. Recurrent seizures (not infrequently heralding tumor recurrence) after surgery continue to pose significant clinical problems.

Keywords: Low-grade glioma; epilepsy; surgery; medical treatment.

Introduction

Patients with low-grade gliomas (LGG) frequently present with epilepsy. In some patients, a LGG is diagnosed during the work-up for a first time seizure. Indeed, new epileptic seizures, in particular partial seizures, in an adult warrant a thorough neuroradiological work-up including an MRI study. In one study, a tumor was diagnosed in 8% of cases as the underlying cause in patients >15

years [96]. Early diagnosis of a brain tumor will facilitate treatment. Preoperative tumor burden is an important prognostic parameter in patients with LGG [101].

Other patients, e.g. with (para)limbic gliomas will develop medication-refractory epilepsy, and the impact of the seizure disorder on the patients' quality of life may dominate treatment decisions rather than the mere oncological aspects [54, 99]. These patients require carefully designed tumor operations with removal of non-neoplastic brain tissue in addition to the removal of the tumor, i.e. "epilepsy" surgery [10, 19, 122].

Quality of life is an important issue for patients with all types of brain tumors. Neurological and neuropsychiatric impairments caused by the disease are often inevitable. Surgical and non-surgical treatments may inflict additional deficits. Aggressive treatment can result in new functional impairments. The respective risks have to be balanced against their presumed oncological benefits. However, successful treatment of the tumor may also improve her or his quality of life. In particular, surgical removal of the tumor will often cure (or at least ameliorate) the patient's epilepsy [67, 24].

Epileptic seizures are not always benign. Even among patients with epilepsy without an underlying neoplastic condition, there is a considerable excess mortality [51]. Casuistic evidence suggests that seizures rank prominently among the treatable causes of unfavorable outcomes after brain tumor surgery [31]. Early postoperative seizures often indicate some surgical complication such as a hematoma [43]. Late recurrence of seizures or a modification of the seizure pattern in brain tumor patients may herald tumor recurrence [24].

In summary, epilepsy is a major issue for patients with low-grade gliomas and their physicians. For this review we have therefore summarized the available data on the incidence, pathogenesis, and treatment of epilepsy in LGG patients. In particular, we will focus on the surgical treatment and pharmacological management of tumor-related epilepsy.

Tumor-related seizures: semiology and classification

Epilepsy is a chronic disease of the brain characterized by 'an enduring predisposition to generate epileptic seizures' ([39] Definitions by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)). There is a general consensus that in the neurooncological setting a single epileptic seizure suffices to diagnose epilepsy. By definition, symptomatic tumor-associated epilepsy is a focal epilepsy, and many patients will present with partial seizures. However, secondary generalization is common, and the focal beginning of a seizure may be clinically inapparent and pass so quickly that one often will have the impression of a primary generalized grand mal

epilepsy. In one large study, generalized seizures alone were seen in 33% of patients with LGG presenting with epilepsy, complex and simple partial seizures alone in 16% and 22%, respectively, and more than one seizure type in 29% [24].

Ictal semiology reflects the somatotopic distribution of brain functions. Hence, focal epileptic syndromes can be classified according to their site of origin. In earlier times, focal seizures played an important role in localizing brain tumors. Because of the availability of high quality neuroimaging this is no longer an important clinical issue. Temporal lobe epilepsy (TLE) is characterized by complex partial seizures usually preceded by an aura. Auras may consist of unfocused fear, memory distortions (déjà-vue), and visceral sensations (e.g. epigastric auras). Oral and motor automatisms (e.g. dystonic posturing) are frequent. Secondary generalization is common. TLE can be further subdivided into mesial and lateral (neocortical) TLE based on the precise location of the epileptogenic zone. Complex visual and acoustic hallucinations, and vertigo are more frequently seen in lateral TLE, while epigastric auras and dystonic posturing are more characteristic of mesial TLE [48, 81]. Frontal lobe epilepsy presents – depending on the exact origin – with contralateral, single or serial, clonic convulsions, which may spread as a Jacksonian march. Impairment of consciousness, speech arrest and complex automatisms (e.g. body rocking) may also occur. If the epileptic focus is located close to the occipital pole or in its vicinity, simple (flashes or scotomas) or complex (e.g. micropsy or macropsy) visual and even scenic hallucinations may occur.

Drug-resistant epilepsy is common in patients with LGG. In the series reported by Chang *et al.* [24] 132/332 (39.8%) patients suffered from pharmacoresistant seizures. Pharmacoresistance can be defined as failure to control epilepsy by at least two first-line antiepileptic drugs, with a seizure frequency of at least one per month for 18 months [82]. Distinguishing between patients presenting with a first or with occasional seizures vs. drug-resistant epilepsy has important implications. Surgical treatment strategies, and the biology and/or histology of the tumor will differ between these patient groups (see below). However, sometimes the distinction between controllable and drug-resistant epilepsy in tumor patients may become blurred. Some LGG patients are diagnosed following their first seizure and will undergo surgery before the seizure disorder has proven pharmacoresistant.

From a clinical point of view, it is also important to distinguish between early and late postoperative seizures. Seizures shortly after surgery often herald a surgical complication such as a hemorrhage [43]. Newly occuring seizures in a seizure-free patient, seizures with a new semiology, or a worsening of seizure frequency are often seen in the context of tumor recurrence [24].

Tumor-related seizures: the role of histology and tumor location

Histology

The incidence of seizures varies widely with tumor histology and location reflecting the respective growth pattern and the susceptibility of the brain structures involved. Astrocytomas and oligodendroglial tumors WHO grade II account for the majority of LGG. Seizures occur in 50 to >90% of patients with WHO grade II astrocytomas and oligodendroglial tumors [73, 24]. Chang and colleagues studied a series of 129 astrocytomas, 109 oligoastrocytomas, and 95 oligodendrogliomas. Eighty-nine percent of the patients with oligodendroglial tumors, and 68% of astrocytoma cases had preoperative seizures [24]. Oligodendrogliomas are said to cause seizures more frequently because of their more cortical location as compared to astrocytomas which tend to primarily involve white matter tracts [61].

Patients with certain rare intrinsic brain tumors almost exclusively present with seizures. Glioneural tumors are a prime example. Dysembryoplastic neuroepithelial tumors (DNTs) most often affect the temporal lobe, but also grow in other parts of the brain including the brainstem [75]. Only very few patients with DNTs do not have epilepsy [84]. Similarly, the majority of gangliogliomas occur in the temporal lobe. In a series of 184 gangliogliomas from our institution, 79% temporal tumors were observed. Only 6 patients (3%) presented with symptoms other than seizures [68]. Clinical presentation is an important prognostic factor in ganglioglioma. In a study of 4 recurrent/progressive WHO grade I gangliogliomas, 21 gangliogliomas with atypical histological characteristics (WHO grade II) and 5 anaplastic gangliogliomas (WHO grade III), progression-free and overall survival was worst for patients without seizures [69].

Supratentorial pilocytic astrocytomas also frequently cause seizures. In a series of 44 adult cases with pilocytic astrocytomas, 19/20 (95%) patients with lobar tumors presented with epilepsy [103]. The series reported by Brown *et al.* [20] included 5 patients with seizures out of a total of 13 cases with lobar tumors (38%). Pilocytic astrocytomas of the deep midline structures, brainstem and cerebellum usually present with symptoms other than seizures [38, 103]. Fouladi *et al.* reported seizures in 8/12 of their (pediatric) patients with cerebral pleomorphic xanthoastrocytomas (PXA) [40]. Subependymal giant cell astrocytomas (SEGA) are assigned to the WHO grade I. These tumors typically grow in the wall of the lateral ventricles and present with hydrocephalus and seizures. SEGA may complicate the clinical course of 6–14% of patients with tuberous sclerosis (tuberous sclerosis complex, TSC). Patients with apparently spontaneous SEGA may develop further signs of TSC during follow-up [2, 97].

The recently revised WHO classification [18] includes several other rare glioma and glioneural tumor subtypes assigned to the WHO grades I and II

which present with seizures, i.e. angiocentric glioma WHO grade I [60, 115], papillary glioneuronal tumor WHO grade I [56], glioneuronal tumor with neuropil-like islands WHO grade II–III [108], and (extraventricular) neurocytomas [17]. Finally, there are some data to indicate that long-standing epilepsy may be the clinical hallmark of some LGG entities which have not yet been comprehensively characterized. Such tumors may ('isomorphic astrocytoma', [11, 93]) or may not [5] display specific histomorphological features.

Tumor location

The location of the tumor may be an even more important determinant of tumor-associated epilepsy than its histological composition. Clinical experience with tumor patients and patients with penetrating and non-penetrating head trauma suggests that certain areas of the brain, in particular the cortex near the central sulcus, the hippocampus and others parts of the (para)limbic system, and the frontal and temporal lobe in general are more likely to generate seizures than others [36]. Accordingly, Liigant *et al.* [61] reported an association between tumor location in the frontal, frontoparietal, temporal and frontotemporal region and the occurrence of seizures in a series of 165 brain tumor patients with epilepsy.

Chang *et al.* [24] studied 332 diffuse supratentorial LGG. Frontal lobe involvement was significantly associated with preoperative epilepsy in the univariate analysis, while a subcortical location with tumor growth in the deep midline structures was less likely to result in seizures. However, multivariate analysis revealed only tumor histology (oligodendroglial tumor) and involvement of midline structures as significant independent positive and negative predictors of preoperative epilepsy, respectively [24]. Duffau *et al.* reported seizures in 39/40 patients with fronto-precentral, 8/8 rolandic, and 6/7 parieto-postcentral LGG [32].

Seizures are also very common in temporal lobe tumors. Many of these patients suffer from drug-resistant epilepsy. In the series reported by Chang *et al.* 86% of 111 patients with LGG of the temporal lobe presented with epilepsy [24]. Intractable epilepsy is particularly often seen in tumors which involve the temporo-mesial structures. In a recent series of 235 operations for temporo-medio-basal tumors (24% malignant gliomas, 76% gliomas and glioneural tumors WHO grades I and II) from the authors' institution, 91% of patients had seizures. Drug-resistant epilepsy was diagnosed in 72% of cases [94]. This is not to say that seizures are infrequent in patients with purely lateral (neocortical) temporal lobe tumors. Luyken *et al.* reported a series of 229 neuroepithelial, supratentorial hemispheric tumors presenting with intractable epilepsy of more than 2 years duration. This series included 113 (55%) cases with temporo-mesial but also 57 (28%) patients with temporo-lateral tumors [67].

Not only involvement of the mesial aspect of the temporal lobe, but also tumor growth in the paralimbic and limbic system in general will often cause epilepsy. Thirty-four of 36 patients (94%) with WHO grade I and II paralimbic (insular) gliomas operated at the authors' institution presented with epilepsy (Fig. 1; [99]). Similarly, all of the 42 patients with insular low-grade gliomas reported by Duffau *et al.* suffered from preoperative epilepsy [34]. Yasargil observed seizures in 50/60 (83%) benign intrinsic insular tumors. Twenty-one of Yasargil's 24 patients with benign tumors of the cingulate gyrus (88%) had epilepsy [119].

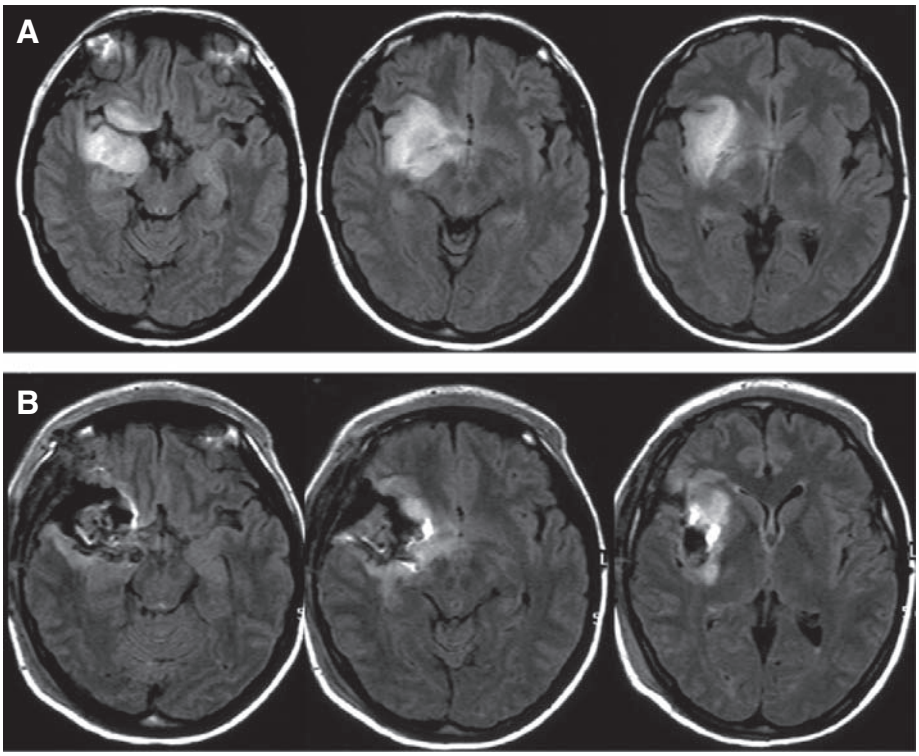

Fig. 1. A) Preoperative FLAIR images of a right paralimbic (insular) astrocytoma WHO grade II. The 40 year old female patient presented with a history of two generalized seizures and multiple complex partial seizures. The tumor involves the uncus but not the hippocampus (Yasargil type 5A). There is also minor tumor growth in the frontoorbital area. B) Postoperative FLAIR images depict a $>70\%$ resection of the tumor. There was no postoperative neurological deficit. At the most recent (three year) follow-up there was no tumor progression. The patient reported occasional auras but no complex partial or generalized seizures. Her antiepileptic medication is currently switched from carbamazepine to levetiracetam because of protracted leucopenia (see Table 1 for side effects of common anticonvulsants). (Dr. Neuloh, Dept. of Neurosurgery, Univ. of Bonn, helped with the preparation of this figure)

However, the high overall incidence of epilepsy in patients with lobar low-grade glioma together with the relatively high number of tumors affecting the frontal, temporal and insular lobe [32] limits somewhat the clinical implications of regional differences in the epileptogenic potential of the various cortical brain areas. In addition, there are clinically important correlations between tumor location and histology. As already pointed out above the majority of glioneural tumors occur in the temporal lobe. Duffau and Capelle have provided some evidence that diffuse low grade astrocytomas and oligodendrogliomas may have preferential locations, too. In contrast to malignant gliomas, low-grade gliomas tend to grow in secondary functional areas close to but rarely directly within primary eloquent parts of the brain [33].

LGG of the deep midline structures, the brainstem and the cerebellum rarely cause seizures [24]. Seizures in such patients often reflect treatment complications such as a cortical bleeding following a stereotactic biopsy of a tumor of the basal ganglia. Some of these patients have undergone placement of a ventriculoperitoneal or ventriculoatrial shunt. Seizures in shunt patients may occur in the context of a shunt infection or malfunction. However, this risk is generally overestimated [55]. In a large French series the risk to develop a seizure in a formerly seizure-free patient with a shunt malfunction but without obvious clinical signs of increased intracranial pressure was only 3.5% [14].

Intraoperative and postoperative seizures

Intraoperative and early postoperative seizures

Seizures occuring during surgery are sometimes dramatic events accompanied by impressive brain swelling. This usually raises the possibility of a disastrous complication somewhere remote from the surgical site. Treatment includes irrigation of the surgical field with cold saline or Ringer's lactate [89]. Intraoperative mapping and monitoring may induce seizures. Controlling seizures in patients undergoing awake craniotomies may be more of a problem, since barbiturates and relaxation can not be used in patients not operated under general anesthesia. Fortunately, these are rare events. In the series reported by Szelény *et al.* [104], only one of 63 patients (1.6%) presenting with symptomatic epilepsy, and only one of 66 patients without a history of preoperative epilepsy (1.5%) experienced a stimulation-induced seizure.

The overall incidence of perioperative seizures in glioma patients is not high. An 8% perioperative seizure rate has been reported for 499 glioma WHO grade III and IV patients enrolled in the Glioma Outcome Project. These authors prospectively recorded all complications occurring within the first 21 days following surgery [25]. Using a 30 day observation period, Sawaya *et al.* [90] noted a 2.5% seizure rate in series of 400 craniotomies

including 40 low-grade and 166 high-grade gliomas. Somewhat higher numbers have been reported in some older series [43]. Of note, seizures rank prominently among the treatable causes of unfavorable outcomes after brain tumor surgery [31].

Seizures in the immediate postoperative period should always alert the neurosurgeon to the possibility of a surgical complication. Fukamachi *et al.* diagnosed 9 hemorrhages and 4 infarctions in 44 patients presenting with a seizure within the first 48 h following craniotomy [43]. However, inadequate anti-convulsant levels are probably the most important risk factor for early postoperative seizures [58]. At the authors' institution, a CT scan is urgently obtained in all non-epileptic patients experiencing a seizure within the first 24–48 h following surgery.

Late postoperative seizures

Recurrent seizures or a change in seizure frequency or semiology in a glioma patient will usually prompt an MR investigation to rule out tumor progression. Several authors have reported significant correlations between seizure recurrence and tumor progression. Hwang *et al.* investigated tumor-associated epilepsy in 101 astrocytomas WHO grades II–IV. Tumor recurrence or malignant progression was diagnosed in as many as 10 of 18 patients with late onset seizures [50]. In the large series of LGG reported by Chang *et al.*, time of tumor progression could be ascertained for 79 of the 161 patients who were seizure-free at the 6-month follow-up. Forty-one of these 79 cases had a seizure prior to progression. On the other hand, recurrent seizures do not always herald tumor progression. In the same series, 73 patients had experienced seizure recurrence at eighteen months, however, tumor progression was noted in only 11 cases [24].

Overall seizure outcomes after surgery for intrinsic brain tumors may not be as stable as generally thought, in particular after incomplete resections. In the study by Chang *et al.*, 73 of 161 patients (45%) who were seizure-free at the 6 months follow-up, developed recurrent seizures by 18 months. A complete tumor resection had been achieved in 48%, and 37% of the cases had presented with uncontrolled seizures [24]. Nevertheless, long-term seizure outcomes can be excellent even in patients presenting with drug-resistant epilepsy [67]. These authors reported a $>80\%$ seizure control rate after 10 years of follow-up.

Pathogenesis of tumor-related seizures

The etiology of tumor-related seizures is probably multifactorial. Though various mechanisms of epileptogenesis in brain tumor patients have been

suggested, the specific events leading to tumor-related epileptic activity are still not fully understood [109]. There is evidence that the mechanisms of seizure generation vary for different tumor types [112], and this may also explain the differences in seizure frequency between tumor entities. LGG and other slow-growing tumors have been suggested to produce an epileptogenic milieu by partial deafferentation of cortical brain regions, thus causing denervation hypersensitivity [35, 112, 118]. Developmental tumors consist of well-differentiated cells, which are able to release neurotransmitters and other modulators involved in epileptogenesis [118]. They may be associated with structural abnormalities of the cortex, which are likely to cause epileptic activity. In contrast, high-grade brain tumors, such as glioblastoma multiforme, and metastasis are assumed to induce seizures via tissue damage or mass effect due to necrosis or tumor bleeding and edema, respectively [8, 85], leading to impaired vascularisation and ischemic changes in the surrounding tissue [79].

Secondary epileptogenesis is a phenomenon predominantly seen in younger patients with slow-growing, low-grade tumors of the temporal lobe, and implies, that the tumor induces distant, actively discharging epileptogenic foci [71, 45, 66, 109]. Certain morphologic changes in the peritumoral brain tissue, such as persistent neurons in the white matter, inefficient neuronal migration [47], changes in synaptic vesicles, and alterations in glial gap-junction coupling are also believed to contribute to seizure generation [8, 113].

Voltage-gated ion channels controlling cell excitability and synaptic processes are involved in the generation of seizures. Hence, changes in the local concentrations of gamma amino butyric acid (GABA) and glutamate are thought to affect tumor-related epileptogenesis through imbalances between inhibitory and excitatory factors [6, 8]. Ion and amino acid level changes, neuroreceptor disturbances as well as enzymatic changes and immune-mediated mechanisms all have been shown to play a role in tumor-related epilepsy [8]. Hypoxia in neoplasms and adjacent regions due to an imbalance between blood perfusion and an increased metabolism may lead to changes of the pH in the peritumoral brain tissue with consecutive cell damage and, therefore, increased neuronal excitability [8].

Surgical treatment for tumor-related seizures

Epilepsy in low-grade glioma (LGG) patients: a good indication for surgical treatment

Surgery for LGG is still somewhat controversial, and no prospective study specifically investigating the role of the tumor resection has been conducted. However, the extent of resection has been shown to be a major prognostic

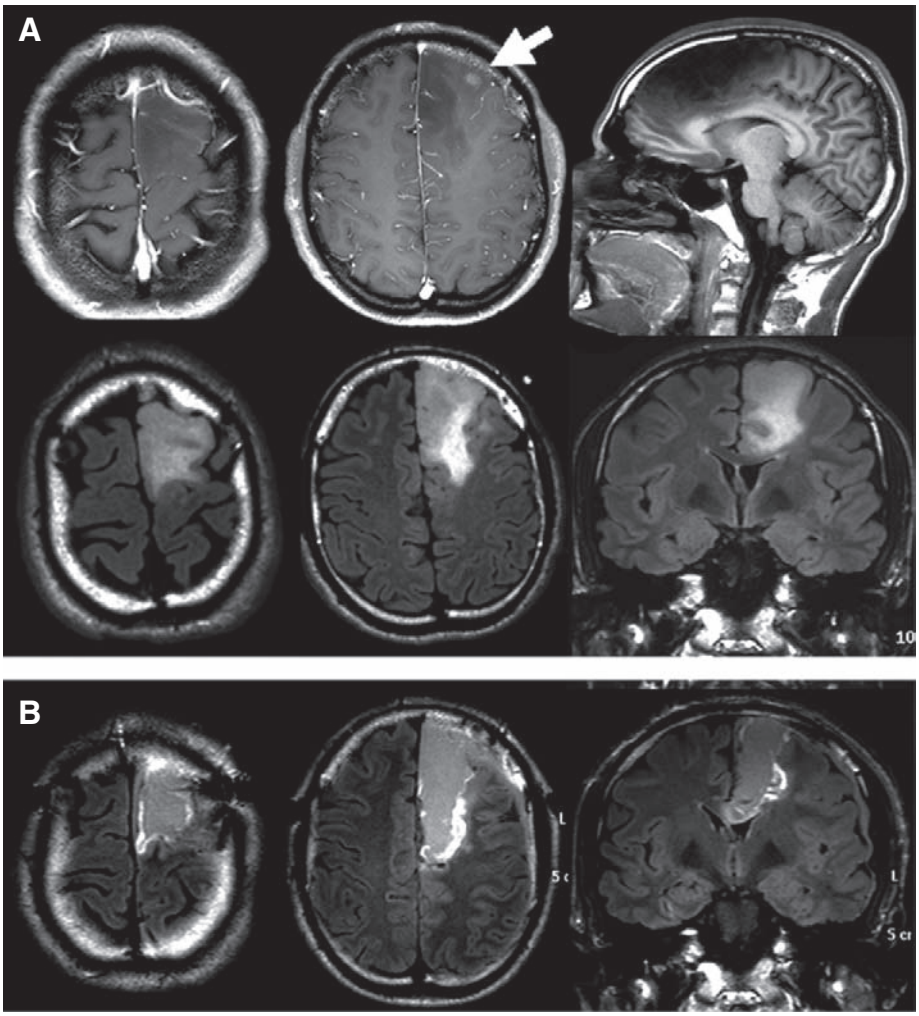

Fig. 2. A) Preoperative T1 weighted (after administration of contrast medium, *upper row*) and FLAIR (*lower row*) MR scans depicting a diffuse glioma of the left mesial frontal lobe (i.e. the superior frontal gyrus and the cingulum) which involves the SMA (supplementary motor area). The tumor was diagnosed in a 24 year old male following two generalized seizures. There is focal contrast enhancement (*arrow*). Nevertheless, the histological diagnosis was astrocytoma WHO grade II. B) Postoperative FLAIR images showing a complete tumor resection. The tumor was removed under continuous electrophysiological monitoring. As expected, there was a transient hemiparesis and aphasia (SMA syndrome). One year after the surgery, the patient has only minimal speech difficulties. He had two auras but no further generalized seizures in the year after the surgery and is treated with lamotrigine by his neurologist

factor in many and in particular in the more recent studies [59, 101]. In contrast, there is little disagreement that LGG patients with seizures will very often experience a substantial relief from their epilepsy. Recurrent seizures have a major negative impact on the patients' quality of life [54]. Age-related mortality is increased two- to threefold in epileptics. At least some cases are caused by seizures and not by the underlying disease [51]. Finally, there is some evidence to suggest that epileptics will benefit from early treatment and respond with better seizure control [66, 71]. Together, these are three good reasons to recommend surgery to a patient with a LGG presenting with epilepsy.

Epilepsy control after "tumor surgery"

A radical tumor resection, i.e. the complete removal of the tumor as defined by imaging criteria, offers a good chance for seizure control in many patients with LGG (Fig. 2). In the series reported by Chang *et al.*, 74/83 (89%) patients were seizure-free at 6 months following a gross total resection as compared to only 94/165 cases (57%) after a biopsy or a subtotal tumor removal [24]. A gross-total resection has been identified as a positive predictor of seizure control in many other case series as well. Packer *et al.* have described a cohort of 60 children with seizures and cortical low grade intrinsic brain tumors. Forty-seven of their patients underwent a total or near-total tumor resection, 45 of which (96%) became seizure-free [78]. Surgical removal of temporal lobe tumors presenting with epilepsy will result in postoperative seizure control in 65 to 77% [26, 121].

Patients with tumor-related epilepsy may sometimes derive substantial benefits even from incomplete tumor resections. As mentioned above, 57% of the LGG patients with a subtotal resection or biopsy in the study by Chang *et al.* were seizure-free during short-time follow-up [24]. In a series of 101 operations for insular gliomas from the authors' institution removal of $>90\%$ of the tumor mass was achieved in 42%, and a 70–90% resection in 51% of cases. 83 surgeries were performed in patients with seizures. Epileptological one-year outcomes were available in 55 cases with more than one preoperative seizure: 42 patients (76%) were seizure-free or experienced only auras or simple partial seizures (Engel class I) (Fig. 1; [99]).

"Epilepsy surgery" for tumor-related drug-resistant epilepsy

Conceptually, successful surgical treatment for epilepsy requires the complete removal of the epileptogenic zone (i.e., the cortical area indispensable for the generation of epileptic seizures). In brain tumor cases the epileptogenic zone typically consists of the tumor and variable amounts of surrounding tissue. The epileptogenic zone does not extend substantially beyond the borders of the tumor in most cases with occasional seizures. Hence, as summarized above, a

gross-total tumor resection is quite appropriate for the majority of patients with LGG and tumor-associated epilepsy.

In contrast, the epileptogenic zone may include significant extra-tumoral cortical areas in patients with drug-resistant tumor-related epilepsy. This is nicely illustrated by the experience with stereotactic lesionectomies for focal intractable epilepsy. The term 'lesionectomy' refers to the resection of pathological tissue only (the 'lesion') in the context of surgical treatment for epilepsy. A stereotactically guided procedure is probably the purest form of lesionectomy. Stereotactic lesionectomies resulted only in a 56% seizure control rate in the series of 23 patients with drug-resistant partial epilepsy reported by Cascino *et al.* [22].

Indeed, considerable clinical evidence suggests that a more comprehensive approach aiming at the identification and removal of the epileptogenic zone (i.e. 'epilepsy surgery') will result in improved epilepsy outcomes in patients with tumor-associated intractable epilepsy. Seizure outcomes after lesionectomy vs. 'epilepsy surgery' for patients with intractable epilepsy have been compared by several authors. Rossi *et al.* [88] reported a 66% seizure control rate after lesionectomies and 79% following epilepsy surgery for 28 temporal and 20 extratemporal WHO grade I–II gliomas. Jooma *et al.* [52] analyzed their experience with 30 temporal lobe tumors presenting with complex partial seizures. Sixteen patients underwent only a lesionectomy, and 14 patients a resection of the lesion with electroencephalographic delineation and excision of the presumptive epileptogenic zone. Seizure control was achieved in 13 (93%) of the latter patients, while only three (19%) of the lesionectomy only patients became seizure-free. A further eight of these cases underwent a temporal lobectomy as a second procedure, 5 (63%) of which became seizure-free. Lombardi *et al.* analyzed 22 cases of LGG associated with intractable epilepsy including 8 temporo-lateral (extra-hippocampal) and 7 temporo-mesial tumors (with invasion of the amygdalo-hippocampal complex). Only 4/8 (50%) patients with temporo-lateral tumors were seizure-free after a lesionectomy. However, in 2 of the 4 patients with an unfavorable seizure outcome, a second pathology ('dual pathology', tumor and hippocampal atrophy) was present which was not surgically addressed. Both patients became seizure-free after a temporal lobectomy [63]. The experience detailed in the latter two studies underlines the important role of the temporo-mesial structures in many cases of tumor-associated temporal lobe epilepsy. One of the central issues in surgery for temporal lobe tumors presenting with intractable epilepsy is to determine if the amygdalo-hippocampal complex is part of the epileptogenic zone or not.

Surgical treatment for tumor-associated frontal lobe pharmacoresistant epilepsy poses specific problems. Frontal lobe tumors often grow close to the motor and/or language cortex. This often limits the possible extent of

resection. Zaatreh *et al.* operated on 37 patients with drug-resistant tumor-associated frontal lobe epilepsy including 28 cases with intrinsic brain tumors. A gross-total resection was perfomed in 27 patients. Only thirteen (35%) patients were seizure-free or had only auras (Engel class I) during longterm follow-up [120]. Experience at the authors' institution has been somewhat more rewarding. In a series of 68 operations for intractable frontal lobe epilepsy, 54% of all patients, and 58% of the 34 tumor cases had an Engel class I outcome. Of note, the epileptogenic zone was electrophysiologically defined in 81%. If the epileptogenic zone included eloquent cortex (25%), a partial resection and MST (multiple subpial transections) were perfomed [92].

"Epilepsy surgery" for tumor-related drug-resistant epilepsy: how to define the epileptogenic zone

Performing an extended lesionectomy rather than a lesionectomy alone, i.e. resecting not only the tumor but in addition a rim of 0.5–1 cm of surrounding cortex will remove the epileptogenic zone in many patients with tumor-related intractable epilepsy. Similarly, the resection of a temporo-mesial tumor can be extended to include the amygdalo-hippocampal complex (or parts thereof). This simple strategy has been quite successful with respect to epilepsy control [91, 28]. Good seizure control rates have also been reported after mostly extended lesionectomies for focal epilepsies in pediatric patients [15].

A more aggressive approach to tumor-associated epilepsy in LGG patients involves the electrophysiological identification (Fig. 3) and resection of extratumoral seizure foci. If questions remain after the non-invasive work-up, two basic surgical options exist which help with the delineation of the epileptogenic zone: intraoperative electrocorticography (ECoG) and extraoperative mapping after implantation of depth and subdural strip and grid electrodes. Intraoperative ECoG (Fig. 3A) allows for the intraoperative identification of the irritative zone, i.e. the cortical area capable of producing interictal electrographic spikes. Disadvantages include the influence of anesthesia and short recording times. Intraparenchymal (depth) and cortical surface (subdural) electrodes can be used to record not only interictal electrical activity but also genuine seizures, i.e. help to delineate the seizure onset zone. Subdural electrodes can also be used to map eloquent cortical areas (Fig. 3B). However, two operations (electrode placement and tumor resection) are required, and the implantation of subdural and intraparenchymal electrodes carries a small but significant complication rate, e.g. the development of subdural hematomas necessitating emergency evacuation. Of note, neither intraoperative ECoG nor the use of subdural/intraparenchymal electrodes followed by extraoperative mapping allows to always precisely delineate the epileptogenic zone. The epileptogenic zone is operationally defined by the absence of seizures after its

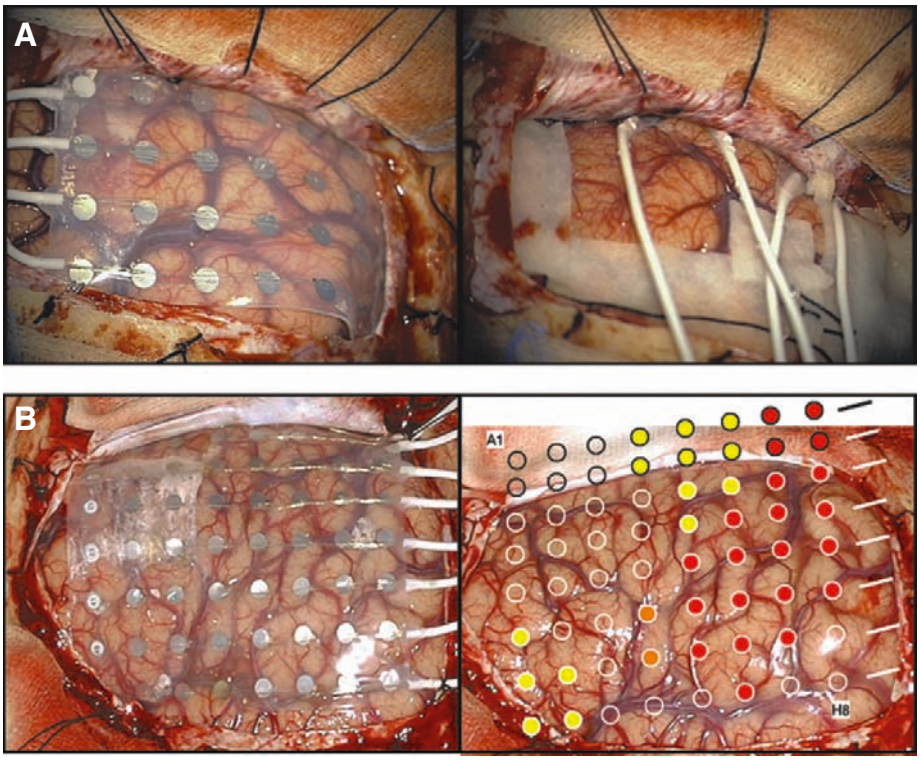

Fig. 3. A) Intraoperative electrocorticography of the right temporal lobe. A grid electrode (*left*) and four temporo-basal strip electrodes (*right*) are used sequentially to record interictal electrographic spikes in order to map the *irritative zone*. The planned resection is indicated by cottonoids. B) Placement (*left*) of a large frontal grid electrode covering the eloquent areas of the dominant frontal lobe. The craniotomy is closed and the electrodes allow for the recording of actual seizures occurring in the days following surgery. These recordings help with the delineation of the *seizure onset zone*. In addition, ''extraoperative'' electrophysiological mapping makes the functional identification of the precentral gyrus (*red* and *orange* dots) and the cortical language areas (*yellow* dots) possible. Resective epilepsy surgery aims at removing the *epileptogenic zone*. Of note, both the *irritative* as well as the *seizure onset zones* are approximations of but do not equal the *epileptogenic zone*. (The photographs used for this figure were provided by Dr. Clusmann, Dept. of Neurosurgery, and Prof. Elger, Dept. of Epileptology, Univ. of Bonn, Germany)

removal, and not by the production of interictal electrographic spikes or the onset of seizures [95].

Intraoperative electrocorticography (ECoG) has been used by many groups to improve seizure outcomes in patients with intrinsic brain tumors and epilepsy. Berger *et al.* employed ECoG as an adjunct during surgery for 45 low-grade tumors with drug-resistant epilepsy. Forty-one of their patients

(91%) were seizure-free after surgery (with and without medication) [10]. Britton *et al.* treated 51 patients with medication-refractory focal epilepsy and LGG. Seventeen patients had a lesionectomy and in 34 cases an additional corticectomy was performed after ECoG. Sixty-six percent of patients were seizure-free during follow-up [19].

At the authors' institution, both intraoperative ECoG and implantation of subdural and depth electrodes have been used to optimize seizure outcomes in patients with drug-resistant epilepsy and (mostly) low-grade intrinsic brain tumors. In a series of 146 operations, intraoperative ECoG was employed in 42 cases (29%), and extraoperative mapping in 40 patients (27%). Of the 124 patients with a follow-up exceeding 6 months, 71% became seizure-free [122]. However, the number of patients undergoing intraoperative or invasive extraoperative electrophysiological mapping has declined in more recent years. In particular, growing experience and improved neuroimaging have resulted in a lesser number of invasive evaluations for tumor-associated temporal lobe epilepsy. Schramm *et al.* [91] reported 62 cases with drug-resistant neocortical temporal lobe epilepsy including 35 patients with tumors. An extended lesionectomy without electrophysiological mapping was performed in 50 cases. 89% of the tumor cases became seizure-free (or had only isolated, non-debilitating seizures = Engel class I). Clusmann *et al.* [28] described 74 patients with mesial temporal lobe epilepsy (including 55 tumor cases) undergoing limited temporal lobe resections. Engel class I outcomes were seen in 78%. Only 24% of the patients had an invasive preoperative evaluation. Patients with extratemporal intractable epilepsy are still commonly evaluated using subdural grid electrodes and sometimes intraoperative ECoG. Of note, in these cases the need to obtain a reliable map of functional cortical areas influences the decision to proceed with the invasive evaluation just as much as epileptological concerns (Fig. 3).

Effects of cranial irradiation and chemotherapy on tumor-related epilepsy

Radiotherapy

While the beneficial impact of surgery on a seizure disorder in brain tumor patients is well recognized, there are also some data indicative of a reduction of seizure frequency by radio- and/or chemotherapy. However, data on this issue are rare and mainly stem from a few small series. In a retrospective analysis including 5 patients with low-grade astrocytoma Rogers *et al.* [86] observed a reduction of seizure frequency of more than 75% with a follow-up time up to 8.2 years from the first date of irradiation. Similar results were found by another group [23], and Rossi *et al.* [87] observed that stereotactic interstitial irradiation had a positive effect on epilepsy in patients with unre-

sectable gliomas. Improved seizure control after irradiation may be due to a reduction in tumor size. Further theories include damage to epileptogenic neurons in the surrounding of the tumor or alterations of local metabolic effects by radiotherapy [86]. However, cerebral irradiation may also lead to a transient increase in seizure frequency as a result of secondary complications such as edema, bleeding or necrosis. Moreover, the risk of late-onset neurotoxicity with seizures as part of the clinical problem has to be considered before initiating brain irradiation, especially in younger patients with a presumably better prognosis.

Chemotherapy

There is some preliminary evidence that pharmacological antitumor treatment might be associated with improved seizure control. Chemotherapy with the alkylating agent temozolomide was reported to reduce seizure frequency in 50% to 60% of patients with progressive LGG [77]. Similar data were presented in another clinical trial: 54% of patients with symptomatic epilepsy due to WHO grade II gliomas experienced a reduction in seizure frequency [16]. Besides temozolomide nitrosourea-based chemotherapeutic regimens, such as PCV (procarbazine, CCNU, vincristine) chemotherapy play a role in the treatment of LGG. In a small clinical trial all ten patients treated with a nitrosourea-based regimen had clinical improvement with a reduction of seizure frequency, and 60% of the patients even became seizure-free [42]. Further clinical studies of much larger patient series seem warranted to substantiate this effect of chemotherapy on tumor-related epilepsy.

Pharmacological treatment

Who should be treated with anticonvulsants, and how long?

Medical treatment for tumor-related epilepsy is not satisfactory so far, and data derived from prospective, placebo-controlled studies are scarce. Anticonvulsive therapy is generally recommended after occurrence of a first and single seizure in neurooncological patients [109, 116]. In contrast to previous data [41], Wick *et al.* [117] found in a retrospective analysis of the seizure history of 107 glioma patients undergoing surgery, that preoperative seizures were not a predictor for the occurrence of postoperative epilepsy. These data may justify withholding treatment with AEDs in LGG patients after an uneventful gross total resection of the tumor and weaken the indication for long-term anticonvulsive treatment in cases with pre-operative seizures.

There is no general indication for prophylactic antiepileptic therapy in glioma patients. Primary prophylactic treatment with phenytoin, phenobarbital or valproic acid in patients with primary brain tumors, meningiomas, or brain

metastases was found to be ineffective in two meta-analyses (AAN standard, [46, 100]). The use of anticonvulsants in patients who are undergoing surgery for a brain tumor is also not generally indicated. Primary prophylaxis with phenytoin in patients with cerebral metastasis and supratentorial primary brain tumors was not effective in two randomized clinical trials [29, 30]. However, prophylactic preoperative treatment with anticonvulsants may be helpful in some cases because of casuistic evidence pointing to perioperative seizures as a major treatable cause of adverse outcomes after brain tumor surgery [31].

According to a consensus statement published by the Quality Standards Subcommittee of the American Academy of Neurology [46] primary prophylaxis with antiepileptic drugs (AEDs) should not be used, anticonvulsants discontinued in patients who have never experienced seizures, and – following brain surgery – it is recommended to discontinue AEDs after one week in patients without a history of seizures. Patients who presented with a single seizure, but remained seizure-free after surgery may be kept on antiepileptics for 3 months [117], but there are no randomized trials on this issue so that treatment may be discontinued even after a shorter time interval. Patients with persistent seizures after surgery usually need long-term anticonvulsive treatment, and the decision for drug withdrawal should be made on an individual basis if the tumor is stable, the patient has not experienced seizures for at least one year, and the EEG does not show abnormal discharges suggestive of an increased predisposition to seizure generation.

At the authors' institution, no routine preoperative antiepileptic prophylaxis is prescribed. Patients assumed to be at a particularly high risk for complications following a seizure are given anticonvulsants. A typical example would be a large frontotemporal convexity meningioma in a septuagenarian. Of note, patients with presumed LGG rarely – if ever – fall into this category. Patients presenting with a first seizure are not routinely treated. Antiepileptics are used in cases with more than one preoperative seizure. The antiepileptic medication is discontinued after three months, if the patient remains seizure-free and has had a complete resection. Patients undergoing epilepsy surgery are typically maintained on their preoperative anticonvulsant medication for two years.

Common antiepileptic drugs (AEDs) and recommendations for first line therapy

Only a few prospective, randomized studies specifically dedicated to the medical treatment of seizures in neurooncological patients have been published. Simply following treatment guidelines for symptomatic localisation-related epilepsy [53] can not be recommended for patients with brain tumors without carefully taking into account pharmacokinetic and pharma-

codynamic mechanisms, potential drug interactions and interactions with concomitantly administered chemotherapy, as well as possible side effects and co-morbidity.

Enzyme-inducing AEDs (EIAEDs) such as the first-generation anticonvulsants carbamazepine, phenytoin and phenobarbital are no longer considered first-choice anticonvulsive drugs for tumor-related seizures because they may lead to accelerated metabolism, reduced plasma concentrations and thus lower anticancer activity of simultaneously given chemotherapeutics via an influence on the cytochrome P450 enzyme system of the liver. The increasing use of chemotherapy for recurrent and progressive LGG renders this more than a theoretical concern [16, 42, 77]. Various chemotherapeutics are substrates of the cytochrome P450 enzyme system, and EIAEDs have been proved to reduce the effects of taxanes, methotrexate, irinotecan and nitrosureas [4, 111]. Conversely, antineoplastic agents can lead to accelerated metabolism and thus diminished plasma concentrations of EIAEDs with the consequence of impaired seizure control. This has been reported for antineoplastics such as cisplatin, vincristin or methotrexate if given together with carbamazepine, phenytoin or valproic acid.

In a retrospective analysis of patients with glioblastoma multiforme treated with adjuvant chemotherapy (most patients receiving CCNU) after surgery and irradiation, patients who were given EIAEDs (80% carbamazepine) had a significantly shorter overall survival than patients on non-EIAEDs (80% valproic acid), 10.8 versus 13.9 months, respectively [74]. This effect could be due to an accelerated metabolism of CCNU in patients receiving EIAEDs and/or a potential intrinsic antitumor effect of valproic acid. Valproic acid inhibits histone deacetylase, leading to growth arrest and apoptosis of malignant cells [37, 62]. Being an enzyme inhibitor, valproic acid may decelerate the metabolism of concomitantly administered antineoplastic drugs and – by raising their plasma concentrations – increase their activity but also toxic effects [13]. The use of add-on anticonvulsant medication might be necessary since monotherapy with valproic acid often does not achieve sufficient seizure control [112].

On the basis of the interactions and characteristics of the classic EIAEDs and valproic acid outlined above, it seems reasonable to consider the new (second generation) anticonvulsants with a reduced potential for interactions and side effects such as levetiracetam, gabapentin, pregabalin, and zonisamide, as well as lamotrigine and topiramate for the primary therapy of patients with brain tumors (Table 1; [12, 27, 102]). No relevant interactions with chemotherapy or other simultaneously given drugs have been reported for gabapentin and levetiracetam. Some drugs have already been established as first- or second-line antiepileptic agents for the treatment of neurooncological patients. Phenytoin and benzodiazepines may still be used for the treatment and prevention of early

Table 1. *First-generation and new (second-generation) antiepileptic drugs (AEDs)*

Generic name (trade names)	Dose range (mg/day)*/ monotherapy	Therapeutic serum level (μg/ml)†	i.v.	Common and relevant side effects	Pharmacokinetic interactions
Levetiracetam (Keppra®)	1000–3000	10–80‡	+	Sedation and fatigue (rare), irritability, nervousness and other mood changes	Probably none
Gabapentin (Neurontin®)	900–3600	‡	–	Sedation and fatigue, possibly cognitive problems	Probably none
Pregabalin (Lyrica®)	300–600**	‡	–	Vertigo, fatigue, weight gain, irritability, incoordination	Probably none
Zonisamide (Zonegran®)	300–500**	15–40‡	–	Anorexia, irritability, depression, ataxia, dizziness, diplopia, cognitive impairment, kidney stones	No enzyme induction (but co-administration with cytochrome P450 inducers or inhibitors may change its pharmacokinetic profile; [7]
Lamotrigine (Lamictal®)	100–600	2–15‡	–	Allergic skin reactions, Stevens-Johnson syndrome, tremor, ataxia, insomnia (rare)	Possibly weak enzyme induction
Topiramate (Topamax®)	50–200	7–20‡	–	Dizziness, paresthesia, weight loss, fatigue, sedation, kidney stones, neurocognitive side effects	Possibly weak enzyme induction
Oxcarbazepine (Trileptal®, Timox®)	600–2400	10–35	–	Similar to carbamazepine but less frequent, except: >1% hyponatriemia	CYP450 induction
Carbamazepine (Tegretal®, Timonil®)	400–2000	4–9	–	Hyponatriemia, dizziness, fatigue, nausea, ataxia, skin reactions, elevated liver enzymes, leuco- and thrombopenia	CYP450 induction

Table 1. (*continued*)

Phenytoin (Phenhydan®, Zentropil®)	200–350	5–20	+	Elevation of liver enzymes, dizziness, nausea, ataxia, headache, allergic skin reactions, gingival hyperplasia, cerebellar atrophy, cardial arrhythmia and conduction defects	CYP450 induction
Phenobarbital (Luminal®)	50–300	10–40	+	Drowsiness, headache, allergic skin reactions, irritability and aggressive mood changes, constipation	CYP450 induction
Primidone (Liskantin®, Mylepsinum®)	500–1500	5–15	–	Tiredness, headache, allergy; also see phenobarbital	CYP450 induction
Valproic acid (Ergenyl®, Orfiril®)	1200–2400	40–100	+	Hepatotoxicity, weight gain, tremor, alopecia, edema, teratogenicity, thrombopenia, coagulopathy (?)	Enzyme inhibition

* Dose rates must be adapted to concomitant medication with respect to possible pharmacokinetic und -dynamic interactions.
** Only add-on therapy (zonisamide: licensed for use as adjunctive therapy for partial seizures in adults).
† Varying in different laboratories; here: according to the standards of the Neuropharmacological Laboratory, Department of Epileptology, University of Bonn.
‡ Not assessed routinely; indications as follows: survey of compliance, occurrence of side effects or signs of intoxication, insufficient control of epilepsy or relapse after a period of satisfactory seizure control, polypharmacotherapy with anticonvulsants and concomitant drugs – to assess possible interactions, severe comorbidity and metabolic disturbances with e.g. malabsorption.

postoperative seizures, if the clinical scenario necessitates an immediate therapeutic effect.

Lamotrigine may be used for tumor-related epilepsy, but has the disadvantage of a protracted dosage schedule and may cause severe skin reactions such as Stevens-Johnson syndrome. Pregabalin and zonisamide are licensed for use as add-on anticonvulsants and may also become important in the neurooncological setting as they do not exhibit relevant interactions with chemotherapeutics and other drugs. In addition, zonisamide acts through a combination of multiple mechanisms that are potentially complementary to other AEDs [7, 57]. However, while some authors report overall good tolerability of zonisamide with the majority of side effects being mild-to-moderate [7], others observed limiting adverse events leading to discontinuation of therapy (Table 1).

The authors prefer monotherapy with levetiracetam as first-line anticonvulsive treatment for patients who will presumably need chemotherapy or long-term treatment with corticosteroids when anticonvulsant therapy is required. A randomized trial on levetiracetam monotherapy for treatment of newly diagnosed partial epilepsy found that levetiracetam was as effective as monotherapy with carbamazepine and associated with fewer side effects [9, 109]. Levetiracetam can be administered intravenously if necessary, and therapeutic dose rates can be achieved within 3 days [70, 72]. The efficacy of levetiracetam – both as monotherapy and add-on agent – appears to be higher than that of gabapentin [110, 76]. In addition, treatment with levetiracetam does not seem to be affected by multidrug efflux transporters such as P-glycoprotein (PGP) or multidrug resistance proteins (MRPs) located at the level of the blood–brain barrier [83]. While these multidrug transporters are thought to actively restrict the penetration of many AEDs into the brain, Potschka *et al.* [83] showed that inhibition of these multidrug transporters does not alter the blood-brain barrier penetration of levetiracetam in an animal model. These authors concluded that levetiracetam is not a substrate for these transporters.

Toxicity and side-effects of anticonvulsant drugs

AED side effects occur more frequently in patients with brain tumors than in the general population of patients with epilepsy [46, 116] This was also observed in a cross-sectional study on 195 patients with LGG mainly addressing neurocognitive sequelae in the course of the disease [107]. Frequent and important side effects of selected AEDs are detailed in Table 1. Generally, neurocognitive deficits, myelosuppression, liver dysfunction with elevated liver enzymes, and dermatological reactions may occur with anticonvulsant therapy, leading to discontinuation or modification of treatment in approximately 20% to 40% of patients. Bone-marrow toxicity necessitating a change of the anticonvulsant

therapy is seen in 3%. Hemostatic and coagulation disorders have been associated with the use of valproic acid [1, 44], however, this has not been substantiated in other studies [3, 117]. At the authors' institution, pre-treatment with valproic acid is not regarded as a contraindication against elective surgery. These patients undergo a careful preoperative hemostaseological evaluation and any (potential) deficits are corrected using von-Willebrand factor/factor VIII, vasopressin, and thrombocyte concentrates as indicated.

Second line therapy and mechanisms of pharmacoresistance

Anticonvulsant treatment of tumor associated epilepsy is often not very effective. One hundred and thirty-two patients (40%) in the unselected low-grade glioma series reported by Chang *et al.* had uncontrolled seizures before surgery [24]. One should expect that over time 60–70% of patients continue to have seizures despite treatment with AEDs. Hildebrand *et al.* analysed a series of 234 primary brain tumors including 93 patients with low-grade gliomas (40%) for epileptic seizures during follow-up after surgery. They noted at least one seizure within two months in two-thirds of their patients, 88% of which were treated with antiepileptic drugs [49]. Chang *et al.* reported 108 patients with persistent and 73 with recurrent seizures at 18 months among 269 LGG patients (67%) presenting with epilepsy [24].

Several anticonvulsants have been recommended as add-on anticonvulsive therapy, if first-line therapy fails [70, 80, 98, 114]. Combining valproic acid and levetiracetam may be a good first choice, if monotherapy with either drug is insufficient. Levetiracetam and gabapentin both can be used as add-on agents if monotherapy with other antiepileptics, such as carbamazepine, lamotrigine, oxcarbazepine, phenytoin or topiramate, has turned out to be ineffective. Pregabaline and zonisamide may also be used for add-on treatment. Various clinical trials with add-on levetiracetam showed a substantial reduction of seizure frequency [70, 72, 114].

Pharmacological treatment may fail because of a loss of receptor sensitivity, tumor growth, overactivity of AED-resistance pathways [105] or because of pharmacokinetic and pharmacodynamic interactions with concomitantly administered medications and chemotherapy. Genes encoding different MRPs have been shown to be up-regulated in human epilepsy and brain tumors. These proteins are constitutively expressed in human endothelial cells and contribute to the function of the blood–brain barrier. Up-regulation of these genes may limit the access of drugs to the brain. This appears to be one important cause of pharmacoresistance of seizures associated with brain tumors [21, 64]. Whereas there is evidence that carbamazepine, phenytoin and phenobarbital as well as lamotrigine and topiramate are substrates for multidrug resistance protein-1 (MRP1) [64], levetiracetam does not seem to

be affected by MRP1 expression or other multidrug resistance proteins (see above). It has been suggested that valproic acid might even reduce the expression of MRP1 via its histone deacetylase-inhibiting effects [106].

Key facts and conclusion

- Seizures complicate the clinical course of >80% of patients with LGG. Medical therapy alone will frequently fail to control symptomatic epilepsy in LGG patients. In contrast, surgery will often control tumor-associated epilepsy. Irradiation and chemotherapy may have some minor beneficial effects on the patients' seizure disorder.
- Seizure control in patients with drug-resistant epilepsy requires 'epilepsy surgery' rather than a simple gross total tumor resection, i.e. the removal of epileptogenic brain tissue in addition to the tumor.
- Enzyme-inducing antiepileptic drugs (EIAEDs, i.e. carbamazepine, phenytoin, and phenobarbital) are no longer first choice AEDs for tumor-related seizures. Use of the newer (second generation) non-enzyme inducing antiepileptic drugs (non-EIAEDs), such as levetiracetam, gabapentin, pregabalin, zonisamide, as well as lamotrigine and topiramate, is encouraged since they do not interfere with other medications including chemotherapy.
- There is no general indication for prophylactic antiepileptic therapy in LGG patients. Patients who present with a single seizure may be treated with antiepileptics for up to 3 months. In cases with persistent seizures after surgery long-term anticonvulsive treatment is usually necessary. After surgery for drug-resistant epilepsy anticonvulsive medication is usually continued for two years.
- AED withdrawal can be considered if the tumor is stable, the patient has not experienced seizures for at least one year, and the EEG does not show abnormal discharges suggestive of an increased predisposition to seizure generation.
- Recurrent seizures after surgery (not infrequently heralding tumor recurrence) continue to pose significant clinical problems.

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Present day's standards in microsurgery of low-grade gliomas

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With 6 Figures and 2 Tables

Contents

Abstract

Low-grade gliomas are slow growing intrinsic lesions that induces a progressive functional reshaping of the brain. Surgical removal of these lesions requires the combined efforts of a multidisclipinary team of neurosurgeon, neuroradiolo-

gist, neuropsychologist, neurophysiologist, and neurooncologists that all together contribute in the definition of the location, extension, and extent of functional involvement that a specific lesion has induced in a particular patient. Each tumor has induced particular and specific changes of the functional network, that varies among patients. This requires that each treatment plan should be tailored to the tumor and to the patient. When this is reached, surgery should be accomplished according to functional and anatomical boundaries, and has to aim to the maximal resection with the maximal patient functional preservation. This can be reached at the time of the initial surgery, depending on the functional organization of the brain, or may require additional surgeries, eventually intermingled with adjuvant treatments. The use of so called brain mapping techniques extend surgical indications, improve extent of resection with greater oncological impact, minimization of morbidity and increase in quality of life. To achieve the goal of a satisfactory tumor resection associated with the full preservation of the patients abilities, a series of neuropsychological, neurophysiological, neuroradiological and intraoperative investigations have to be performed. In this chapter, we will describe the rationale, the indications and the modality for performing a safe and rewarding surgical removal of low-grade gliomas by using these techniques, as well as the functional and oncological results.

Keywords: Low-grade gliomas; brain mapping; fMRI; fiber tracking; neuropsychology.

Introduction

The term low-grade glioma refers to a series of primary brain tumors characterized by benign histology (low proliferation, low neo-angiogenesis phenomena) and aggressive behaviour related to the slowly progressive tendency to invade the normal brain parenchyma [22, 64, 80, 84, 107, 131]. These neoplasms are classified as grade II (out of IV) by the World Health Organization classification of brain tumors and include the following entities: grade II astrocytoma (further divided in fibrillary and protoplasmic), grade II oligoastrocytoma and grade II oligodendroglioma [72, 73]. Pilocytic astrocytomas, or grade I astrocytomas, are occasionally referred to as low-grade gliomas but due to their peculiar behaviour, require separate considerations. In this chapter, the term low-grade glioma will refer only to grade II tumors of the WHO classification.

Low-grade gliomas are slow growing tumors, typically affecting younger individuals (median age 35), mainly males (male/female ratio 1.5) which clinically present with seizures (often partial seizures) [83]. Headache, personality changes and focal neurological deficits represent the other most common symptoms. The neurological symptoms include motor/sensory deficits, dys-

phasia/aphasia, disinhibition, apathy, visuo-spatial disturbances and others according to the tumor location and size [22, 97, 110]. Interestingly, some authors reported the tendency of low-grade gliomas to occur in eloquent areas or in their proximity [40].

Overall, the median survival of low-grade gliomas is about 10 years and well defined negative prognosticators include older age (more than 40 years old), larger size (more than 5 cm), eloquent location and reduced Karnofsky performance status.

The optimal treatment for low-grade gliomas has yet to be determined. In fact, watchful observation, needle biopsy, open biopsy as well as surgical resection have all been advocated by different authors [10–12, 41, 44, 64, 81, 95, 106, 118, 135]. No evidence of class I, II or even III exists regarding the optimal management of these patients, even if the more modern tendency is to obtain at least some type of tissue diagnosis [67, 130]. Briefly, the rationale behind the observational or "wait and see" policy was the occasionally indolent or very slowly progressive behaviour of these tumors [81, 109, 135]. On the other hand, following the modern oncological concepts, some authors proposed to perform a biopsy in order to have a histopathological confirmation of the nature of the neoplasm before deciding the further management. Surgical resection of low-grade gliomas is still matter of debate but recent studies are increasingly supporting its role [10, 12, 26, 45, 67, 126, 130]. Surgery can in fact achieve multiple aims: first, it allows to obtain a more reliable histological diagnosis with eventually the molecular profile (e.g. 1p/19q loss and MGMT status); second, it permits to relieve symptoms; third, it has a beneficial effect on seizure control; in addition, surgery could decrease the rate of recurrence and of malignant transformation, as confirmed by recent studies [26, 45, 130]. Nevertheless, surgery carries its unavoidable risks, which even though low can potentially and permanently affect the patient quality of life.

Given this general information on low-grade gliomas behaviour and the possibility of treatment, it is clear that a modern surgical approach to low-grade gliomas has the goal to maximally resect the tumor mass, while at the same time minimizing the postoperative morbidity in order to preserve patient's functional integrity [12, 26, 45, 130]. In fact, since the natural history of the tumor can be relatively long (with or without surgery), the conservation of simple and complex neurological functions of the patients is mandatory. To achieve the goal of a satisfactory tumor resection associated with the full preservation of the patients abilities, a series of neuropsychological, neurophysiological, neuroradiological and intraoperative investigations have to be performed. In this chapter, we will describe the rationale, the indications and the modality for performing a safe and rewarding surgical removal of low-grade gliomas.

Rationale and indications

The major aims of surgical treatment are: 1) obtaining adequate specimens and representative tissue to reach a correct histological and molecular diagnosis; 2) achieving a cytoreduction in order to decrease the rate of recurrence and malignant transformation, possibly prolonging survival; 3) improving the neurological symptoms of the patients; 4) obtaining a better seizure control. These goals can be reached by tailoring the surgical approach on the peculiar features of location, modality of growth, and biological behaviour of low-grade gliomas.

Histological and Molecular Diagnosis: It is well known that astrocytomas or more in general primary brain tumors represent a challenge for the neuropathologist, mainly in the choice of the grading of the tumor. In fact, the specimens available are often not adequate in terms of size (e.g. needle biopsy) or not representative of the tumor to permit an accurate diagnosis. The size or the number of needle biopsy specimens does not always allow to perform all the eventually required immunohistochemical or molecular analysis, reducing the pathologist armamentarium for a correct diagnosis. In addition, the problem of the site of the biopsy can significantly change the final results because gliomas are typically very heterogenous and can have areas with different grades of malignity. Recently, the use proton MR spectroscopy of MR perfusion can partly overcome this last problem, giving informations on the presence of choline peaks (index of membranes production and malignancy) or areas of increased angiogenesis which can guide the surgeon in the decision of the best location for performing the biopsy [23, 50, 57]. In any case, the risk of underestimating, or more rarely overestimating, the grade is a concrete possibility for needle and even open biopsies eventually resulting in significant changes in the choice of the most appropriate treatment for the patients.

Molecular markers have become a standard for the determination of the type of low-grade glioma. In fact, chromosome 1p/19q loss of heterozygosity plays a very important role in the distinction between oligodendrogliomas and astrocytomas or oligoastrocytomas. The relevance of this molecular marker stays not only in the histotype definition but also in the different therapeutic implication [6, 24, 65, 129, 134]. In fact 1p/19q loss, as well as MGMT methylation (another important marker) resulted to be able to predict the response to certain chemotherapeutic agents [24, 48]. Obviously, inadequate or incorrect sampling of the tumor can dramatically impair the possibility of a molecular analysis.

Cytoreduction, Size and Location: Most of low-grade gliomas are localized close or within the so called eloquent areas, such as the areas of the brain which control motor, language or visuospatial functions. In a recent series, as well as in the experience of our group, 82.6% of tumors were located within eloquent motor or language areas (27.3% of cases within the SMA, 25.0% in the insula,

18.9% in language centers, 6.0% in the primary somatosensory area, 4.5% in the primary motor area) [6, 40]. As for the modality of growth, these tumors are characterized by a prevalent diffusive pattern of growth [40, 86]. In fact, groups of tumor cells or single tumor cells diffuse away from the main tumor mass along vessels or short and long white matter tracts [80]. These features are responsible for the typical aspect of low-grade gliomas seen in MR images, which is characterized by a morphology strictly resembling that of white matter tracts along which the tumor grows and diffuses. In addition, despite their occasional apparently indolent behaviour, low-grade gliomas are characterized by a continuous growth, with periods of faster and lower rates of growth during the entire time of the natural history of the tumor [86]. Some authors pointed out that most of the lesions judged as stable, actually did show various degrees of growth, and that minor changes in the diameter (e.g. 1–2 mm) reflect a significant cellular growth in term of volume [86]. For sake of simplicity, the rate of growth of a tumor can be quantified by measuring the maximal diameter onto FLAIR MR images. Repetitive measurement on representative sections demonstrated that the tumor continuously grows and that the mean increase of the tumor diameter is around 4 mm/year. Furthermore, an increase in tumor diameter larger than 8 mm/year, even in the absence of contrast enhancement or modification of T2 or FLAIR images, is associated with a high tendency toward malignant transformation and aggressive biological behaviour [105]. These data stress the point that serial measurements of tumor volumes are an important tool to determine the biological behaviour of the tumor. At the same time, it is clear that tumor volume is an important prognostic factor, able to determine per se the biological behaviour of the tumor overtime. In fact, larger tumor volumes are more frequently associated with a higher risk of malignant transformation and shorter patient survival [130]. Obviously, tumor volume is associated with the risk of developing neurological symptoms, increase in the risk of seizures, and probability of impacting in the social and professional life of patients.

Neurological symptoms: The majority of patients who are diagnosed with low-grade gliomas usually come to medical attention because of sudden occurrence of seizures [97, 130]. These patients are generally intact at the gross neurological examination, but they frequently present more subtle symptoms affecting complex neurological functions (memory, language, character, visuo-spatial orientation, etc.) which require a specific testing by a neuropsychologist [17, 53, 54, 55, 114]. As will be detailed below, this type of testing is mandatory when considering surgery for this type of lesions because it allows to tailor the intraoperative testing to the patient and permits to finely assess the impact of surgery on the patients superior neurological functions [1, 2, 59, 75, 76, 133].

Those patients who present with frank neurological deficits (e.g. hemiparesis, ataxia, aphasia) are usually candidate to surgery because their symptoms

are related to direct mass effect of the tumor on the cortex or on the subcortical white matter tracts. In this case, tumor removal can significantly relieve symptoms depending on the degree of the preoperative impairment as well as on the degree of parenchymal disruption. Obviously, this category of patients carries higher surgical risks in terms of morbidity and mortality than that of neurologically intact patients. Nevertheless, in terms of surgery, the presence of mass effect is a straightforward indication for tumor resection since a waiting policy will quickly bring to further neurological deterioration and even death in a limited span of time.

Seizures: Large tumors and insular locations are usually associated with a higher risk of developing seizures, which are difficult to be controlled by antiepileptic drugs, requiring the administration of multiple medications [25, 60]. Despite poly-therapy, seizure control can still be very poor. In these latter cases, surgery becomes an appealing option to improve seizure control. In fact, it has been clearly shown that surgical resection of low-grade gliomas is associated with a marked improvement in terms of seizures occurrence. In other cases, patients might be severely disabled by the side effects of multiple anti-epileptic medications and again surgery can allow to decrease the drugs administration. It is matter of debate whether surgical resection of low-grade gliomas for seizure control should be performed in an epilepsy surgery setting (with surface and eventually deep electrodes recordings, with resection of all the foci) or in a purely oncologic setting (with neurophysiologic monitoring including electrocorticography, but no deep electrodes and no resection of normal brain foci).

As mentioned above, surgery for gliomas aims to maximally remove the tumor mass and at the same time to preserve patient's functional integrity. This policy applies to the resection of any glioma but more specifically to those located close or within eloquent areas. The concept of eloquence refers not only to those areas which are involved in motor, language or visuospatial functions but also, more widely, to any area affecting the well-being of the individual (e.g. memory, socio-affective behaviour, specific tasks performance, etc.). In all these cases, extensive resection and maximal functional integrity can still be achieved through the intraoperative use of brain mapping techniques [6, 11, 12, 14, 36, 41, 45, 130].

The brain mapping technique

Performing brain mapping requires a series of pre-operative evaluations and intra-operative facilities which involve different specialists. A complete neuropsychological evaluation is generally the first step of the process permitting to select the suitable patients and to individualize the intraoperative testing. Then, sophisticated imaging techniques including fMRI and DTI-FT (Diffuse Tensor Imaging, Fiber tracking techniques) give the opportunity to attentively plan the

surgical strategies. In addition, these images can be loaded into the neuronavigation system becoming thus available peri- and intraoperatively for orientation. Intraoperative MR can be used as well, if available. Finally and most importantly, a series of neurophysiological techniques are employed at the time of surgery to precisely guide the surgeon in the tumor removal. These include cortical and subcortical direct electrical stimulation (DES), motor evoked potentials (MEP), multichannel EMG, EEG and ECoG recordings. All these techniques will be detailed in the next paragraphs. For reasons of simplicity, the management protocol will be divided in three parts: pre-operative, peri-operative, and post-operative.

Pre-operative protocol

The pre-operative part includes the neuropsychological and neuroradiological evaluation, which complete the standard neurological exam. A neuroanesthesiological evaluation should be performed as well for the selection and preparation of the patients from this perspective.

Neuropsychology

Neuropsychological evaluation is composed of a large number of tests for the assessment of various neurological functions such as the cognitive, emotional, intelligence, and basic language functions. Such a broad spectrum evaluation provides information on how the tumor has impacted on the social, emotional and cognitive life of the patient, who is generally intact at the neurological exam. It is important that the testing is the largest possible because the tumor which grows along fiber tracts, may alter the connectivity between separate areas of the brain, resulting in the impairment of functions which might not be documented in case of a neuropsychological examination limited to the testing of those functions strictly related to the area of the brain in which the tumor has grown [6, 42, 45]. When this extensive testing is administered, some alterations in the aspects of the neuropsychological exams can be documented in more than 90% of the patients [6, 45]. These data represent the baseline toward which the effect of surgical and future treatment should be compared. Additionally, when the tumor involves language or visuospatial areas or pathways, a more extensive specific evaluation should be added. Other than better defining the preoperative status of the patients, the neuropsychological assessment allows to build up a series of tests, composed of various items, which will be used intraoperatively for the evaluation and the brain mapping of various functions, among which memory, language in its various components, and visuospatial orientation are some of the most important. For language evaluation, patients are submitted preoperatively to extensive language testing composed of a battery of tests aimed to evaluate oral language production and comprehension, together with repetition [6, 36, 43, 103].

Table 1. *Neuropsychological assessment before and after surgery for low-grade glioma (Milano battery)*

Language examination (BADA): This is a psycholinguistic battery, exploring the sublexical, lexical, and morphosyntactic aspects of language and includes nonword and word repetition, sentence and phrase repetition, phonological discrimination
+
Token Test (norms and adjusted score for age and education)
Verbal fluency on phonological and semantic cue (norms and adjusted score for age and education available)
Word comprehension (alternatives of the same semantic category) (48 stimuli)
Object picture naming [six semantic categories: living (animals, fruit, vegetables) and non living (cloth, vehicles, tools)] (48 stimuli)
Action Picture Naming (50 stimuli)
Auditory Sentence Comprehension (80 stimuli)
Famous Face Naming (100 stimuli: 50 famous faces and 50 unknown) (norms and adjusted score for age and education available)
Short term memory:
Digit span (norms and adjusted score for age and education available)
Digit span backward
Corsi span (norms and adjusted score for age and education)
Assessment of long term memory:
Rey-Osterrieth complex figure test – delayed recall (norms and adjusted score for age and education available)
Prose recall (norms and adjusted score for age and education available)
Rey 15-word list learning (norms and adjusted score for age and education available)
Assessment of executive function and attention:
Verbal fluency on phonological cue (norms and adjusted score for age and education available)
Wisconsin Card Sorting Test (norms and adjusted score for age and education available)
Visual search, Stroop test, Trail making Test (norms and adjusted scores for age and education available)
Weigl Test (norms and adjusted score for age and education available)
Gambling Task (in case of frontal lesions)
Apraxia:
Face apraxia test (norms and adjusted score for age and education available)
Ideomotor apraxia test (norms and adjusted score for age and education available)
Rey-Osterrieth complex figure test – Copy (norms and adjusted score for age and education available)
Assessment of visuo-spatial abilities:
battery of tests like: letter cancellation, line cancellation, star cancellation, line bisection, sentence reading and copying task

(*continued*)

Table 1. (*continued*)

Line bisection (10 cm–15 cm–25 cm) (norms and adjusted score for age and education available)
Albert Test (norms and adjusted score for age and education available)
Diller Test (norms and adjusted score for age and education available)
Star Cancellation Test (norms and adjusted score for age and education available)
Copying Task
Sentence reading
Clock Drawing Test

Hemispheric language dominance is evaluated through the Edinburgh Inventory Questionnaire and fMRI. The following tasks are usually performed: Spontaneous speech; Oral controlled Association by Phonemic Cue; Famous face naming; Object Picture Naming; Action Picture Naming; Word Comprehension; Sentence Comprehension; Transcoding tasks. In addition the Token Test, the digit span, and counting are also performed. Ideomotor apraxia and face apraxia are also assessed. The majority of the tests generally used have been standardized on the normal population. In addition, different tests aimed to study the previous aspects of language can be found and adjusted according to the nationality of the patient. Generally, some tests as the BADA are available in different languages, others have to be normalized to the population. The list of the tests generally used in our center is reported in Table 1. It is important to include in the battery both qualitative and quantitative tests, and normative data must be available for the quantitative procedure. It is also important that a Speech therapist and a (neuro-)psychologist are managing the patients assessments. As mentioned above, preoperative language evaluation is also used to build up a series of tests, composed of various items, which will be used intraoperatively for the assessment of language during surgery. Among these tests, the object naming is probably the most important. In case of tumor located in dominant or parietal areas, number recognition and reading, as well as calculation or writing should be added in the preoperative testing and considered for the intraoperative evaluation [35, 51, 121]. When the patient is bilingual or is speaking more than two languages, it is important to include a large evaluation of the various languages in the preoperative testing [5, 52, 85, 120, 123]. Accordingly, the patient can be defined as early or late bi- or multi-lingual, depending on the time at which he or she has learned the various languages. In any case, a multi-lingual assessment is generally recommended.

Visuospatial functions are usually evaluated for tumor located in the parietal lobe, generally on the right side [45]. Unilateral spatial neglect is a complex and disabling syndrome that tipically results from right hemisphere damage, and it is characterized by an impairment of awareness of contralesional left half

of space, objects and mental images. In this case, the patient is presented with various tests such as the line bisection test or the star cancellation test to evaluate his or her spatial awareness (Table 1).

Imaging and neuroradiology

The neuroradiological examination is composed of basic exams, such as morphological T1, T2, and FLAIR images, as well as post contrast T1 images. These images together with volumetric sequences provide information on the site and location of the tumor, and allow to determine its relationship with various structures, such as major vessels, and to measure tumor volume. Further MR studies include MR spectroscopy, which provides information on the metabolic characteristics of the tumor, and allows to design a map of areas within the tumor in which tumor metabolism is more or less pronounced (multi-pixel MR spectroscopy map) [50, 57]. This is of great help in the tissue sampling at the time of surgery for histological and molecular purposes. In addition, perfusion MR studies are useful for designing perfusion maps, or maps in which the blood flow is depicted in the different tumor areas [8, 32, 79, 92, 93]. Being the regional blood flow dependent on tumor angiogenesis, these maps provide additional and complementary information of the biological behavior of the tumor and help in the tissue collection for histological and molecular purposes at the time of surgery [23]. Metabolic information may be also obtained by performing SPECT or PET, and these data may be incorporated into the navigation system for surgical guidance as well.

The neuroradiological investigations include functional studies, such as fMRI, and anatomic studies such as DTI-FT. The former provides functional information on the location of cortical sites which activates in response to motor tasks, or various language tasks [15]. Motor fMRI is generally used to design a map of the cortical motor sites and to establish their relationship with the tumor [62]. fMRI for language provides a map of the cortical sites which activate during various language tasks, such as denomination (object naming), verb generation, verbal fluency [121, 124]. All these data are put together to form a complex map of how the various components of language are organized at the cortical level and allow to establish the spatial relationship between these cortical areas of language activation and the tumor mass. It is usually recommended that language fMRI is performed with the same tests that are used for language evaluation in order to increase its reliability.

DTI-FT techniques allows to depict the connectivity around and inside a tumor, by reconstructing and visualizing the fiber tracts which run around or inside the tumor mass [4, 21]. DTI FT provides anatomical information on the location of motor tracts, mainly the corticospinal tract and various language tracts [7, 13, 27, 56, 63]. For a better visualization of tracts in low-grade gliomas, a FA (Fraction of Anisotropy) of 0.1 should be used, and additional

ROI for particular tract such as the anterior part of the superior longitudinalis or the SMA portion of the CST can be added [7]. The basic DTI FT map includes the CST for the motor part, and the such as the superior longitudinalis (SLF) which includes the fasciculus arcuatus, and the inferior fronto-occipital (IFO) tract for the language part [7, 36, 43]. The SLF is the basic tract involved in the phonologic component of language, the IFO is the basic tract involved in the semantic component of language. Additional tracts that can be reconstructed are the uncinatus (UNC) and the inferior longitudinalis (ILF) tracts, which provide information on the semantic and phonologic component of language in the frontal and temporal lobe, or the subcallosum fasciculus, involved in the phonologic component of language, sited in the lateral border of the lateral ventricle. Generally, preoperative DTI FT show that in low-grade gliomas most of the tracts involved either in language or motor function, are located within the tumor mass, and infiltrated or interrupted by the tumor. Although DTI FT maps are only anatomical and do not provide any functional information, DTI FT map can be used to predict resectability of a tumor. Globally considered, preoperative neuroimaging produces an impressive amount of information concerning the anatomical and functional boundaries of the lesion to be resected. Together with the volumetric morphological images, the DTI-FT images are usually loaded into the neuronavigation system, and help in the perioperative period in performing the resection. However, the imaging gives information based on probabilistic measurements, and although they may have a relatively high sensitivity or specificity, they still carry a certain amount of mistake which cannot, at least nowadays, be considered as sufficient for performing a safe and effective resection. This is the reason why the neuroradiological information loaded into the neuronavigation system has to be always supported during surgery by the results of the brain mapping. In other words, only the intraoperative brain mapping by means of electrical stimulation allows the surgeon to identify functional regions, that may be displaced and infiltrated by the tumor both at a cortical and a subcortical level, and thus to define the strategy of resection in order to maximize the extent of tumor removal while reducing the risks of permanent neurological deficits.

Anesthesiology

Besides the standard anesthesiological work up, the patient should be examined for his or her ability to be submitted to intraoperative awake monitoring when needed. A preparation and selection of the patients by anesthesiologists with expertise in awake surgery is recommended [29, 30]. In our Institution, the only absolute contraindication to awake surgery are the lack of cooperation, patients older than 65 years, or carrying obesity, those with difficult airways or affected by severe cardiovascular or respiratory diseases.

Intraoperative protocol

General policy of the surgical treatment is to remove the maximal amount of tumor and to preserve the functional integrity of the patient. This can be done by removing the tumor according to anatomical and functional boundaries. The anatomical boundaries can be defined by using neuronavigation or intraoperative MR; the functional boundaries can be defined by using neurophysiological, and neuropsychological adjuncts. The intraoperative protocol includes: anesthesia modalities; neurophysiology; neuropsychology; intraoperative imaging (neuronavigation and intraoperative MR).

Anesthesia

The patient can be maintained either awake for the full time of surgery, or awakened for the phase of the surgery during which the mapping is performed [5–7, 29, 30, 35, 36, 46, 127, 130]. Total intravenous anesthesia with propofol and remifentanil is used in our Institution for performing these procedures. In patients requiring only motor mapping, the patient is intubated through the nose and a light surgical anesthesia is maintained throughout the procedure. No muscle relaxants are employed during surgery to allow the neurophysiological assessment. When the language or the visuospatial functions have to be tested during surgery, the patients receive a laryngeal mask, which is maintained till after the craniotomy and dural opening [49]. At this point, the patients are awakened, while adequate analgesia is maintained, to allow functional monitoring. Time for awakening varies between 20 and 50 min, depending on the ability of the patient to metabolize the anesthetics. The anesthesiologist should be able to keep the patient awake for the entire time of subcortical mapping, which may require particularly during long lasting operations, to alternate period of resting with those during which the patient is fully awake and responsive. Patients fatigue is observed in most of the patients, and its appearance correlates with the duration of the mapping, and the difficulties of the testing (extensive language and visuospatial mapping) [5, 47, 50, 137]. Five percent of patients require the suspension of the mapping for a period longer than 20 min. The occurrence of seizures is the most important complication during the awake time of surgery, and can be controlled either by cold saline irrigation or by the infusion of a small bolus (1 ml) of propofol. Vomiting is a rare complication, and can be controlled by the administration of anti-emetics at the beginning of the phase of mapping [88].

Neurophysiology

The major components of the neurophysiological protocol are EEG, ECoG, EMG, DES and MEP techniques. The protocol includes mapping and monitoring procedures [9, 11, 16, 19, 28, 114, 117, 138].

In our Institution, EEG activity is recorded bilaterally by four subdermal needle electrodes, providing four bipolar leads. EEG is registered to monitor brain activity when EcoG is not available, i.e. at the beginning and the end of surgery, and, moreover, to assess brain activity at distance from the operating field, such as the contralateral hemisphere.

EcoG activity from a cortical region adjacent the area being stimulated is recorded by subdural strip electrodes with four to eight contacts, in a monopolar array, referred to a midfrontal electrode. Cerebral activity was recorded with a bandpass 1.6–320 Hz, and displayed with a sensitivity of 50–100 micron/cm for EEG and 200–400 micron/cm for EcoG. Continuous electrocorticographic recordings (Comet, Grass) are used during the entire duration of the procedure, to monitor the brain basal electrical activity, to define the working current (as that immediately below the one which induced an afterdischarge), to monitor for the occurrence of afterdischarges or electrical seizures during the resection.

A continuous multichannel EMG recordings (Comet, Grass) is used throughout the entire duration of the procedure. Several separate muscles belongings to agonist or antagonist muscles are monitored, either in the contralateral or ipsilateral body. Motor responses are collected by pairs of subdermal hooked needle electrodes inserted into contralateral muscles from face to foot. Each pair of electrodes records two different muscles in the same body segment, in order to sample as many muscles as possible (i.e. a flexor and an extensor muscle in the forearm). A number of 16 channels are used on average for each procedure. The most used setting is comprehensive of face (upper and lower face), neck, arm, forearm, hand, upper leg, lower leg. A computerized video and image capturing system is continuously coupled with the EMG recordings (Comet, Grass), to further monitor and register the motor activity. In addition to EMG recordings, motor activity is also evaluated clinically.

Direct electrical stimulation (DES) for cortical and subcortical mapping is performed by the use of a bipolar hand-held stimulator with 1-mm electrode delivered stimulation, according to Berger and coll., tips 5 mm apart, connected to Ojemann Cortical Stimulator (Integra Neuroscience) or a Osiris stimulator (Inomed, Germany), which is delivering biphasic square wave pulses, each phase lasting 1 ms, at 60 Hz in trains lasting 1 s for cortical mapping and 1–2 s for subcortical mapping. For subcortical mapping, either the same current used for cortical mapping or a current raised of 2 mA, is applied, and the stimulus is continuously alternated with resection.

For continuous monitoring of motor function, MEP recordings can be performed. The train of five technique, being introduced for surgery in anesthetized patients has been described as sensitive to detect imminent lesions of the motor cortex and the pyramidal pathways. A strip electrode containing 4 to 8 electrodes is placed over the precentral gyrus. In awake patients a single

stimulus or a double pulse stimulus (individual pulse width 0.3–0.5 ms, anodal constant current stimulation; interstimulus interval 4 ms, stimulation close to motor threshold) is usually delivered. The muscle motor evoked potentials (MEP) have to be recorded with either needle or – more convenient in awake patients- with surface EMG electrodes. MEP recordings is usually alternated with direct cortical motor mapping.

The purpose of the mapping procedure is to reliably test motor, language and cognitive function. For starting the mapping procedure, the initial activity is to define the stimulation parameters. As previously reported, a low frequency of 60 Hz is used, and the initial work is to establish the working current. As movement is easy to observe, it is advisable to start the procedure with mapping of motor function. Once determined the intensity of the current for stimulation, the same is used in most of the cases throughout the procedure, also for the mapping of cognitive and language functions. Initially, a low current intensity (2 mA) is used, and then progressively increased till a movement is induced. A stimulus duration of 1 or 2 s is usually enough to generate a motor response. At this point, it is good practice to stimulate the areas close to that in which the current induced the movement, in order to map them and to check if the current is able to evoke motor responses also in these zones. If not, the current intensity may be increased and adjusted in order to evoke appreciable motor responses. It is also recommended to check with the ECoG if the applied current may induce afterdischarges, in the nearby brain areas. In fact, only the current which is immediately below those which are inducing afterdischarges have to be used for mapping. If afterdischarges are seen, the current should be set up at least 0.5 mA under the previous one. In any case, ECoG recording is used to detect the appearance of afterdischarges during mapping, in order to keep the test reliable. In fact, only the responses evoked in absence of afterdischarges are considered to be trustworthy (Fig. 1).

For language mapping, the current which has evoked motor responses is tested. The initial test used is counting. The current is usually applied onto the face premotor cortex, and the test is aimed to check if the current is able to stop the patient to count. This has to be repeated several times and the counting to be stopped at least three times, in order to be reliable. If not, the current intensity is increased till this is produced. When the current is establish, the current is applied to whole brain surface exposed, and the occurrence of afterdischarges checked in the ECoG. The duration of the stimulus is between 3 to 4 s. Only the current which is not inducing afterdischarges in the entire brain surface to be mapped is used for mapping. In case of afterdischarges, the current intensity is decreased at least of 0.5 ms.

For cortical mapping, it is common practice to stimulate the whole of the exposed cortical area every 5 mm^2, to avoid the stimulation of the same cortical area twice consecutively. Each site have to be tested at least 3 non consecutive

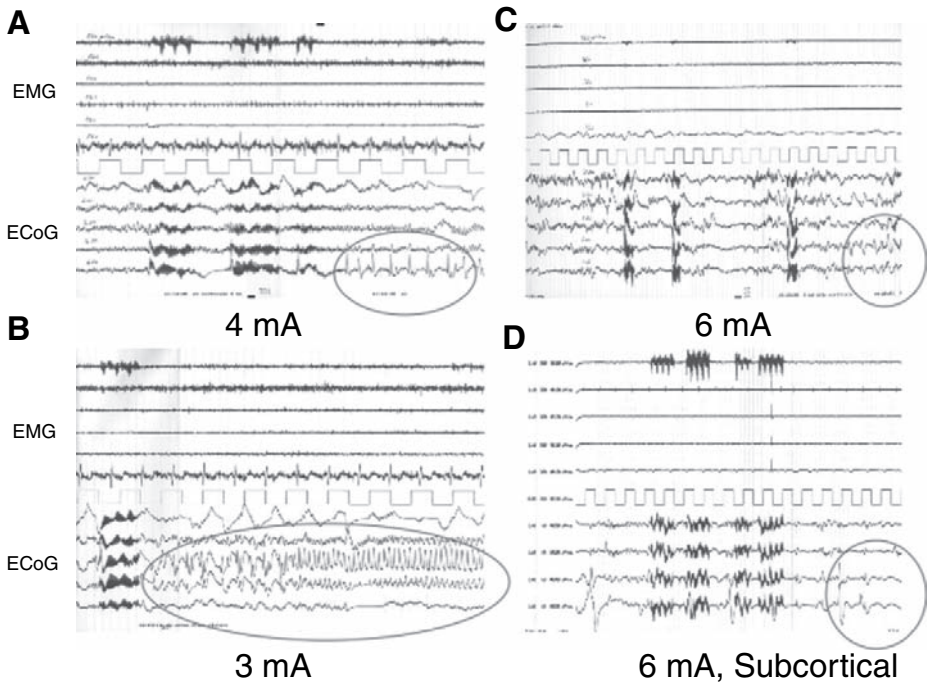
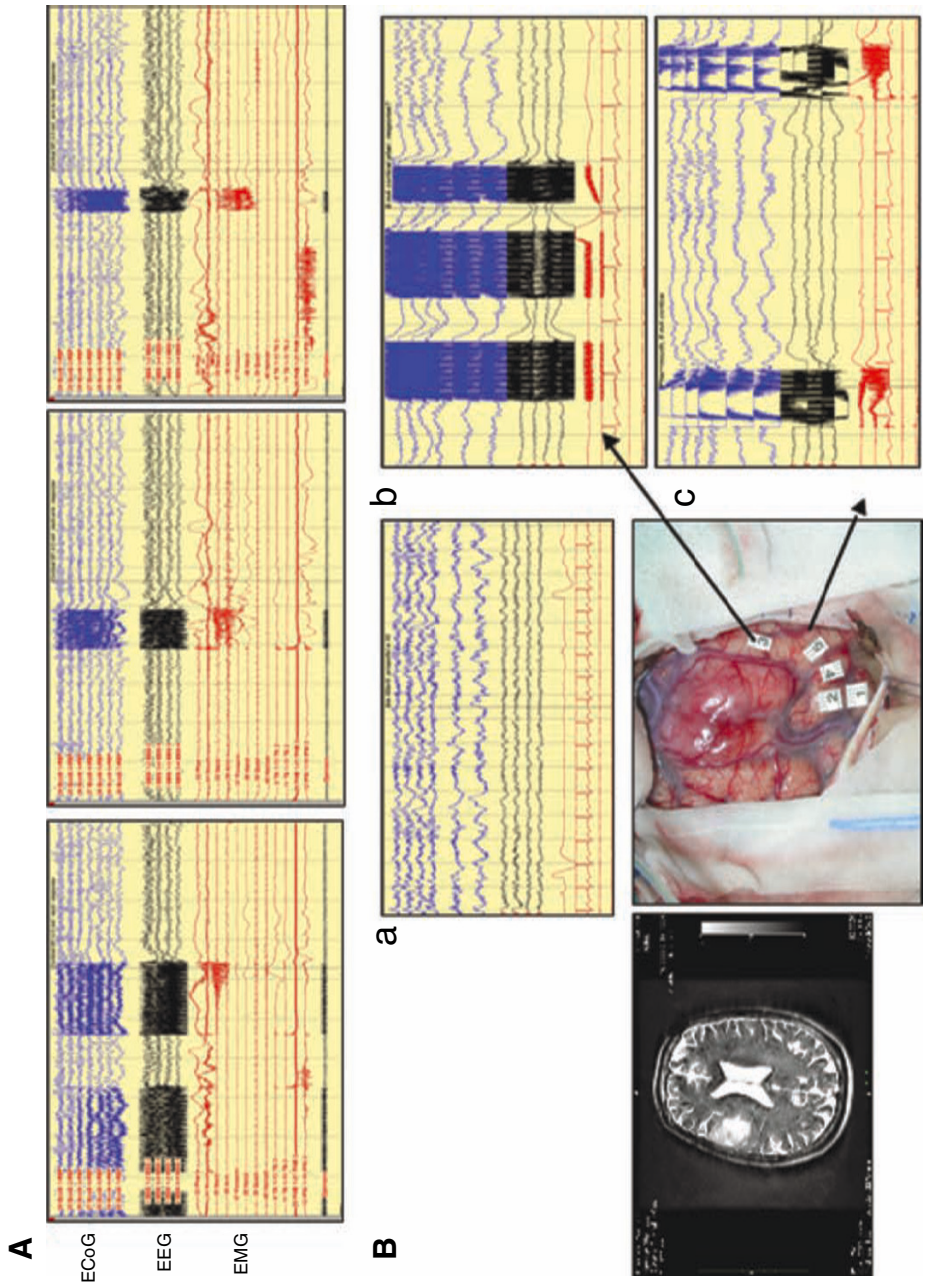


Fig. 1. ECoG monitoring during cortical and subcortical mapping. A, B) ECoG can be used to monitor the occurrence of afterdischarges. Afterdischarges (encircled) can appear as single or short train for spikes after the application of a stimulus. Intensity which can elicit the apperance of afterdischarges may vary according to the exitability of the cortex. C) Occasionally, spikes can organized and a electrical seizures may occur. EMG (upper lines) shows that no clinical activity was present. The electrical seizure was controlled by cold irrigation, D) rarely, single spikes may occur also during subcortical stimulation, when the stimulus is applied in the upper part of the pathways, not too far from the cortex

times before considering it either positive or negative. This is done to check the reproducibility of the responses, and to avoid the generation of responses due afterdischarges or electrical seizures.

It is important to keep the surfaces to be stimulated moist, not to stop mapping after identifying only one eloquent site, but to search for possible redundancies; a negative mapping does not protect, but creates the problem of questionable stimulation reliability. Stimulation intensity should be decrease during "control stimulations" in areas of "decompressed" brain tissues, in order to limit the risk of inducing a seizure. During deviation from optimal stimulation intensities, intra-operative electrocorticography can be very useful.

For subcortical motor mapping, the evoked responses are checked with EMG recording or clinically. For visuospatial subcortical mapping, the patient


A
ECoG
EEG
EMG
B
a
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c

is presented with bisection or the cancellation test, for language subcortical mapping with a language test composed mainly of object naming or verb generation. Also during subcortical mapping ECoG is continuosly monitored to look for the occurrence of asfterdischarges and to assess for the occurrence of seizure and for the reliability of the responses (Fig. 1).

MEP monitoring is usually used the beginning of the procedure, and helps in identifying the location of the motor strip. During resection, MEP recording is alternated with subcortical motor mapping and provide additional information of the integrity of the motor pathways.

Results of the mapping or monitoring procedures

The previously described neurophysiological protocol has been applied on 400 consecutive patients submitted at our Institution during the last three years at surgical resection of gliomas located close or within motor, visuospatial or language areas or pathways. The majority of these cases were low-grade gliomas (79%), with a mean age of 37.6 years (ranging from 16 to 68 years).

Motor mapping

Motor responses were observed in all patients with lesions located close or within motor areas or pathways. We usually map motor responses in patients with tumors located in rolandic or premotor or parietal region. In addition, motor mapping is also applied at cortical and subcortical level for lesions located in the insula or deep temporal region, in which motor pathways can be encountered during resection. For lesions located in the non-dominant hemisphere, the patient is kept under general anesthesia, and the tube positioned through the nose. This allows the placement of a series of electrodes in the inner palate and pharyngeal muscles, as well as in the tongue, which are useful to detect responses from these muscles (Fig. 2). For lesions close or within visuospatial or language areas of pathways, the patient is always awak-

Fig. 2. Cortical motor mapping. A) The stimulus is applied over the area of the brain which is supposed to be the motor cortex. Stimulation of M1 induce quite sharp tonic responses; the stimulation of the motor cortex and allows to sequentially identify the areas of the brain which stimulation evokes movements of the mouth (upper and lower lips, left panel), of the hand (central panel) and of the forearm (right panel), allowing to define the progression of the motor homunculus. B) In patients under general anesthesia, electrodes can be place into the mouth, tongue, and pharyngeal muscles, allowing to identify the portion of the motor strip involved in these movements. Evoked responses are characterized by a EMG pattern (b) which is similar to that observed during spontaneous movements (such as swallowing), during the phase of discontinuation of anesthetics (a). The intraoperative picture shows the relationship between the tumor and the motor cortex. Arrows indicate the correspondence with the EMG responses. (c) indicates upper and lower lips evoked motor responses

ened during the procedure. In case of mapping performed under general anesthesia, the current intensity range between 5 and 15 mA, and the level of anesthesia which strongly influences the excitability of the cortex can be monitored by ECoG. In case of awake patients, a current intensity ranging between 2 and 8 mA is usually enough to evoke motor responses. In these patients, there are no electrodes placed in the mouth, and the activity of the muscles of this region can be checked by monitoring the responses of the patients and by overt inspection. Awake patients are asked to relax before and during stimulation, and to assist in the description of induced movements or in the sensory changes. A stimulation duration of 1 or 2 s is usually enough to generate a motor response. Cortical stimulation induces focal motor responses. EMG recording provided an excellent view of the whole contralateral body at the same time, reducing the risk to miss responses in segments difficult to inspect, due to the position of the patient on the operating table or to detect, such as the mouth or pharyinx (Fig. 2). We observed different morphologies of EMG responses: cortically evoked responses showed great variations in amplitude, but they appeared always as continuous, tonic bursts of activity, often incrementing during stimulation. Smallest amplitudes were observed in the neck and the shoulder, or in the mouth. Occasionally in patients under general anesthesia and receiving a large amount of anti epileptic medications, it might be difficult to evoke cortical motor responses, even after the current intensity has been increased till to that which might induce the appearance of afterdischarges. In these patients, the use of MEP recording can be useful for identify the location of the motor cortex and to plan the site of incision, allowing continuing resection. During subcortical stimulation, motor responses appeared as focal (few muscles) when the tract is stimulated in close vicinity to the surface, while they appeared on multiple muscle groups with deep stimulation. Subcortical stimulation evoked both tonic bursts and on-off activity, i.e. a M-shaped response, peaking at the onset and the end of stimulation. For resection of tumors located in premotor cortex, the placement of electrodes in the ipsilateral muscles allows to detect during resection responses coming from these segments. In addition, when resection is approaching deep portion of the tumor, subcortical stimulation it allows to detect small motor responses without overt muscle activity, which indicate that the resection is becaming close to motor pathways (Fig. 3). When these warning responses are identified, resection should became particularly careful in this region and can proceed till more pronounced motor responses are identified, usually when the tip probe is touching and stimulating the motor pathways. The identification of such pathways is therefore particularly useful for performing a sage and effective resection.

The simultaneous use of CUSA and DES at subcortical level in proximity of the cortico-spinal tract may bring to the abolition of previously evident motor responses. This abolition is generally fully reversible after turning the

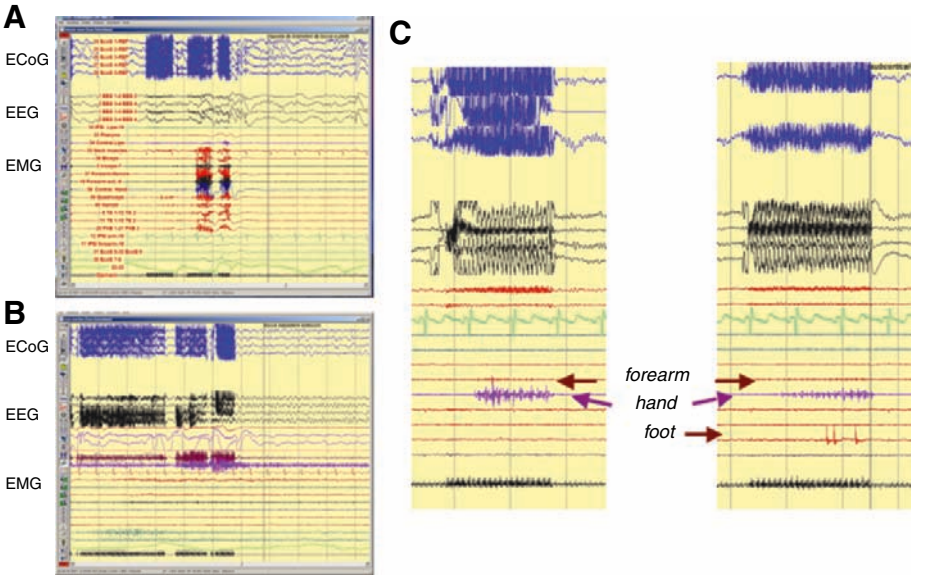


Fig. 3. Subcortical motor stimulation. A) EMG allows to monitor subcortical motor mapping responses. When the resection is approaching the internal capsule, the stimulation of the peripheral portion of the corticospinal tract induce evoked motor responses which involves all the segments of the body, from the upper to the lower arm (upper panel). B) The placement of electrodes in the pharyngeal muscles allows to identify the subcortical tracts which are involved in this function. C) The use of EMG allows to identify motor tracts before that overt motor responses are visible. This is particularly useful in the deeper part of the resection cavity, and reduce the risk of motor tract injury. The responses for the forearm, hand, and foot were not clinically visible and were induced for stimulation of deeper part of the resection cavity, close to the internal capsule

CUSA off. An analogous pattern of inhibition of motor responses can be also evident when the DES is applied cortically and CUSA used subcortically close to motor pathways. This interference with motor mapping may be interpreted as a transitory inhibition of axonal conduction. The clinical significance of this interference is relevant when CUSA and DES are used simultaneously for motor mapping because it can decrease the sensitivity of the brain mapping technique, and should be kept in mind by the surgeon when during resection is using both tools [20].

Motor monitoring

For continuous motor monitoring with MEP, a second EcoG strip electrode is placed over M1, delivering monopolar pulses to elicit Motor Evoked Potentials (MEP) in a few target muscles: MEP are monitored throughout the surgery,

except when the surgeon needs direct subcortical mapping for mapping purposes. MEP monitoring is very useful because it provides on line information of the integrity of the motor pathways during resection of large part of the tumor not closely located to functional structures. In addition, MEP provides warnings of impending brain ischemia, due to critical vessel interruption, mostly in deep temporal or insular regions [96].

Language and visuospatial monitoring

The current intensity generally applied for language mapping in awake patients is ranging between 2 and 9 mA. To identify malcompliance or impairment not related to stimulation e.g. a non-convulsive seizure, each stimulation should start before the presentation of the material started. Each stimulation should be followed by at least a task without stimulation, and two tasks are the standard. Being the duration of the stimulation longer than that for motor mapping (4 s vs. 1–2 s) repetitive stimulation might trigger afterdischarges or seizures.The stimulus is applied immediately before the item is presented to the patient, and a neuropsychologist who is present in the OR is evaluating the performance of the patient during the various tests administered at both cortical and subcortical level to maintain patient language integrity. Various type of mistakes can be encountered during the performance of the tests (Table 2). The mistakes can occasionally occur without stimulation, or more frequently during stimulation. It is important during the administration of each test to check the ECoG and EEG for the occurrence of afterdischarges or electrical seizures. Only the mistakes in the absence of ECoG disturbances are reliable. In addition, a site can be define as essential for language when it produces language disturbances at least three time in various non consecutive stimulation. Cortical language sites coding for object naming, verb generation, face naming, word or sentence comprehension, numbers or colors can be identified in several regions in the frontal, temporal or parietal lobe, which a distribution which differs according to patient and patient gender. For subcortical language mapping, the patient is asked to perform a object naming and a verb generation task during which the surgeon can continue to perform resection which is alternated with stimulaton.

Table 2. *List of the most common mistakes encountered during cortical and subcortical language mapping*

– Anomia, misnamimg or incorrect word insertion
– Phonemic paraphasia
– Semantic paraphasia
– Use of complex sentences
– Initiation disorders
– Latency of response
– Voice disturbances: sillabic modification, pseudo-accent, hypophonia

When a language disturbance is produced, the site is then carefully tested for the occurrence of semantic or phonemic paraphasia. Each tract is characterized by involvement in the semantic (inferior fronto occipital tract, uncinatus,. . .) or phonemic (superior longitudinalis, inferior longitudinalis, subcallosum) and can be recognized at a subcortical level by the appearance of semantic or phonemic paraphasia associated with typical language disturbances, such as for examples speech arrest for the subcallosum. Also during subcortical language mapping it is very important to check for the occurrence of afterdischarges or electrical seizures, in order to minitor the reliability of the testing. During subcortical mapping it is also possible to evoked motor responses, due to the identification and stimulation of motor fibers belonging either to the premotor component of the face which induce anarthya, or to the corticospinal tract, which induce various type of muscle activation depending on the location and deep of stimulation. Generally, this occurs in 20% of cases.

Visuospatial mapping is performing usually in patients with lesions located in the parietal lobe, and in case of dominant location it is intermingled with language mapping. The patient is usually requested to look at the appearance of a line in a touch screen and to bisect the line, by touching its center with a pen. A deviation toward right or left over 2 cm is usually considered as pathologic, and associated with an interference in the visuospatial function. The current intensity is the same as for cortical motor mapping. The same procedure is also performed at subcortical level by using the same current intensity or a current up to 2 mA over the previous one. Subcortical visuospatial mapping identified a small and discrete tract usually running al the lateral mid border of the tumor which is involved in this function. The preservation of this tract as well as of the cortical sites, prevents the occurrence of neglect during the post operative course. As for language and motor mapping, ECoG and EEG should be monitored during the entire duration of the test to check for its reliability.

EEG and ECoG monitoring

EEG and ECoG recordings should be kept during the entire duration of the procedure because it allows to monitor for the occurrence of afterdischarges, electrical seizures or even clinical seizures. Group of ECoG spikes or electrical seizures occur in up to 30–40% of cases, and can be or not related to stimulation. In any case, when they appear it is recommended to irrigate the cortex and the surgical cavity with cold saline, that result in the majority of the cases in the control and reversal of the situation. Clinical seizures occur in 8% of cases, and most of them are focal. The use of cold saline irrigation is able to control and totally revert most of them. In these cases, the EEG is useful to look for the cases of diffusion of the seizure, either at the same or even worse at the contralateral hemisphere. The few clinical seizures we observed appeared most frequently at the end of tumor resection, when cortical stimulation was applied

to assess the integrity of the motor pathway. The current was subsequently reduced, and no seizure was observed anymore. This stress the point that at the end of the surgical resection it might be requested to reduce the intensity current, due to the reduction of the mass effect exerted by the tumor mass of the surrounding functional parenchyma. In selected cases, ECoG can be used to detect generation of spikes in specific areas of the cortex, in close or not vicinity with the tumor mass, and that are responsible for sustaining electrical activity.

Intraoperative imaging

The neuronavigation system is loaded with morphologic volumetric T1 and T2 images, along with motor and language fMRI and DTI FT images. Neuronavigation helps during surgery to localize the tumor, and to define the relationship between the tumor and the surrounding functional and anatomic structures, both at cortical and subcortical level. As estimate for the clinical navigation accuracy, the target registration error localizing a separate fiducial, which is not used for registration, is usually performed at the beginning of surgery. The target registration error should be less than 2 mm. The main limitation of the use of a neuronavigation system, particularly in case of large tumors, is the occurrence of brain shift, which occurs already at the beginning of surgery, when the dura is opened, and increases with the progress of tumor removal [7, 66, 68, 101, 113, 125]. Resection should be performed in order to maintain the maximal accuracy of the neuronavigation system, to reduce the problem of brain shift: repeated landmark checks are performed during surgery to ensure overall ongoing clinical navigation accuracy; the use of a craniotomy limited to the minimum necessary to expose the tumor area and a limited portion of the surrounding brain, allows to minimize brain shift; in case of frontal tumors located in the proximity of CST, resection is started from the posterior border where the CST is located and, after its identification, the tract is followed inside the tumor mass. Afterwards the remaining anterior part of the tumor is removed. Similarly, in case of parietal tumors, resection is started from the anterior border following the same principle. The value of the localization of functional areas obtained from fMRI in tumors has been studied by correlating fMRI data with intraoperative cortical stimulation. For motor correlation, the results of the direct cortical stimulation matches those obtained with fMRI, both positively and negatively, although the extent of the functional activations was larger than the area defined with intraoperative mapping, and results are strictly dependent on the type of task used for testing [15, 82]. These data indicates that motor fMRI can be safely used for planning surgery. For the language correlation, the results are variable and different according to series. Naming and verb generation tasks are those which are most widely used for language fMRI studies. Generally, language fMRI data obtained with naming or

verb generation tasks were imperfectly correlated with intraoperative brain mapping results (sensitivity 59% and specificity 97% when the two fMRI are combined) [108, 121, 124, 136]. Generally, fMRI is showing larger activation than those observed with direct cortical mapping, which on the contrary, demonstrates only essential language sites. In our experience, the sensitivity can be increased up to 72% by using in the fMRI naming tasks the same figures used during surgery. Nevertheless, also in this condition, false negative can be documented in up to 8% of patients. Therefore, language fMRI could not be used to make critical decisions in absence of direct brain mapping. As for DTI FT, it is important to remember that DTI FT is providing anatomical information whereas subcortical mapping functional ones. This affects the correspondence and concordance between DTI FT images and functional

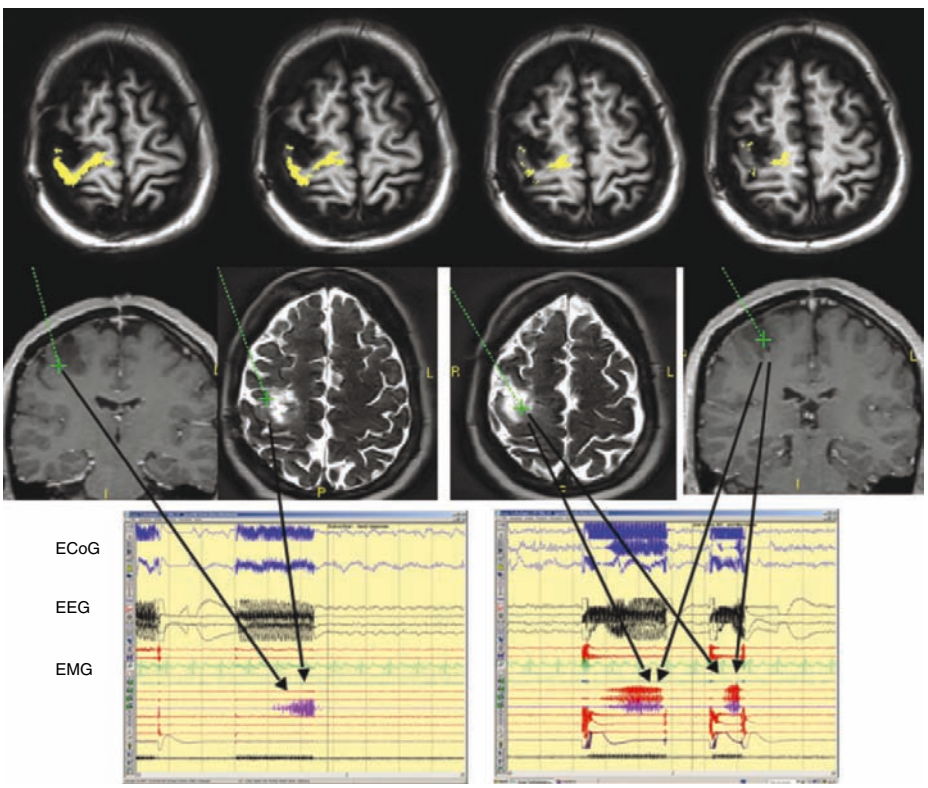
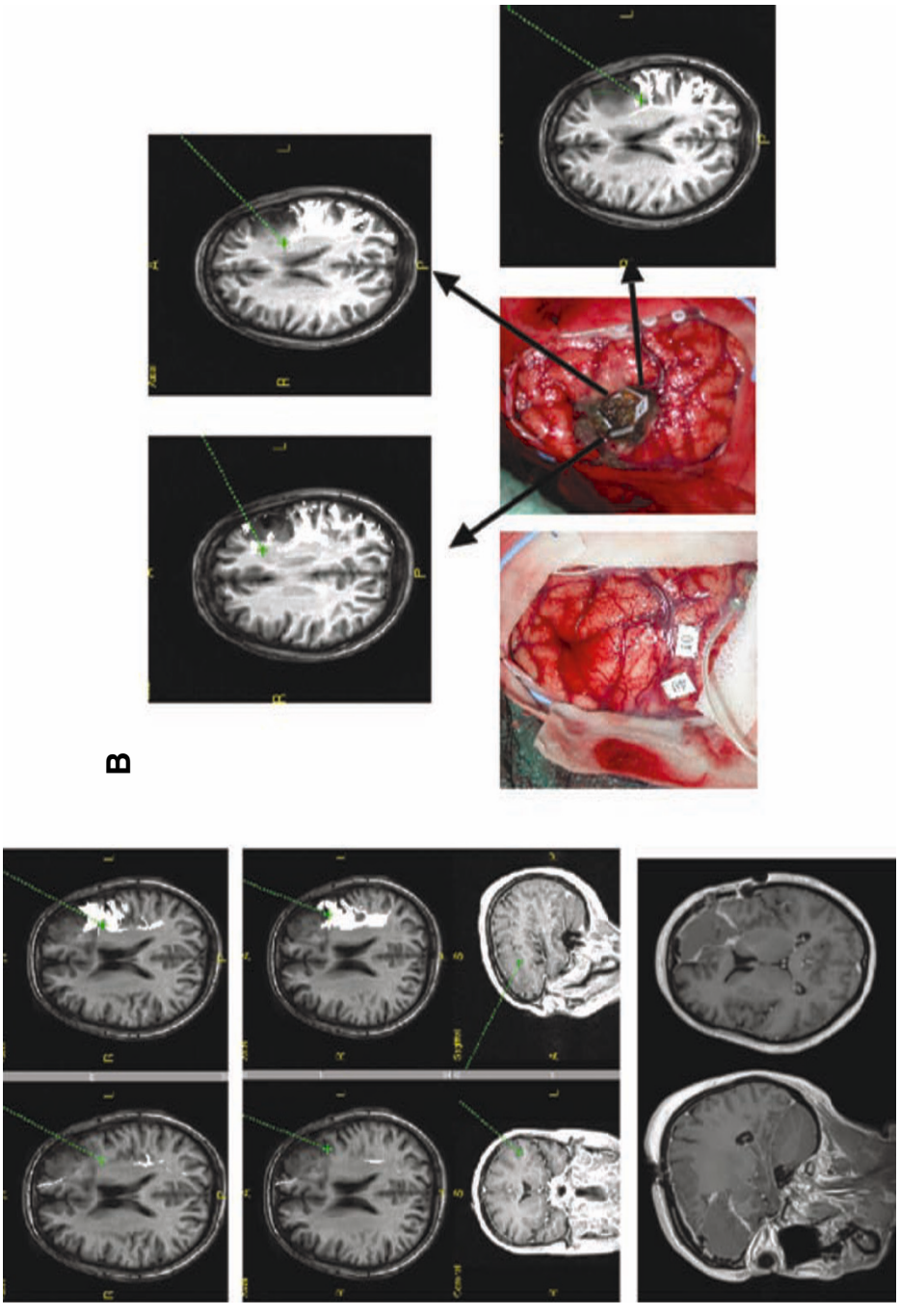


Fig. 4. DTI FT and subcortical motor mapping. When combined with subcortical mapping, DTI FT helps the surgeon in the safe identification of subcortical motor tracts, which like in this case of motor grade II oligodendrogliomas, were located at the peripheral portion of the tumor. Stimulation of these tracts elicited evoked motor responses for the hand (left lower panel) in the superior part of the resection cavity, the hand, lower and upper lips (right lower panel) when the resection was approaching the deeper part of the tumor

information obtained with subcortical mapping [7, 13]. This is of relative importance for CST (Fig. 4), but of particular relevance for language tracts, in which the anatomical distribution of the tract as depicted by DTI is larger than the functional ones obtained with mapping. Therefore, large part of the tract as depicted by DTI FT can be removed because not functional for the function tested at that time. When a FA of 0.1 is used for tracking, there is usually a good concordance between DTI FT data and subcortical motor mapping (sensitivity for CST = 95%, language tracts = 97%). Some pitfalls may occur for low-grade gliomas located in rolandic or SMA areas. DTI FT may fail in reconstructing portion of CST, particularly in area of extensive tumor infiltration. Even the placement of additional ROI at this level only partially improves reconstruction. As for SLF, the anatomic distribution of this tract is usually quite larger than the functional ones when language subcortical mapping is performed (Fig. 5). This is particular the case of frontal and temporal tumors. In low-grade gliomas, SLF is often depicted inside the tumor mass. As for the IFO, the anatomic distribution of this tract is small and usually corresponds to the functional one depicted by subcortical mapping (Fig. 6). Some problems may occur for F3 low-grade gliomas in which DTI FT may fail in reconstructing the more superior part of the tract at the inferior border of the tumor, when the tumor infiltration in this area is quite extensive. As for the UNC, the anatomic distribution of this tract is small and usually corresponds to the functional one depicted by subcortical mapping. The reconstruction of this tract in F3 tumors requires the placement of an additional ROI at this level. In F3 low-grade gliomas, the tract is usually inside the tumor mass, and the

Fig. 5. DTI FT and subcortical language mapping. DTI FT for SLF were fused with T1 weighted MR images and loaded into the neuronavigation system. A) The DTI FT reconstruction of the SLF is larger than the functional ones identify by subcortical language mapping and the non functional portion of the tract visualized by DTI FT can be safely removed. The upper panel is showing an intraoperative snapshots from the neuronavigation system which indicates the location of a subcortical sites where phonemic paraphasias were evoked. The portion of the SLF place anteriorly to this point was safely removed because not functional. The mid panel is showing showing an intraoperative snapshots from the neuronavigation system which indicates the location of a subcortical sites where phonemic paraphasias were evoked, demonstrating in this case a good correlation between DTI FT reconstruction and subcortical language mapping data. The lower panel is showing post operative post contrast T1 weighted MR images. B) A case of left frontal F3 grade II oligodendroglioma, in which SLF constitutes the anterior, upper medial and upper posterior border of the resection cavity. Arrows indicate the correlation between intraoperative snapshots and subcortical sites at the border of the resection cavity. The lower left picture shows the results of the cortical motor and language mapping. The tags indicate areas of the cortex in which stimulation induced speech disturbances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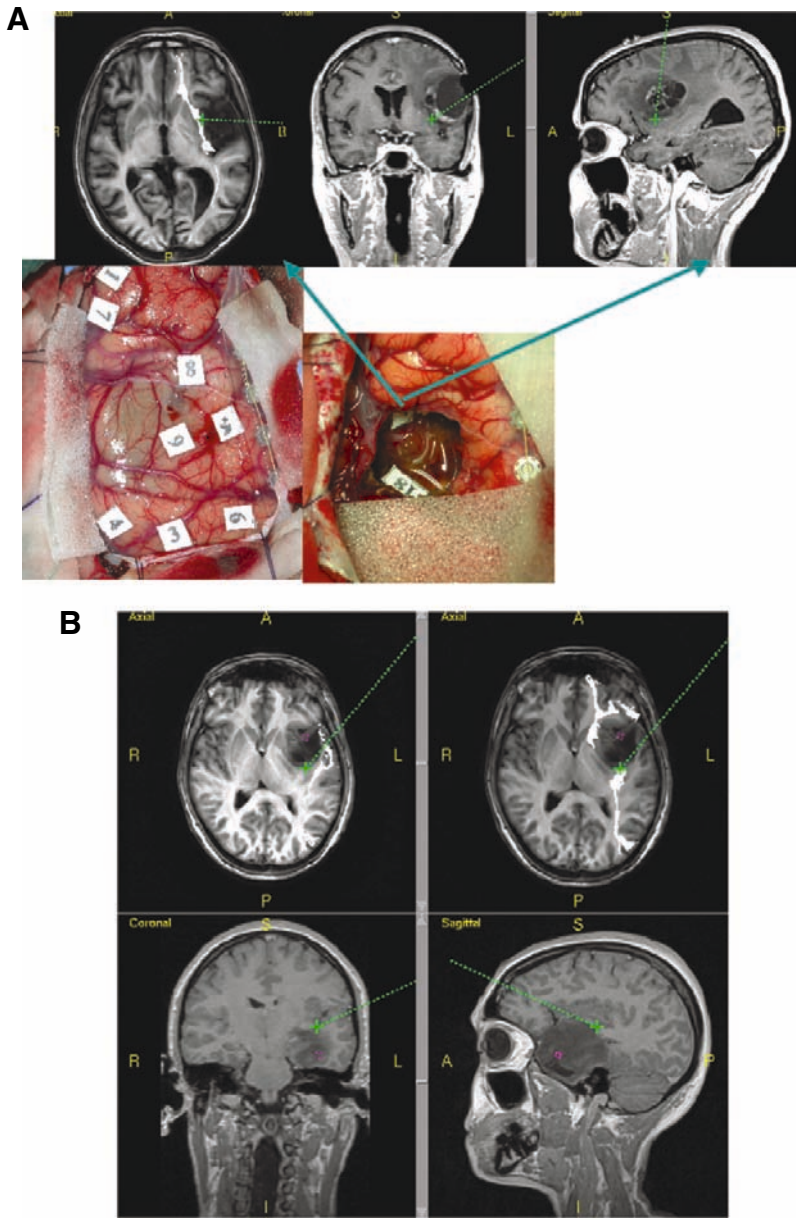

Fig. 6. DTI FT and subcortical language mapping. DTI FT for IFO were fused with T1 weighted MR images and loaded into the neuronavigation system. The IFO is small discrete tract, and when encountered is always functional. A, B) Examples of good correlation between DTI FT reconstruction for IFO and suncortical language mapping. In A) the IFO constitutes the medial inferior margin of the resection cavity of a cystic recurrent grade II oligodedroglioma. In B) the upper medial margin of a left temporal grade II oligodendroglioma

depicted fibers are usually found as functional by subcortical mapping. In temporal LGG tumors, the tract is still described as inside the tumor mass, but the fibers are extensively infiltrated and interrupted, and not functional.

Intraoperative MR has been more widely used for surgical treatment of low-grade gliomas [26, 69, 90, 98, 100]. Surgery for low-grade gliomas has been performed by using both low (0.2 or 0.5) or high (1.5) magnetic fields. The advantage of using intraoperative MR images is to have a precise jugdement of surgical removal while the patient is still in the operating room. In addition, by performing repeated images during surgery, it is possible to update morphological images and by transferring them into the neuronavigation system, to overcome the problem of brain shift [132]. Progression of surgery can be followed, and the occurrence of intraoperative complications monitored [91]. Furthermore, associated MRI software allows for a more precise estimation of initial and resected MRI tumor volume, permitting an improved measurement of the exposure variable. Usually in at least in 20% of cases of low-grade gliomas, a remnants of the tumor can be visualized in the field, and further removed [94]. The main limit of the intraoperative MR system is the cost of the machine and of the instrumentarium. The use of low field may permit the use of nonmagnetic surgical instruments, and are characterized by a lower cost of installation and of the machine. Varies low field machine are available, either the 0.2 Polestar or the 0.5 GE machine. The 0.5 GE prototip allows on time intraoperative images during surgery, but is limited by the restricted surgical room and by the need of using a complete nonmagnetic surgical tools. In addition, low magnetic fields do not permit to perform fMRI or DTI FT studies. Intraoperative high-field magnetic resonance (MR) system is at present one of the most sophisticated technical methods providing a reliable immediate intraoperative quality control. It enables intraoperative imaging at high quality that is up to the standard of up to date pre- and postoperative neuroradiological routine diagnostics. High-field MR imaging offers various modalities beyond standard anatomical imaging, such as MR spectroscopy, diffusion tensor imaging, and functional MR imaging which may also be applied intraoperatively, providing not only data on the extent of resection and localization of tumor remnants but also on metabolic changes, tumor invasion, and localization of functional eloquent cortical and deep-seated brain areas. Various systems have been developed and variable used. In most of them the patient is located into a bed and moved with into the magnet for MR images. Recently 3T MR systems have been put in place, or are under construction, like in our Institution. Both fMRI and DTI FT have been demonstrated to be feasible in these systems. Nevertheless, fMRI requires the patients to be awake and perform tasks inside the scanner. In addition, the quality of the generated data is often not as good as what can be achieved pre operatively. Furthermore, the time needed to acquire and process the data is often substantial. An alternative

approach used in recent device is therefore to acquire fMRI and DTI FT pre operatively, and track the anatomical changes that occur during surgery using intraoperative MR images and apply the changes found to the pre operative data [3, 99, 100, 102].

Ultrasound is another imaging option used for intraoperative visualization of low-grade gliomas. Advances in ultrasound technology have made the image quality of the ultrasound comparable to intraoperative MR [112]. Recent studies showed that the integration of intraoperative ultrasound with neuronavigation represents an efficient and inexpensive tool for intraoperative imaging and surgical guidance. Brain shift detected with intraoperative ultrasound could be used to update pre operative image data such as fMRI and DTI FT in order to increase the value of this information thorought the operation. The ability of these methods to reveal forgot tumor remnants is lower than that of intraoperative MR systems.

Immediate post operative course

When resection is perfomed according to functional boundaries, this is associated with a high incidence of development of immediate post operative deficits (over 70%), due to the functional blockage of the system (see the following paragraph). During this period patients are submitted to neuropsychological evaluation, motor rehabilitation, to follow deficit recovery, and to standard post operative imaging, including T1, T2 and flair volumetric sequences, to evaluate extent of resection.

Functional results of surgery

When brain mapping techniques are applied to low-grade glioma surgery, functional results can be evaluated either at early (within one week) to late (from one month to three months) time after surgery. The purpose of brain mapping techniques is to identify and preserve at the time of surgery cortical and subcortical essential sites. Resection was in fact stopped when language and/or motor, or visuospatial, cortical or subcortical areas were encountered. In most of in low-grade gliomas, motor or language disturbances were evocated either inside the tumor mass as well as at the tumor margins, because most of the essential sites particularly at the subcortical level are located within the tumor. The preservation of subcortical tracts is therefore critical for patient integrity [6, 7, 12, 36, 41, 43]. Evaluation of motor or language deficits during post operative course and at follow-up, showed that the chance to develop a new deficit or to worsen a preexisting one in the immediate post operative period was 72.8% and 65.4% in the group of patients in which language or motor related areas were identified subcortically during resection, and very low in the

group of patients in which no subcortical sites were identified [6, 70]. The chance was also higher in patients with a pre-existing motor or language deficit, which correlates with the higher percentage of subcortical tracts identified in the same patients. Most of the deficits were transient and disappeared within one month from surgery. Nevertheless, in the group of patients in which a subcortical language site was identified during resection, the likelihood to develop a permanent deficit was 3.8% independently from histology and location, that reached 7% in patients with a pre-existing motor or language deficit. In contrast, when no subcortical sites were found at the time of surgery, the chance to induce permanent deficit was very low (2%). This percentage further reinforce the concept that when a subcortical site is found, the surgeon is very close to the subcortical pathway. Therefore, when a subcortical response is reliably detected, resection must stop and should be continued in the neighborhood structures, because there is a high chance to damage functional structures [6, 43, 70]. If no subcortical structures are found, the resection can be continued, because the chance to hamper essential structures is low. These data indicate subcortical stimulation as a reliable tool able to guide surgical resection, and at the same time to predict the likelihood to develop deficit post operatively. The low incidence of post operative deficits in patients in which no subcortical tracts were identified is usually due to vascular damage and at the development of ischemic areas. MEP monitoring can help in monitor and preventing the appearance of motor deficits due to vascular injury [96]. When subcortical stimulation was systematically applied during resection of low-grade gliomas located within language areas or pathways, 79.5% of patients had a long term post operative normal language, 18.6% showed mild disturbances still compatible with a daily life useful language, and only 2.3% showed a long term impairment. Similar figures were observed for resection of gliomas close to motor areas or pathways. These functional results were totally different from those obtained when subcortical stimulation was not applied. Analysis of patients with high- or low-grade gliomas operated on in our Institution before the use of direct electrical stimulation, showed 23% of permanent language or motor deficits, in accordance with what has been previously reported in other series [6, 33, 41]. These data support the relevance of subcortical stimulation as a useful surgical adjunct during removal of lesions involving motor or speech areas, as further demonstrated by the high percentage of patients (91.8%) who returned to work at three months after surgery.

Oncological results of surgery

From an oncological point of view surgery, wishes to different aims: precise histological and molecular diagnosis, relief symptoms, reduce the incidence of

seizures, reduce the rate of recurrence and of malignant transformation, and possibly increase patient survival.

The ability of surgery to allow the pathologist to reach a more precise histological diagnosis and to relief symptoms particularly in case of large tumors inducing a mass effect, is at now less a matter of debate, although simple biopsy without resection, will continue to be theoretically acceptable and will continue to be practiced until better evidence is available.

The effect of surgery on the incidente of seizures has been recently documented by several authors [16, 43]. Seizures play an important role in the clinical presentation and postoperative quality of life of patients who undergo surgical resection of low-grade gliomas [74]. At least 50% of patients have a seizure at diagnosis and in more than 81% seizures persist after diagnosis even when the patient are under anti epileptic drugs (AED) treatment. Cortical location and oligodendroglioma and oligoastrocytoma subtypes are significantly more likely to be associated with seizures compared with deeper midline locations and astrocytoma. Forty-nine percent of patients have pharmacoresistant seizures before surgery. A particolar case is that of insular or paralimbic tumors. In these cases, intractable epilepsy is observed in 30% to 58% of cases and patients may experience up to 10 partial seizures per day despite more than 2 AEDs. Seizure control is more likely to be achieved after gross-total resection than after subtotal resection/biopsy alone. In fact when total or subtotal resection is achieved, in a more than 80% of cases a positive impact on seizures is documented, with reduction in the number of AED administered. In addition, suppression of AEDs is possible in 30% of cases [43]. Also in more than 80% of cases of insular low-grade gliomas with intractable epilepsy, a positive impact on seizures can be again documented. It is of relevance to remember than in low-grade glioma patient in which a seizure control has been reached after initial surgery, seizure recurrence is associated with tumor progression [16].

The first oncological result of when surgery is performed according to brain mapping techniques, is the increase in the number of cases who are submitted to surgical treatment, that in accordance of what has been previously reported in the literature, in our series moved from 11% of cases when mapping was not available, to 81% when mapping was applied, with a significant decrease in the number of cases that were submitted to biopsy only [6, 33, 41]. The second oncologic result, already discussed in the previous paragraph, is the decrease in the percentage of post operative permanent deficits, that felt from 33% to 2.3%, either for language or motor functions [6, 41, 43, 130]. The influence of extent of resection on time to recurrence, time to malignant transformation, and patient survival, is still a matter of debate. Nevertheless, a large number of class III and II evidences suggests that more extensive resection at the time of initial diagnosis may be a favorable prognostic factor for this type of tumors [10, 12, 18, 26, 41, 67, 89, 118, 126, 130]. The evalua-

tion of extent of resection is usually performed on post operative FLAIR volumetric images, by the aid of semi automatic segmentation software [71, 87]. The ability to achieve a complete resection (no abnormalities seen on post op FLAIR images) or subtotal resection (a post operative volume on volumetric post op FLAIR images less than 10 ml) is influenced by both the pre operative tumor volume and by tumor involvement of eloquent tissue, particularly at the subcortical level [130]. Pre operative tumor volume is a significant predictor of patient survival and progress free survival per se, as well as the involvement of subcortical tracts. Patients with tumors larger than 50 ml has a much shorter overall survival and progression free survival than those with tumors smaller than 25 ml. When the effect exerted by these two variables is analyzed together, the intraoperative finding of subcortical tracts is the parameter which mainly influences the ability to perform a complete removal, independently from tumor volume [6]. In a recent work [130], Berger showed that, after adjusting for the effects of age, KPS, tumor location, and tumor subtype, postoperative tumor volume remained a significant predictor of overall survival and progression free survival. Patients with a complete resection of FLAIR images have a significantly longer over all survival compared with patients having any residual FLAIR abnormality. In the same work, Berger and collegues subdivided patients with subtotal resection, in two subgroups, on the basis of postoperative tumor volume to specifically address the risk of relatively small volumes of residual tumor. Patients with residual FLAIR abnormality volume between 0.1 and 5.0 or between 5.1 and 15.0 ml demonstrated significantly shorter overall survival compared with patients who had complete resection of FLAIR abnormality. In addition, lower was the post operative volume, longer was the overall survival. Similarly, progression free survival was influenced by the post operative tumor volume. In our series of primary low-grade gliomas, no recurrence were observed at 5 year when the tumor was complete removed (no FLAIR abnormalities), whereas the percentage of recurrence at 5 year was 16.7% in case of subtotal removal (residual tumor volume less than 10 ml) and 38.5% in case of partial removal (residual tumor volume higher than 10 ml). In Berger analysis, after adjusting for the effects of age, KPS, tumor location and tumor subtype, extent of resection remained a significant predictor of overall survival and of time to malignant transformation. In our series, time to malignant transformation was 3.8 years in case of partial surgery, and 7.8 years in case of subtotal removal. Patients with at least 90% removal had 5- and 8-year overall survival (OS), progression free survival (PFS), and malignant progression free survival (MPFS) rates of 97% and 91%, 75% and 43%, and 93% and 76%, respectively, whereas patients with less than 90% removal had 5- and 8-year OS, PFS, and MPFS rates of 76% and 60%, 40% and 21%, and 72% and 48%, respectively. Patients with complete resection of all FLAIR abnormality had 5- and 8-year OS, PFS, and MPFS

rates of 98% and 98%, 78% and 48%, and 96% and 79%, respectively. When multivariate analysis was used, extent of resection was predictive of overall survival, whereas preoperative volume of progression free survival and time to malignant transformation [10, 130]. Globally considered, these data stress the importance of extent of resection in controlling tumor growth and influencing survival. Pre operative tumor volume strongly influences progression free survival and time to malignant transformation. This stress the point that smaller is the tumor better is the patient outcome, and that delaying surgical intervention may increase the risk of malignant transformation.

In Berger's work, the percentage of patients in which a total and subtotal resection was achieved was 35% and 27%, respectively. These figures are in accordance of what was reported by other groups, and in our experience. This stresses the point that when brain mapping techniques are used, this results in an increase in the percentage of total and subtotal resection. For example in our series, the percentage of total and subtotal resection raised from 11% in the period in which no mapping was available, to 52.8% of the time in which brain mapping techniques were applied. When intraoperative MR was used in combination with brain mapping techniques, this resulted in a further increase in the percentage of cases in which a total resection was achieved [26].

Strategy for large, diffuse or recurrent tumors; the concept of brain plasticity

Low-grade gliomas may present as a variable type of tumors ranging from discrete and apparently well defined lesion, to either diffuse and less discrete lesion. The therapeutic strategy for the more defined type of tumors are those we previously described. Large diffuse tumors still represent a challenge. Most of them are histologically diffuse astrocytoma. The majority of these tumors contain functional subcortical tracts, and a total or subtotal resection as initial strategy is quite difficult to be achieved. Although partial removal may still be beneficial [130], particularly in those cases in which a mass effect is present, the majority of these patients underwent to stereotactic biopsy only, usually guided by spectroscopy MR images, followed by adjuvant treatments. A recent strategy to increase the rate of resection in these as well as in those tumors in which a contralateral invasion of tumor cells in visible through the corpus callosum, is represented by the use of upfront pre operative chemotherapy. Limited class IV evidence show that when TMZ is administered upfront to these tumors up to a period of six months, this resulted in a decrease in tumor cell invasion, and reduced tumor cell infiltration along large fiber tracts, such as the corpus callosum, which in selected cases may help in reach a greater percentage of tumor removal [44]. Alternatively, chemotherapy may be use as adjuvant treatment, after partial removal, and in these cases it may further decrease post

operative tumor volume till to a value of 10 ml, which from an oncological point of view is associated with a better prognosis [6, 65, 111, 116]. In addition, in case of large tumors, a two time surgical strategy may be chosen, particularly in case of large tumors involving language areas or pathways. In these cases, in which during surgery is requested a long time patient collaboration, the initial surgery is continued till the patient collaboration and responsiveness is maintained, then is resumed from one week to various months later. In our Institution we adopted the policy that a period up to four to six months is used before submitting the patient to a second surgery. This is done to get the patient to recover from the initial surgery, secondly to let the phenomenon of brain plasticity to take place [43].

Despite of aggressive and early treatment, low-grade gliomas tend to recur. As already discussed in the previous paragraph, the rate of recurrence is influenced by the pre operative tumor volume and to a lesser extent by the extent of surgical removal [10, 43, 130]. A tumor recurrence may still retain the morphological feature of low-grade gliomas, or may show signs of tumor progression, such as contrast enhancement. The appearance of contrast enhacement is usually associated with a large pre operative volume, and with the presence of limited or focal enhancement in the pre operative MR images. Generally, when a total or subtotal removal were achieved at the time of initial surgery, the recurrent tumors has a higher chance to recur still as a low grade. When only a partial removal was obtained, the percentage of recurrence toward a higher grade is much higher. When a tumor recurs, various therapeutic options are available: surgery, chemotherapy, radiotherapy, or a wait and see policy [43, 104, 116]. Surgery usually is intermingled with the other therapeutic modalities, and is the treatment of choice when a subtotal or even a total removal can be predicted, such as in case of discrete lesions. When this is feasible, the prognosis of the patient is still favourable. Brain mapping techniques can be still applicable in case of recurrent tumors, even after radiotherapy. Alternatively, surgery may be used to decrease the tumor volume, in order to enhance the effect of chemo or radiotherapy. Generally, a patient with a low-grade gliomas may undergo to several surgeries during the entire time of the disease, and surgery is used with different purposes, and strictly associated with the other therapeutic modalities [128]. Up to 30% of patients in our series underwent to 4 surgeries, and 12% were submitted up to 5 operations. We observed a decrease in extent of resection with the increase in the number of surgeries, but this was not associated with an increase in the occurrence of transient and permanent post operative deficits.

An important observation that helps in planning surgeries is the occurrence of the phenomenon of brain plasticity [45]. Cerebral plasticity could be defined as the continuous processings allowing short, middle and long-term remodeling of the neurono-synaptic organization, in order to optimize the functioning of

the networks of the brain – during phylogenesis, ontogeny, physiological learning and following lesions involving the peripheral as well as the central nervous system [45]. The occurrence of brain plasticity in low-grade gliomas has been recently known [31, 37]. Plasticity may occur in the preoperative period and in this case, it is the results of the progressive functional brain reshaping induced by these slow growing lesion. This is suggested by the fact that in the preoperative period many patients despite large tumors and extensive invasion of eloquent structures, experienced very few or no neurological deficits [45]. This is further reinforced by neuroimaging functional studies with fMRI or PET which demonstrated that areas of activation have been found also around the tumor or into the contralateral hemisphere, suggesting that the reshaping mechanisms have induced the acquisition or the unmasking of functions by areas of the brain that were previously less involved in mediating specific functions [119]. Various types of reshaping can be observed: intrinsic reorganization within injured functional areas, recruitment of other regions implicated in the functional network, in the same hemisphere (close or even far away to the damaged area), or in the contralateral hemisphere. The presence of an already existing redundancy in the functional network is also observed during the resection, when unmasking of functional activity can be observed in previous silent areas, probably due to either hyper-excitability or lowering of the activation threshold of the cortex. This is observed in the particular case of motor functions [34]. The most important observation of the occurrence of brain plasticity is the post operative period. This has been shown by submitting patients that have recovered from post operative deficit status, to functional neuroimaging studies some months after surgery and when a recovery has occurred, demonstrating the activation of different areas of the brain, close or remote to those were involved in the preoperative period [78]. Plasticity may occur either at a cortical level, or, although less frequently at a subcortical level, where it can be explained by the recruitment or unmasking of parallel and redundant subcortical circuits [40]. The occurrence of such phenomenon of compensation is of particular relevance because it allows to extend surgical indications. It allows to extend the initial surgery till when functional boundaries are encountered allowing the patient to recovering in the post operative period due to the activation of redundant functional areas, when the essential are preserved at cortical or subcortical level. Secondly, the functional reshaping induced by the initial surgery, can be used to perform a second surgery wit the aim to remove areas of the brain initially essential for function, and that due to the functional reshaping induced by the initial surgery or to the continuous slow growth of the tumor, have lost their essentiality in term of function. This functional reshaping phenomenon can be observed up to a period of six months after the initial surgery, and allows to perform a more radical second surgery with an increase in the oncological benefit for the patient. The neuro-

surgeon should gain a better knowledge of these plasticity phenomena, and their variability among patients, in order to try to integrate this potential in the surgical indications and in a dynamic surgical planning. In other words, the extent of resection and the number of surgical acts necessary to perform a tumor resection should be adapted to the individual potential of functional compensation, thus to its limits [45].

Conclusions and proposal for the future

Low-grade gliomas are slow growing intrinsic lesions that induces a progressive functional reshaping of the brain. Surgical removal of these lesions requires the combined efforts of a multidisclipinary team of neurosurgeons, neuroradiologists, neuropsychologists, neurophysiologists, and neurooncologists that all together contribute in the definition of the location, extension, and extent of functional involvement that a specific lesion has induced in a particular patient. It is important to keep in mind that each tumor has induced particular and specific changes of the functional network, that varies among patients. This requires that each treatment plan is tailored to the tumor and to the patient. When this is reached, surgery should be accomplished according to functional and anatomical boundaries, and has the aims to the maximally resect the mass and to maximally preserve patient functional integrity. This can be reached at the time of the initial surgery, depending on the functional organization of the brain, or may require additional surgeries, eventually intermingled with adjuvant treatments. The use of so called brain mapping techniques extend surgical indications, improve extent of resection with greater oncological, impact, minimization of morbidity and increase in quality of life. Data available at this time indicate that low-grade gliomas at the time of radiographic diagnosis benefit from surgery because, aggressive early surgery influences the incidence of recurrence, time to tumor progression, time to malignant transformation, and provides seizure control. Smaller is the tumor to treat at the time of initial diagnosis, higher is the possibility to reach a complete surgical resection, better is the prognosis in term of recurrence, and tendency to malignant transformation. This point stresses the need to treat smaller lesion and to reduce the time for observation. Being the diffusive nature of these tumors the main reason that mainly limit the ability to reach a complete oncological resection, the implentation at the time of surgery of imaging method such those offered by intraoperative MR, may helps to remove the tumor and to follow it along the brain. In addition, the implementation of upfront pharmacological strategies capable of reducing the invasion along white matter tracts and compacting the tumor mass, may further enhance this result. The long term oncological results of this multimodality approach requires the evaluation of a large cohort of patients. This has been recently attempted by the development of a LGG

European Network that aims both to collect data on LGG and uniform management and protocols for such tumors all across European countries.

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Is there a place for radiotherapy in low-grade gliomas?

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Contents

Abstract

The optimal management of supratentorial low-grade glioma remains controversial, and only limited definitive data is available to guide recommendations. Treatment decisions have to take into account both the management of symptoms and of tumour control, and must balance the benefits against the potential for treatment-related complications. Overall outcome

is more dependent on patient and tumour-related characteristics such as age, tumour grade, histology and neurological function than treatment. From the pooled analysis of 2 randomized EORTC trials a prognostic score has been derived, median survival is varying from 3.2 to 7.8 years. Radiation therapy is usually the primary treatment modality; however its benefit on initial tumour control may be outweighed by potential late toxicity. To date only 4 large randomized trials in patients with low-grade glioma have been reported. It allows concluding that early radiotherapy does not improve overall survival and supports an initially expectative approach. Similarly, higher radiation doses above 45–50 Gy (fractions of 1.8–2.0 Gy) do not confer a better outcome but may be associated with increased toxicity. The adjuvant use of PCV-chemotherapy in high-risk patients also failed to improve progression-free and overall survival. An ongoing large randomized EORTC/NCIC trial is investigating the primary treatment with temozolomide chemotherapy versus standard radiotherapy in patients "at need for treatment". Tumour material will be collected in all patients, which ultimately may allow identifying on a molecular basis patients for whom one or another treatment strategy may fit best. Irrespective of new chemotherapeutic agents, radiotherapy is also evolving. Highly conformal techniques based on modern imaging as co-registered MRI scans, limiting the amount of normal tissue irradiated without compromising tumour control, will be the future approach in order to reduce neurotoxicity.

Keywords: Low-grade glioma; radiotherapy; prognostic factors; temozolomide; neurocognition; toxicity.

Introduction

The optimal management of supratentorial low-grade glioma (LGG) remains subject of controversy and only limited randomized data is available. Individual prognosis can be extremely variable with some patients' tumours rapidly progressing within a few months, while others may remain stable or only slowly evolving with few symptoms for many years. Treatment has to take into account both the management of symptoms and tumour control, and treatment decisions must balance the benefits of therapy against the potential of acute and late treatment-related complications. Radiotherapy may lead to cognitive impairment, neuroendocrine dysfunction, cerebral necrosis, or second malignancies. Nevertheless, radiation therapy has been the backbone of treatment for most brain tumours, including LGG. Radiation therapy (RT) remains the standard of care in many situations, in particular in patients with rapidly progressive disease and malignant transformation, technological improvements in radiotherapy, better targeting of the tumour volume and more sophisticated irradiation techniques carry the promise of reduced neuro-cognitive toxicity

and other morbidity further contributes to its continued use. Nevertheless, the optimal timing of RT (early versus late in the disease course), the effective total radiation dose, individual patient and tumour-related prognostic factors remain critical questions.

This book chapter addresses the optimal management of patients suffering from World Health Organisation (WHO) grade II low-grade glioma. Pilocytic astrocytoma (WHO grade I) is a paediatric tumour that can be cured with radical surgery alone or, in selected cases exclusive radiotherapy are not included. This article focuses on supratentorial LGG where randomised data are available; paediatric and adult brain stem glioma often treated in analogy are not specifically discussed. The first aims at defining the patients who will need a treatment (whom to treat?), the following paragraphs will address the questions of radiotherapy timing, technique and dosage (when and how to irradiate?), toxicity of radiotherapy and alternative treatment options (chemotherapy).

Indications for irradiation (prognostic factors)

Not all patients with a low-grade glioma will require immediate treatment and for many a wait and watch policy can be recommended, accurate identification of patients benefiting from immediate therapy is needed. The outcome of LGG is highly variable and is dependent on pre-therapeutic patient- and disease related variables. These differences in survival based on prognostic factors are larger than the impact of any therapeutic intervention. Scores and subgroups based on prognostic factors have been identified, and should lead to tailored treatment recommendations [42, 48, 66].

Immunohistochemical staining for the proliferation marker Ki-67 provides additional prognostic information independent of histopathological grading. It has been demonstrated to be clinically useful in identifying aggressive biologic behaviour of tumours [46]. In a retrospective evaluation biopsies of 180 patients (80 patients postoperative radiotherapy, 100 patients RT deferred until progression) with LGG were analyzed for Ki-67 expression; in 7.7% of the specimens $\geq 5\%$ of the tumour cells stained positively for Ki-67, and values of $\geq 5\%$ or $\geq 10\%$ predicted inferior survival. However, Ki-67 was not independent of other prognostic factors, notably age and may not be helpful in defining which patients would benefit from postoperative RT [15].

Several investigators have aimed to retrospectively identify prognostic factors in LGG. Lote *et al.* [35] reported on 379 patients with LGG treated over 15 years at the Norwegian Radium Hospital. In an univariate analysis, younger age, good WHO PS, the absence of neurological deficit and absence of contrast enhancement on imaging were all found to be associated with longer

Table 1. *Prognostic score according to Bauman et al. [1]*

RPA Prognostic classes	Score characteristics	No. of patients	Median overall survival (months)
I	KPS < 70, age > 40	41	12
II	KPS ≥ 70, age > 40, enhancement present	34	46
III	KPS < 70, age 18–40 or KPS ≥ 70, age > 40, no enhancement	138	87
IV	KPS ≥ 70, age 18–40	188	128

KPS Karnofsky performance status.

survival. In a multivariate analysis, performance status, neurological symptoms or initial corticosteroid dependency, contrast enhancement, and age remained statistically significant prognostic factors.

In a subsequent study, the database from the Norwegian Radium Hospital ($n = 160$) was pooled with the databases from the London Regional Cancer Centre ($n = 179$) and the University of California at San Francisco ($n = 62$) [1]. Four different prognostic classes were identified using a recursive partitioning analysis (Table 1).

Younger age, a good performance status and no contrast enhancement on imaging were favourable prognostic factors.

In a randomized trial by the North Central Clinical Trials Group (NCCTG) [57] age, histology, and tumour size were the most significant predictors of overall survival. The degree of resection did not significantly affect overall survival. Significantly better survival was associated with oligodendroglioma or oligo-dominant mixed tumour histology, small tumours (< 5 cm), and/or young age (age < 40). When combined, histological subtype and age were particularly powerful predictors of overall survival. Patients younger than 40 years with oligodendroglioma had a 5-year survival of 82%, compared to only 32% in patients with astrocytoma aged > 40 years.

The European Organisation for Research and Treatment of Cancer (EORTC) developed a prognostic score based on two randomised, multicentre trials with a total of over 600 patients (Table 2) [48]. The first study (EORTC 22844) [26] served to construct a model of prognostic factors, which was validated with the data set of the subsequent trial (EORTC 22845, [25]). In a multivariate analysis, age ≥ 40 years, astrocytic tumour histology, tumour size > 6 cm, tumour crossing the midline, and neurological deficit at diagnosis (before surgery) were retained in the model as unfavourable prognostic factors, a score was established depending on the number of factors. Survival decreased with each unfavourable factor. A favourable (low-risk) prognostic score was defined as no more than two of these adverse factors and was associated with a

Table 2. *Prognostic score and risk groups of EORTC 22844 and 22845 [48]*

Risk group	Score	EORTC 22844 *Construction set (n = 281)*		EORTC 22845 *Validation Set (n = 253)*	
		No. of patients	Median Survival (yr) (95% CI)	No. of patients	Median Survival (yr) (95% CI)
No risk factor present	0	18	9.2 (8.2–NA)	24	9.1 (9.1–NA)
1 risk factor present	1	69	8.8 (7.7–NA)	102	8.6 (7.4–NA)
2 risk factors present	2	113	5.5 (4.7–8.0)	69	6.3 (5.3–7.8)
Low risk group	0–2	200	7.7 (6.5–9.2)	195	7.8 (6.7–8.9)
3 risk factors present	3	55	3.6 (3.2.–4.8)	39	4.4 (3.6.–4.4)
4 risk factors present	4	20	1.9 (1.1–4.3)	16	3.0 (1.9–NA)
5 risk factors present	5	6	0.7 (0.3–NA)	3	2.4 (0.7–NA)
High risk group	3–5	81	3.2 (2.9–3.9)	58	3.6 (2.8–4.6)

Unfavourable prognostic factors: Age ≥ 40 years, largest diameter ≥ 6 cm, tumour crossing the midline, pure astrocytic histology, neurologic symptoms.
yr Year; *CI* confidence interval; *NA* not available.

median survival of 7.7 years (95% CI = 6.6, 9.3). The presence of three to five prognostic factors (a high-risk prognostic score) was associated with a median survival of 3.2 years (95% CI = 3.0, 4.0).

The importance of a baseline neurological function as prognostic factor was evaluated on a subset of patients from a prospective NCCTG Intergroup trial comparing low versus high dose levels of RT [5]. Folstein Mini Mental Status Exam (MMSE) scores and RTOG neurological function score at baseline in combination with multiple other baseline variables were analyzed. The 36 patients with an abnormal baseline MMSE score (≤ 26) had a significantly worse 5-year progression-free survival rate and overall survival rate compared with those with a normal score ($n = 151$), that remained significant on multivariate analysis. In high-risk patients (≥ 40 years old or incompletely resected tumours) median survival was 4.5 months compared to 12.6 months, for patients with an abnormal versus a normal MMSE score, respectively. In the low-risk group (< 40 years, tumours totally resected) the baseline MMSE score was not a significant predictor of survival (median survival 7.4 and 12.3 years) [5].

Timing of radiotherapy

The optimal management of cerebral low-grade glioma is unknown and the identification of patients needing a treatment is based on prognostic factors as

outlined above. In almost all patients tumours will eventually recur or progress over the years following diagnosis. Immediate postoperative RT after complete or nearly-complete tumour resection seems no longer to be considered as the standard of care, but symptomatic patients with large unresectable tumours, patients above the age of 40 years and patients with a neurological deficit are considered to be at a high(er) risk of recurrence or progression and are commonly treated with immediate radiation therapy, in particular in the presence of several risk factors. Radiotherapy is able to control symptoms in up to 80% of the cases. Numerous uncontrolled retrospective studies have suggested a survival benefit for patients receiving immediate postoperative RT [10, 30–32, 34, 39, 41, 43, 47, 53, 55, 60–62, 77, 78]. However, the reported range of presumed improvement over historical controls was broad; patients were treated over several decades with changing diagnostic and therapeutic modalities and modified histological grading and classifications. For subtotally resected tumours the outcome of postoperative RT expressed in 5-year survival rates is reported with a broad range from 36% to 100% [10, 31, 32, 34, 39, 41, 43, 47, 55, 61, 62, 77, 78]. It is likely that the observed differences are due to differences in the studied patient populations including a host of unidentified prognostic factors, pathologic uncertainties, variable extent of resection and other factors [42]. However, despite the uncertainties of retrospective and single centre studies it is generally accepted to recommend RT for younger patients only at recurrence and not immediately after surgery. However, no randomized trial investigated the impact of the extent of surgical resection and the need for immediate additional radiotherapy in incompletely resected patients.

A randomized EORTC trial [25, 71] investigated the question of radiotherapy timing (Table 3). Three-hundred and fourteen patients were randomised to either immediate postoperative (adjuvant) radiotherapy (54 Gy in 1.8 Gy fractions) or deferred RT until radiological or clinical tumour progression. Primary endpoints were overall survival and time to progression. Although improved progression-free survival (5.3 years vs. 3.4 years, $p < 0.0001$) was demonstrated for patients treated with immediate radiotherapy, this did not translate in improved overall survival (7.4 vs. 7.2 years $p = 0.872$) [71] (Fig. 1). By deferring treatment, one third of the patients did not require any radiotherapy until the time of analysis after a median follow-up of 7.8 years [71] (Fig. 1). The study did not evaluate the extent of eventual treatment-related late neuro-cognitive toxicity.

In a more recent trial by the Radiation Therapy Oncology Group study (RTOG trial # 9802) patients were stratified into favourable prognostic and unfavourable prognostic groups [58]. Favourable group patients (age < 40 years, gross total resection) were simply observed in a single arm Phase II study. The 5-year overall survival rate was 93%, although 52% of patients

Table 3. *Randomized studies of radiotherapy for low-grade glioma*

Study	Histology	Treatment arms	No.	5-year survival		P value	
				OS (%)	PFS (%)	OS (%)	PFS (%)
Timing of radiotherapy							
EORTC 22845 [25, 71]	AA, OD, OA	S	157	66	35	n.s.	<0.0001
		S + RT	157	68	55		
Dose of radiotherapy							
EORTC 22844 [26]	AA, OD, OA, PA	S + RT 45 Gy	171	58	47	n.s.	n.s.
		S + RT 59.4 Gy	172	59	50		
NCCTG-RTOG-ECOG [57]	AA, OD, OA	S + RT 50.4 Gy	102	73	55		n.s.
		S + RT 64.8 Gy	103	68	52		
Adjuvant chemotherapy							
RTOG 98-02 [58]	AA, OD, OA	Watch and wait of favourable patients	111	93	48		
		RT vs. RT and PCV for high risk patients	251	62 71	42 60	n.s.	n.s.

AA Astrocytoma; *OD* oligodendroglioma; *OA* oligoastrocytoma; *PA* pilocytic astrocytoma; *S* surgery; *RT* radiotherapy; *Gy* Gray; *n.s.* not significant.

had progressed during the observation period and received salvage radiotherapy. It may therefore be concluded that young patients after gross total resection (neurosurgeon determined) have a $>50\%$ risk of tumour progression 5-years postoperatively, thus needing close follow-up [59].

Radiation technique

Focal or conformal delivery of radiotherapy to the tumour and sparing of surrounding normal tissues at the same time are the most important goals in recent achievements of radiotherapy techniques. New techniques like stereotactic radiotherapy, intensity modulated radiotherapy, image guided radiotherapy or proton therapy are characterized by a high level of accuracy in the

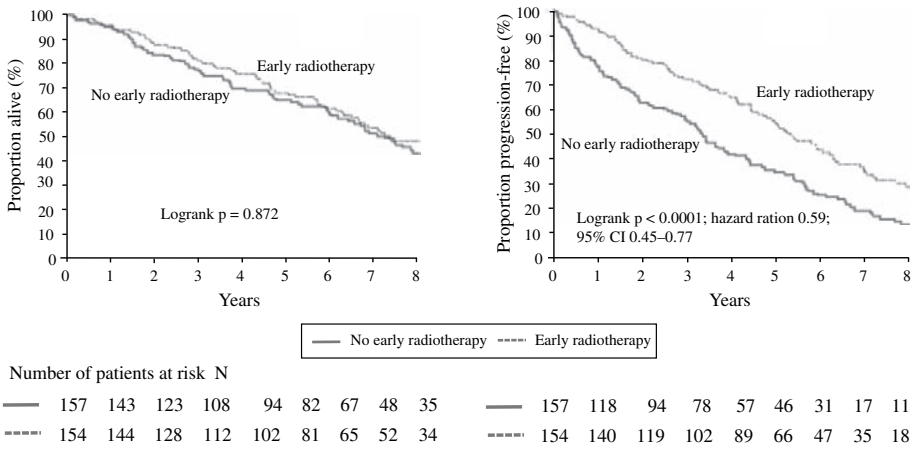


Fig. 1. Overall- and progression-free survival of randomized EORTC 22845 trial (early versus delayed radiotherapy). (Reprinted from The Lancet 366(9490), vd Bent M, Afra D, de Witte O *et al.*, Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial, pp 985–990. © 2005, with permission from Elsevier)

delivery of radiation to tumour tissue, leading to a substantial improvement of treatment results. It is hoped that continuous improvement and developments in the area of focal or conformal radiotherapy will contribute to more specific sparing of defined areas at high risk for neurocognitive toxicity.

It has been demonstrated that the use of CT-based full three-dimensional (3D) treatment planning techniques compared with simple 3D planning techniques in patients with an astrocytoma results in a 30% reduction in the volume of brain tissue treated to a high-dose level (>95% isodose line) [68]. Furthermore, a 50% reduction of normal brain irradiated is observed [68]. As a consequence, there is less intellectual impairment in long-term survivors [18]. Sparing of normal tissue has recently been further developed by the use of intensity-modulated radiotherapy (IMRT) resulting in conformal avoidance of normal brain tissue, for example, the hippocampal area which is hypothesised to be the cause of memory function decline. This specific hypothesis focused on sparing the migrating stem cell compartment in the hippocampus responsible for post-radiotherapy neurogenesis as a component of preserving memory function and was shown to be feasible by the use of IMRT [19].

It can therefore be reasonably assumed that a high level of dose conformity will improve the efficacy of treatment by decreasing normal tissue toxicity and contribute to more specific sparing of defined areas at high risk for neurocognitive toxicity. An example of a conformal localized RT treatment plan is shown in Fig. 2.

Stereotactic radiosurgery, a highly accurate RT treatment technique delivering dose in a single high dose fraction, has been used for recurrent LGG and

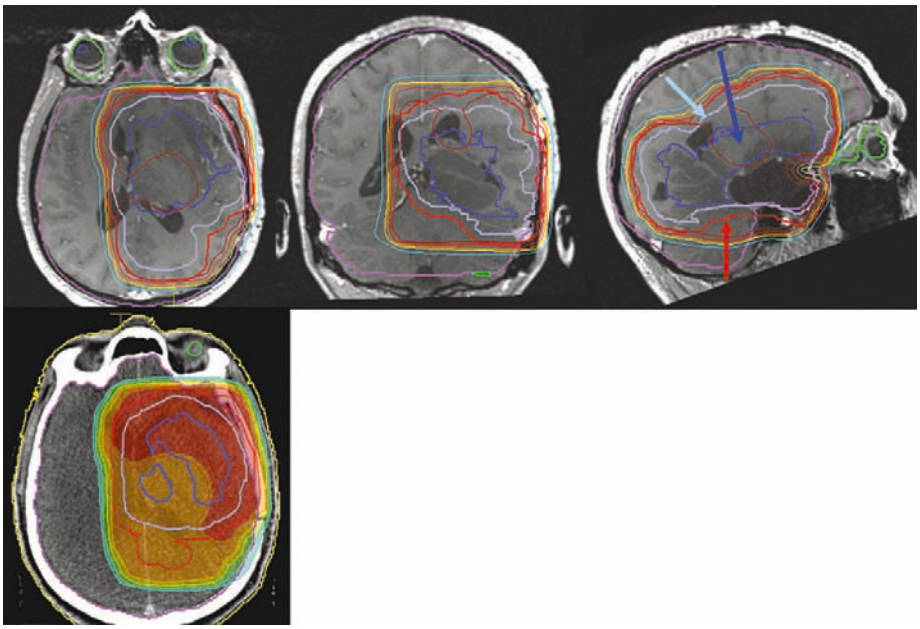


Fig. 2. Example of a conformal RT treatment plan. In the top row, the planning volumes and the calculated dose, represented by coloured isodose lines of different dose levels are projected onto the axial, sagittal and coronal views of the planning MRI scan. Three different planning volumes are defined: 1. the tumour area of postoperative residual tumour and the operation cavity (dark blue volume and arrow), 2. the added safety margin for possible tumour infiltration of usually about 1 cm in three dimensions (light blue volume and arrow) and 3. the planning volume which adds a small margin to take into account possible variations in patient repositioning. In the left lower corner the same treatment plan and volumes are projected onto the planning CT: the yellow and red dose wash shows the area of the prescribed RT dose

residual tumour and small studies reported promising results [20]. However, data are not sufficient to recommend radiosurgery as an effective treatment for LGG. For a very select group of patients with small recurrent lesions, stereotactic radiosurgery and radiotherapy may represent a reasonable treatment option [11, 52]. This is different for fractionated stereotactic radiotherapy. At the German Cancer Centre in Heidelberg 143 patients with a LGG (87 patients with a primary tumour, 56 with a recurrent glioma) were treated by fractionated high-precision RT with a median target dose of 57 Gy with conventional daily fractionation of 1.8–2 Gy [49]. Fifty-eight patients (40.6%) received a total dose of 54 Gy. Higher doses were considered after individual risk estimation based on the prevalence of CM enhancement on MRI before treatment, patient age, KPS, and target volume. The actuarial overall survival and progression-free survival was 58% and 39% at 5 years, respectively. A dose–response relationship was not observed. Severe side effects were seen in 4 patients (2.8%). It was concluded

that fractionated stereotactic RT is effective. Exceeding the tumour dose >55 Gy did not improve the tumour control rate but did enhance toxicity [49].

A combination of proton and photon radiotherapy was investigated in 7 patients with a LGG in a prospective dose-escalation phase I/II trial [16]. Doses prescribed were 68.2 cobalt gray equivalent (CGE) using a conventional fractionation scheme with 1.8–1.92 CGE daily. Actuarial 5-year survival rate for grade 2 lesions was 71% and thus not different from conventional radiotherapy. However, 3 patients died from tumour recurrence, whereas 2 of the 4 survivors had evidence of radiation necrosis. Dose escalation using this fractionation scheme and total dose delivered failed to improve outcome for patients with LGG, and resulted in increased toxicity.

Radiotherapy dose

In daily practice some variation of the radiation doses remains. Many radiation oncologists usually prescribe a total dose of 50 to 55 Gy (1.8–2 Gy/fraction). Some retrospective single arm studies suggested doses >53 Gy being associated with improved survival [55, 75, 78]; others did not [9, 16, 35, 49]. Some studies reported an improved survival for total doses of ≥ 50 Gy [14, 40]. The outcome seems to be dependent on extent of tumour resection and radiation dose [14]. The median survival of patients with a partial resection who received ≤ 50 Gy was 16.5 months while it was over 9 years (109 months) for those who received >50 Gy [14]. In a multivariate analysis radiation dose and extent of resection were significant for overall survival and progression-free survival ($p=0.013$ and $p=0.003$, respectively). The authors concluded that patients with a partial resection should be considered for higher radiation doses (>50 Gy) [14].

Two randomised prospective trials investigated different RT doses in patients with LGG. The EORTC trial #22844 and US Intergroup (NCCTG-RTOG-ECOG) studies showed no advantage in overall survival for higher doses when comparing 45 Gy and 59.4 Gy, and 50.4 Gy and 64.8 Gy, respectively [26, 57] (Table 3). In the EORTC study, 397 patients with a LGG were randomized after biopsy or resection between 45 Gy and 59.4 Gy in fractions of 1.8 Gy. No differences in both progression-free and overall survival were found [26]. In the NCCTG Intergroup trial [57] 203 patients were randomized between low-dose RT (50.4 Gy in 1.8 Gy fractionation) and high-dose RT (64.8 Gy). Patients had undergone a biopsy ($n=103$), subtotal resection ($n=71$) or a total resection ($n=29$). Like the EORTC study, no difference in terms of overall and progression-free survival between both groups was found but an increased toxicity for the high-dose group (see below). Based on these results, a dose of 50.4 in fractions of 1.8 Gy has been widely accepted as the current standard of care.

The latter studies however did not address the possible inter-relationship of residual post-operative tumour volume and radiation dose for which a significant interaction was found (see above [14]). Pignatti *et al.* did also not test for a possible dose-response relationship between amount of surgery and radiotherapy dose [48]. The hypothesis that "one dose may not fit all" should be further pursued in future trials. It should however be taken into account that a higher dose may lead to increased toxicity. New radiation techniques and individualized dose levels based on the volume to be treated could be the answer to this problem and should be integrated into future studies.

Toxicity of radiotherapy

Treatment related late toxicity is of concern, in particular in view of the rather long survival of patients with low-grade glioma. Radiation therapy to the brain is associated with white matter changes, cognitive deficits and radiation necrosis. Reported toxicity from randomized studies is generally mild (Table 4). However, if higher RT doses are used, an increased toxicity is observed: A 2-year actuarial incidence of grade ≥ 3 radiation necrosis of 2.5% has been observed in patients treated with a total dose of 50.4 Gy versus a 5% rate using 64.8 Gy in the randomized Intergroup trial (NCCTG-RTOG-ECOG) [57] (Fig. 3). A similar increase in radiation necrosis was seen when a dose escalation up to 68.2 Gy Cobalt Gray Equivalents (CGE) with a combination of proton and photon irradiation was used [16].

The effects of early versus delayed radiotherapy on quality of life and cognitive functioning have first been analysed in small patient cohorts: in irradiated and non-irradiated patients with a low-grade glioma it did not differ significantly [67]. However, if those patients were compared to a control group suffering from indolent haematological malignancies without CNS involvement, low-grade glioma patients had a significantly worse cognitive function. This was confirmed in a second multi-centre study of 180 patients where cognitive disability in the memory domain was significantly worse in irradiated patients [28]. The latter was pronounced if fraction doses exceeding 2 Gy were applied. Additionally, patients who received 54 Gy compared to 45 Gy in the EORTC 22844 trial tended to report lower levels of functioning concerning quality-of-life [28]. This was especially true for fatigue, insomnia and emotional functioning.

Based on a multi-centre comparison including large patient cohorts of 195 patients with a LGG (of whom 104 were irradiated), 100 low-grade haematological patients and 195 healthy controls based on an extensive neurocognitive test battery, it could be concluded that the tumour itself seems to have the most deleterious effect on cognitive function as well as the use of antiepileptic drugs [29]. Additionally, the results of the multivariate logistic regression anal-

Table 4. *Long term toxicity after radiotherapy as reported in prospective randomized studies*

Author	No.	Dose/ fractionation	Toxicity descriptive	Toxicity (%/absolute)	Remarks
EORTC 22844 [26]	379	45 vs. 59.4 Gy	RT interrupted for >1 week	8% (13/171) low dose 15% (26/172) high dose	
			RT stopped due toxicity	5% (9/172) No RT necrosis	
EORTC 22844 [28]	180	45 vs. 59.4 Gy	Fatigue, malaise, insomnia	Sign. worse for high dose group immediately after RT	QoL evaluation
			Emotional functioning and functioning in leisure time	Sign. worse 7–15 months after RT	
EORTC 22845 [25]	311	54 Gy	Skin erythema	Grade 3: 1 patient	
			Headache	Grade 4: 1 patient	
				Grade 3: 1 patient	
				No RT necrosis	
NCCTG-RTOG-ECOG [57]	211	64.8 vs. 50.4 Gy	Overall toxicity score 0–9	Score 0: 51% Score 1–2: 25% Score 3–4: 16% Score 5–9: 8%	
				2-year actuarial incidence of grades 3–5: 2.5% (1 pt, low dose) and 5% (6 pts, high dose)	Grade 3–5 = necrosis, encephalitis and other CNS toxicity
RTOG 98-02 [58]	251	54 Gy	Acute grade 3–4	9% RT alone: Grade 3: 7% Grade 4: 2% 67% RT and PCV: Grade 3: 53% Grade 4: 14%	Preliminary results. Long term side effects not reported

RT Radiotherapy; *sign.* significant; *Gy* Gray; *QoL* quality-of-life; *pt.* patient; *vs.* versus.

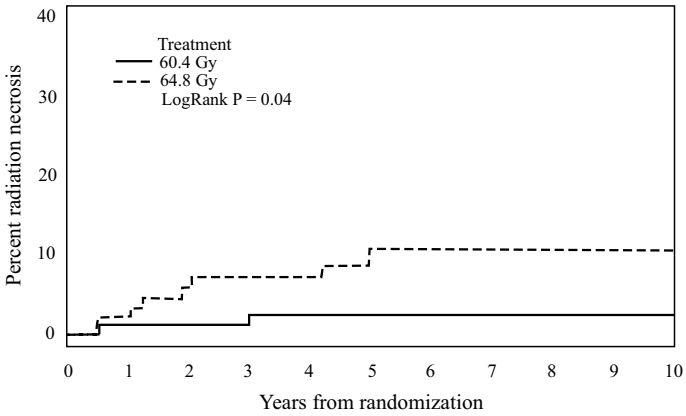


Fig. 3. Kaplan–Meier estimates of time to occurrence of grade 3 (severe), grade 4 (life-threatening), or grade 5 (fatal) radiation neurotoxicity by treatment arm (low-dose or high-dose radiation therapy). (Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved. Shaw *et al.* [57])

ysis were evidential for cognitive disability only in LGG patients who received fraction doses exceeding 2 Gy [29]. Comparing patients treated with postoperative radiotherapy with those having undergone surgery only, a more severe leukencephalopathy and a significantly worse cognitive performance were seen even after correction for confounding risk factors such as histological grading, epilepsy, tumour location, etc. [65]. Evaluating cognitive function only by the Mini-Mental State Examination (MMSE) may underestimate the cognitive deficit [4]. Based on literature review Brown and colleagues concluded that there was only sporadic limited neurocognitive damage from focal radiotherapy at the usually prescribed doses for low-grade gliomas [4]. Prospectively evaluated cognitive function with an extensive battery of psychometric tests at baseline (before RT) and at approximately 18-months intervals for as long as 5 years after completing RT, in a small subgroup of patients from the Intergroup study comparing two different radiotherapy dose schedules (50.4 Gy vs. 64.8 Gy), is reported as being stable after RT during 3 years of follow-up [36]. Interestingly, neuropsychological baseline test scores were below average compared with age-specific norms [36].

A recent study evaluating cognitive function by longitudinal long term follow-up (neuropsychological assessment at 6- and 12 months) in 25 patients showed that both disease duration and treatment with RT and/or chemotherapy contributed to a mild decrement in nonverbal recall and in some aspects of executive functions and quality of life [13]. However, only 5 of those patients were treated by RT, 1 by a combination of RT and chemotherapy and 3 received chemotherapy only. The same authors investigated cognitive functions of 40 patients in a prior study where 16 patients received a treatment (11

conformal RT, 1 RT with chemotherapy, 4 chemotherapy) and 24 no treatment. The results showed lower scores for treated patients on several cognitive domains, particularly in motor speed and non-verbal memory [12]. Antiepileptic polytherapy, treatment history and disease duration jointly contributed to low psychomotor function scores. Both studies showed no differences in reduced cognitive functions between RT and chemotherapy.

Taken together, the studies in which most adverse effects of radiotherapy were observed had used higher total doses and larger treatment fields [44, 65]. In studies using modern standards of radiotherapy, less negative impact on cognition was observed [29, 36, 67, 76]. Radiotherapy is not the sole factor contributing to cognitive adverse effects: the tumour itself by its size and disease duration as well as other therapeutic modalities, notably also anti-epileptic medication will affect the neurocognitive function. Still, the question on the amount of late neurocognitive side effects due to RT is not finally answered yet as the use of neuropsychological testing is not standardised and therefore results are not comparable.

Chemotherapy and radiotherapy

Adjuvant chemotherapy after radiation has been explored in a large randomized RTOG trial (#9803) [58]. High risk patients were randomized to postoperative radiotherapy with or without subsequent adjuvant PCV chemotherapy. After stratification by age, histology, KPS, and presence/absence of contrast enhancement on preoperative magnetic resonance imaging, patients were randomized to either RT alone (54 Gy) or RT followed by 6 cycles of standard dose PCV. The initial analysis after a median follow-up of >4 years did not show an advantage for the administration of chemotherapy [58]. The 5-year overall survival rate was 62% and 71%, respectively for patients treated with RT only or RT followed by PCV chemotherapy. The respective 5-year PFS rates were 42% and 60%. The differences were not statistically significant.

At recurrence after prior radiotherapy low-grade glioma will often have transformed into a higher malignant grade. In general, objective response rates to currently available chemotherapy have been modest [7, 17, 33, 45, 63, 73, 74]. Temozolomide, a novel alkylating agent has demonstrated activity in the treatment of recurrent high-grade glioma. Recent studies have also suggested some activity in low-grade glioma.

Response to treatment and prognosis may vary markedly in low-grade gliomas. The natural history of oligodendroglial tumours is more protracted compared to astrocytic tumours. Furthermore, oligodendrogliomas show a higher sensitivity to chemotherapy. In particular, pure oligodendroglioma with a loss of heterozygosity on chromosomes 1p/19q (recently identified as a translocation) have been identified as a distinct entity with a much more favourable natural history irrespective of treatment, and a particular respon-

siveness to chemotherapy and most likely also to radiotherapy [24]. Response rates after PCV or TMZ chemotherapy as high as 90–100% have been reported for recurrent (and transformed – anaplastic) oligodendroglioma [22, 23, 33], but were also shown in treatment-naive patients [8, 37, 38, 64].

The previous classical combination chemotherapy regimen (PCV; procarbazine, lomustine [CCNU], and vincristine) is now often replaced by single agent TMZ chemotherapy due to its ease of administration and favourable toxicity profile. Response rates for temozolomide as primary treatment of LGG have been reported in the range of 31–61% [2, 22, 33, 50, 51].

EORTC study 26971 evaluated temozolomide as first-line chemotherapy in recurrent oligodendroglioma, a response rate of just over 50% has been shown [74]. Alternatively, dose-intense continuous dosing schedules have been investigated [3, 27] and two studies have shown the feasibility of continuous dosing schedule. In a 21 days on/7 days off schedule patients can be treated with 85–100 mg/m^2 daily with double the dose intensity compared to the standard 5-day regimen [69, 70] and a response rate of 30% for untreated LGG with primary temozolomide has been reported [70]. As low-grade tumours have a limited number of cells in the proliferation phase the investigation of a drug in a more continuous administration is theoretically attractive. Furthermore, increased response is expected by the depletion of the intra-tumour methylguanine alkyl-transferase (MGMT), a DNA repair enzyme being consumed by chronic alkylating agent chemotherapy.

Conclusion

In the treatment of LGG the critical questions to be answered are timing of RT, effective dose and the balance between tumour control and potential toxicity. These questions have been addressed by 3 randomized trials. Dose escalation above 54 Gy does not improve tumour control but increases toxicity. Doses between 45 and 54 Gy in fractions of 1.8 Gy represent the current RT standard practice for LGG. The role of stereotactic radiosurgery, alternate fractionation schemes (hypo- or hyperfractionation), intensity-modulated and stereotactic radiotherapy as well as proton therapy remains undefined. These techniques are to be considered investigational and can currently not be recommended outside a clinical trial.

Toxicity of radiotherapy is mild if moderate total doses are applied; however potential late toxicity remains a concern in patients with long life expectancy. Recent preliminary data suggest an equal distribution of late neurocognitive deficits after treatment with RT or after chemotherapy.

Deferring radiotherapy until tumour progression or recurrence will not negatively impact overall survival and has been accepted as the standard approach for standard risk patients. Immediate postoperative RT may be indicated for high-risk disease according to the prognostic scores as defined by

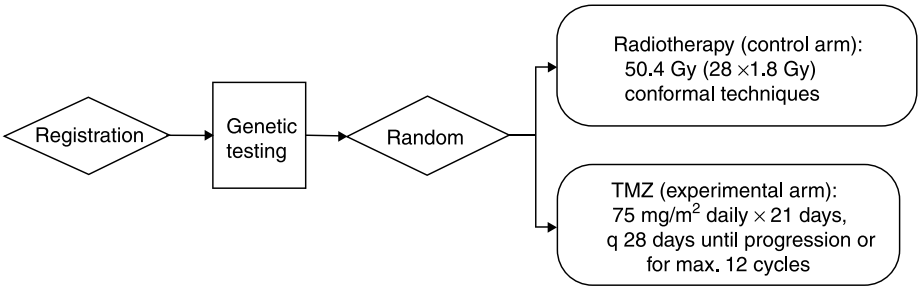
prospective trials and in patients with uncontrolled seizures as RT increased the median progression-free survival by nearly 2 years and improved seizure control. For patients at risk for rapidly progressive disease and malignant transformation, the optimal treatment has yet to be defined. Higher doses of radiation (>45–50 Gy) have failed to demonstrate an improved outcome and are associated with increased late toxicity, notably neurocognitive deterioration and radiation necrosis.

Adjuvant chemotherapy (PCV) after radiation did not translate into improved outcome in high-risk patients in a preliminary analysis with a median follow-up of 4 years. A number of phase II studies have demonstrated antitumour activity of temozolomide in low-grade glioma, both in the recurrent setting and as primary therapy. In particular oligodendroglioma with a LOH of 1p/19q have been indentiffiied as a distinct pathologic entity with a much more favourable prognosis and responsiveness to chemotherapy. Commonly these patients are considered for primary therapy with TMZ, although the available evidence does not support this approach. On an individual basis radiotherapy for smaller and localized tumours may be more appropriate, simpler, less toxic and less costly than prolonged chemotherapy over many months, while for large tumours requiring extended radiation fields primary chemotherapy may be considered.

Future

Management of patients suffering from a LGG remains challenging and is based mainly on the best definition of prognostic factors. Only few prospective randomized controlled studies have been conducted due to rarity of the disease, and the long-term follow-up needed in order to conclude.

In an ongoing international Intergroup study (EORTC 22033-26033, National Cancer Institute of Canada (NCIC) Clinical Trials Group study CE.5; Tasmanian Radiation Oncology Group (TROG), Australia) patients with high-risk disease or with progressive tumours are randomized between primary radiotherapy (28×1.8 Gy, 50.4 Gy, control arm) or primary chemotherapy with low-dose TMZ for up to 1 year (12 cycles) (Fig. 4). In addition to clinical factors patients are stratified according to a molecular analysis of the 1p/19q status. The central collection of tissue will also allow to subsequently identifying additional molecular markers in order to predict individual outcome and response to therapy. Trial endpoints are progression-free survival, overall survival, but also acute and delayed toxicity, quality of life and cognitive function. Two other American cooperative groups, ECOG and NCCTG, are proceeding with a phase III trial that will randomize high-risk patients as defined in the EORTC 22033-26033 study to radiotherapy plus/minus daily low-dose and subsequent standard temozolomide (Fig. 5). As in the EORTC study patients



Eligibility:
Age ≥ 40, or radiological progression,
Uncontrolled seizures/symptoms

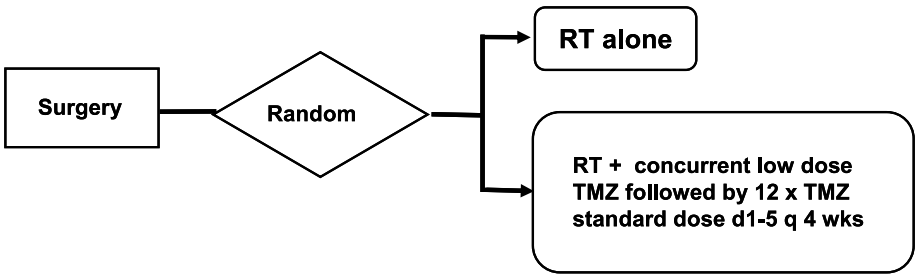
Pre-study:
Genetic testing of 1p deletion
Neuropsychologic testing

Stratification: 1p status, contrast enhancement on MRI, Age (<> 40), WHO performance status

Primary endpoint:
Progression-free survival

Secondary endpoints:
Overall survival,
Quality of life, Mini-mental state examination
Neurocognitive function
Toxicity

Fig. 4. Design of the EORTC 22033–26033/NCI-C/TROG trial for patients with a high risk LGG



Eligibility:
Age ≥ 40, or radiological progression,
or uncontrolled seizures/symptoms

Pre-study:
Central pathology review
1p/19q testing

Stratification:
1p 19 q status

Primary endpoints:
Progression-free survival
Overall survival

Secondary endpoints:
Cognition
Quality of life

Fig. 5. Design of the ECOG E3F05 trial for patients with a high risk LGG

will be stratified by 1p/19q deletion status [54]. Both studies include endpoints of neurocognition and quality-of-life as chemotherapy may have a greater impact on progression-free survival than on overall survival in order to evaluate if an improvement in progression-free survival also translates into an improvement in quality-of-life.

Irrespective of the development of new chemotherapeutic agents, also the radiotherapy techniques are evolving. The EORTC trial will promote conformal three-dimensional radiotherapy. The quality of radiation treatment is prospectively monitored and accompanied by regular supervision of radiation therapy centres within a quality assurance programme.

Highly conformal techniques based on modern imaging as co-registered MRI and PET scans, limiting the amount of normal tissue irradiated without compromising tumour control, will be the future approach in order to reduce late toxicity.

Summary of important facts

- Watchful waiting is appropriate for selected patients with controlled symptoms and in the absence of multiple risk factors.
- Younger patients, with complete or nearly complete resection and tumours with an oligodendroglial component have a more favourable prognosis; nevertheless close follow-up is needed as the risk of recurrence exceeds 50% over 5 years.
- Consideration for early radiotherapy should take into account tumour size and radiation volumes with respect to potential radiotherapy-related toxicity.
- Recent radiotherapy techniques constitute an improvement since they allow more focal or conformal dose delivery, intensity modulated RT may even improve this development.
- Immediate postoperative radiotherapy improves progression-free but not overall survival. Progressive patients can successfully be salvaged at a later stage.
- Higher radiation doses over 45–50 Gy did not translate into better outcome, but were associated with increased toxicity.
- Adjuvant PCV chemotherapy failed to prolong progression-free or overall survival in patients with high-risk low-grade glioma.

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The place of interstitial brachytherapy and radiosurgery for low-grade gliomas

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With 7 Figures and 4 Tables

Contents

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Abstract

Even though stereotactic brachytherapy has been used for treatment of complex located low-grade glioma for many years, its place within modern treatment concepts is still debated and only a few centers have gained experience with this complex treatment modality. The current article reviews selection criteria, treatment protocols, radiobiology, treatment effects, risk models and side effects of stereotactic brachytherapy. Potentially alternative techniques such as radiosurgery were also reviewed under consideration of radiobiological similarities and differences.

Keywords: Stereotactic brachytherapy; radiosurgery; low-grade glioma; gamma knife; iodine-125 seeds.

Introduction

World Health Organization (WHO) grade II glioma are a heterogeneous group of neoplasms usually encountered in younger patient populations with no or only minimal neurological deficits. The natural course of the disease varies considerably and is highly influenced by treatment independent factors such as age, pre-treatment performance score, tumour volume, contrast-enhancement on computerized tomography (CT)/magnetic resonance imaging (MRI) and tumour histology: Young patients with small and non-enhancing tumours, excellent performance score and oligodendroglial differentiation have usually favourable outcome scores (5-year survival rate in the range of 85%). The prognosis, however, dramatically decreases in the case of two or more unfavourable prognostic factors (5-year survival rates in the range of 10–40%) [5, 56, 84]. Over the last decade, molecular genetic markers have gained prognostic relevance and turned out to be helpful in dividing glioma into subgroups with respect to both prognosis and treatment decisions: A mutated TP53 status, for example, has been shown to be associated with a poor prognosis, and, conversely, loss of heterocygosity on 1p/19q predicts a favourable prognosis in case of oligodendroglioma or mixed cell tumours [80, 93, 110].

Clinical and molecular parameters may allow application of risk adjusted individualized management strategies including open tumour resection, various forms of radiation, chemotherapy or combination of these treatment modalities. Even though gross total tumour resection is still considered the therapeutic gold standard [24], its therapeutic impact is limited to a variable degree by a not well-demarcated brain to tumour interface, functional relevant areas within or nearby the tumour, and complex tumour/vessel interrelations [16–18, 61, 81, 82]. Accordingly, the variable "eloquent tumour location" has been identified as an important risk factor of surgery-related complications and as a main caurse of incomplete tumour resections in more recently published series dealing with WHO Grade II glioma [1, 17, 43].

The concept of stereotactic brachytherapy, which might offer minimal invasive treatment strategies for selected glioma patients, is by no ways new: It was introduced as early as 1914 [7] and has been refined and used ever since, with Fritz Mundinger being one of the pioneers [74, 75]. The method requires the permanent or temporary implantation of one or more radioactive sources in the form of seeds (Iodine-125) or wire pieces (Iridium-192) directly into the target volume. Tumour volume and target volume are ideally identical. Since the first implantation of a radioactive source into cerebral gliomas by Mundinger in 1953, his group had already gained an extensive experience with more than 213 Iridium-192 implants in cerebral gliomas by 1978 [74]. As compared to Iridium-192, Iodine-125 has a much lower photon energy spectrum (ranging from 27 to 35 keV), and therefore has a steeper dose decrease from the center of the implanted source to the periphery [57, 58]; accordingly, Iodine-125 is nowadays more often used for interstitial irradiation of low-grade glioma. Common radioactive isotopes utilized for brachytherapy are summarized in Table 1. The current article reviews the role of stereotactic Iodine-125 brachytherapy and other radiosurgical techniques for treatment of WHO grade I and II glioma; these multidisciplinary treatment modalities require the expertise of neurosurgeons, radio-oncologists, neuro-radiologists, and radiation physicists.

Stereotactic Iodine-125 brachytherapy

Rationale for interstitial irradiation

The aim of highly localized therapies, such as stereotactic brachytherapy, is to devitalize a well defined treatment volume and to avoid damage of the surrounding tissue. Conventional fractionated irradiation is delivered to brain tumours at dose rates in the range of 180–200 cGy/min. In contrast, interstitial irradiation is administered much more slowly (dose rate <100 cGy/h). Due to continuous low-dose rate irradiation the therapeutic ratio is increased: Ongoing repair of sublethal damage during irradiation has been shown to be more

Table 1. *Commonly used isotopes in brachytherapy for brain neoplasms*

Isotope	Emission	Mean energy (MeV)	Half-life (days)
Iodine 125	γ	0.028	60.0
Iridium 192	γ	0.38	74.0
Phosphorus 32	β	0.69	14.2
Rhenium 186	β	0.36	3.7
Yttrium 90	β	0.93	2.7

effective in non-neoplastic tissue than in tumour tissue, and neoplastic tumour cells tend to synchronize to the radiosensitive G2 and M phases of the cell cycle at dose rate levels >60 cGy/h [26, 34]. However, because repopulation and redistribution during the treatment are of minor importance in patients harbouring low-grade glioma, a much more protracted course of irradiation with extremely low dose rates (in the range of 10 cGy/h calculated to the boundary of the target volume) appears as a rational treatment strategy. The conventional linear quadratic model, which has been extended to protracted irradiation by Dale, predicts a maximum sparing of the late responding (non-neoplastic) tissue at the boundary of the target volume, and low-dose rate interstitial irradiation has been interpreted as the ultimate form of fractionation [3, 12, 13, 22, 23, 67, 68]. Even though the conventional linear quadratic model describes well the radiobiological advantage of an implant at the boundary of the target volume, it does not account for the effects of extreme dose inhomogeneity associated with brachytherapy. Characteristic tissue effects associated with the high dose zone in the vicinity of the implanted source (≥ 200 Gy) have been described experimentally, i.e. the development of a circumscribed radionecrosis with temporary changes in capillary permeability with a sometimes extensive edema and concomitantly reduced regional cerebral blood flow [19, 27, 39, 40, 45, 78, 79, 108]. Thus, on the one hand stereotactic brachytherapy fulfills one major definition of radiosurgery as given by Larsson [64], i.e. the accurate application of a highly focused necrotizing intratumoural dose with a steep dose decrease from the center to the periphery. On the other hand, continuous low-dose rate radiation exhibits characteristics of fractionated radiotherapy particularly at the boundary of the treatment volume [11, 12, 22]. A typical (inhomogeneous) dose distribution of Iodine-125 brachtherapy is described in Fig. 1: 100% of the defined tumour volume received the prescribed treatment dose of 50 Gy, 60% at least 100 Gy, 32% at least 150 Gy, and 20% at least 200 Gy. The synoptic evaluation of theoretical and experimental data suggests that the complex nexus of radiosurgical and radiotherapeutical effects may predestine interstitial continuous low-dose rate irradiation for aggressive treatment of low-grade glioma, which are generally slow growing infiltrative tumours harbouring an interface of neoplastic and non-neoplastic cells particularly at the boundary of the lesion. Stereotactic brachytherapy should not be confused with stereotactic radiotherapy (which exhibits much less dose inhomogeneity and lower intratumoural (non-necrotizing) doses), and stereotactic radiosurgery (which is – by definition – characterized by the absence of any effects of fractionation) [62–64, 69, 103].

Role of stereotactic biopsy

Histological grading of glioma is mandatory at the time of initial diagnosis to assess prognosis and to guide patients' clinical and therapeutic management.

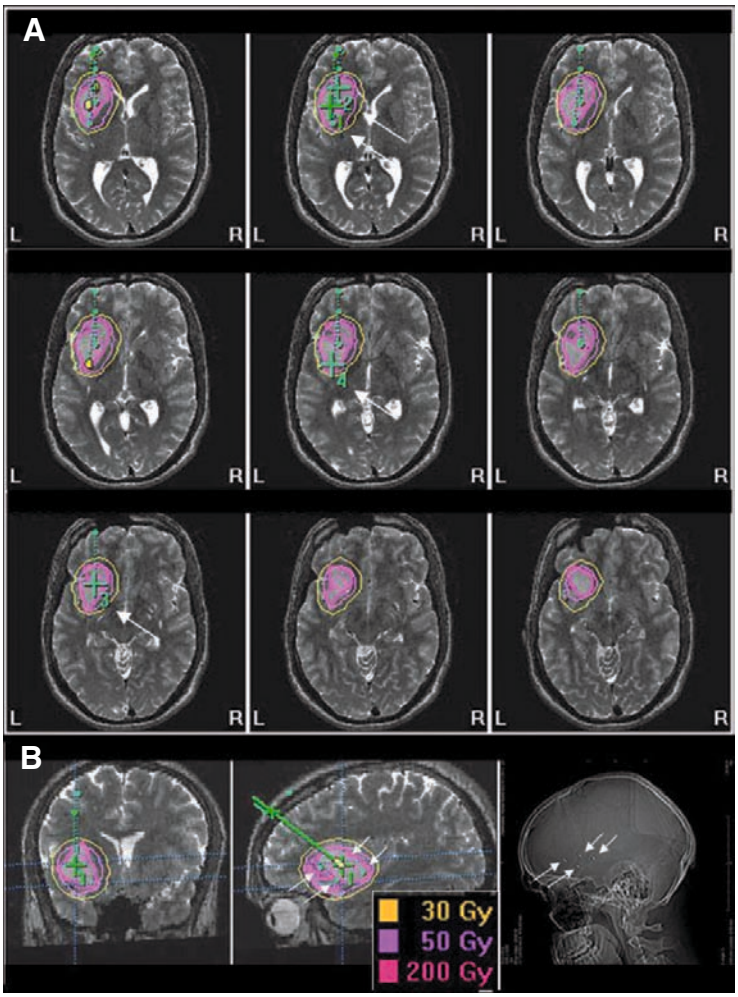

Fig. 1. *Treatment planning (axial, coronal and sagittal reconstruction).* (A) Representative example for treatment planning in a large left sided WHO grade II astrocytoma of the Insula of Reil. Tumour volume (on the basis of T2-weighted images and after fusion with the stereotactically localized CT) was 17.1 ml (defined by the pink line). Four temporary Iodine-125 seeds (activity 7.92 mCi (seed 1–3) and 4.13 (seed 4)) were stereotactically implanted in the rostral and caudal areas of the tumour (white arrows point on seed position as being indicated by the green intratumoural points). The magenta line represents the applied reference dose of 50 Gy calculated to the outer rim of the tumour. The dose rate was 7.1 cGy/h. The dose distribution is extremely heterogeneous: 98% of the tumour received the prescribed treatment dose of 50 Gy, 32% at least 150 Gy, and 20% at least 200 Gy. (B) Coronal and sagittal reconstruction of presurgical treatment planning (white arrows indicate tip of trajectories) (1–4). A sagittal reconstruction of postoperatively performed CT scans shows the four I-125 seeds (white arrows) in place

Conventional MR imaging lacks diagnostic sensitivity and specificity. "Typical" imaging features do not consistently predict the histological diagnosis [4, 49, 72]: Contrast enhanced tumour parts have been found not to be exclusively associated with malignant glioma, and non-enhancing tumours not always with Grade II glioma. Although stereotactic biopsy is often considered the diagnostic procedure of choice, important limitations exist for CT- and/or MRI guided biopsy procedures: As a consequence of the heterogeneous composition of glioma conventional biopsy has been shown to be associated with undergrading of the tumour (non-representative tissue sampling). Moreover, significant perioperative morbidity has been reported in many centers [38, 55]. Thus, high quality standards with regard to tumour imaging, biopsy techniques, and histological and molecular evaluation are essential for obtaining valid results in glioma patients. In the authors' view the inclusion of metabolic/molecular imaging data should be considered an essential step for the definition of representative biopsy trajectories. Multimodal planning following co-registration of CT (1 mm contrast enhanced axial images), MRI (2 mm T1-weighted gadolinium enhanced axial images, 2 mm T2-weighted axial images) and metabolic imaging data (e.g. positron emission tomography with amino acid tracers such as Methionin or O-(2-[^{18}F] fluoroethyl)-L-tyrosine (FET)) allows the definition of trajectories including biologically active "hot-spots" for optimal targeting [85, 109]. The intraoperative evaluation of smear preparations by the attending neuropathologist enables the determination of the extent of the biopsy procedure and might decrease the risk of the procedure [55]. Beyond conventional tissue diagnosis the identification of prognostically relevant molecular genetic features, such as loss of heterozygosity on chromosome 1p and/or 19q, the methylation status of the DNA repair gene O^6-methyl-guanine DNA methyltransferase (MGMT), and the TP53 status by means of small-sized stereotactically obtained tissue specimens will become an important aim of modern stereotactic neurosurgery [25]. Any decision in favour of a specific treatment strategy such as stereotactic brachytherapy should carefully consider delineation and size of the lesion, tumour grading, and results of the obtained molecular genetic evaluation.

Indication, technique, implants and dosimetry

Interstitial irradiation was initially considered to be indicated for patients with a circumscribed tumour with a maximum diameter of 5 cm [52–54, 56, 105] on CT- or MRI-scan, and a clinical (defined as drop of performance scores and/or increasing seizure frequency) or radiographical progress of the disease. Due to the results of available risk-analyses [53, 56], the treatment is now limited to small circumscribed tumours with a diameter not larger than 4 cm. Gliomas have been defined as circumscribed tumours, if tumour size calculations on the basis of T1- and T2-weighted MRI images revealed identical or nearly

identical results. Patients with non-circumscribed (diffuse) tumours or with infiltration of the corpus callosum are not considered suitable for stereotactic brachytherapy.

A detailed description of the stereotactic technique of biopsy and implantation has been given in several reports by Kreth *et al.* [52, 56]. The authors used the Riechert-Mundinger stereotactic device originally developed in 1956 and modified by Mundinger and Birg to be computer-compatible [73, 74]. Stereotactic surgery is usually performed under local anaesthesia (children under the age of 18 are operated under general anaesthesia). Unlike published in previous reports [52], the authors prefer to initiate stereotactic brachytherapy approximately one week after the biopsy procedure. This staged approach allows for a better counseling of the patient and a more individualized approach under consideration of the exact tissue diagnosis and the molecular genetic findings.

Iodine-125 seeds can be used for permanent or temporary implants, and exclusively low activity Iodine-125 seeds (<20 mCi) should be implanted. Due to the fact that experimental data pointed out an increased risk of prolonged edema for permanent implants [19, 27, 39, 52, 78, 79], the mode of implantation was changed and solely temporary implants have been used since 1985 by the authors. Permanent 125-Iodine seeds were designed to deliver a reference dose of 70–100 Gy to the tumour boundary. Temporary implants are nowadays selected to deliver a dose of 50 to 60 Gy to the tumour margin using a dose rate of approximately 10 cGy/h. Treatment parameters are summarized in Table 2. After the 125-Iodine seed (length: 4.5 mm), encapsulated in the tip of a teflon catheter, has been stereotactically implanted (usually via a 2 mm burr-hole for each catheter), the catheter is cut to the appropriate length and is secured at the burr-hole with a hemo-clip. The skin is then closed and re-opened for seed-removal after 20–30 days (local anaesthesia, no stereotactical equipment needed). CT-scan follow-up is performed one day after surgery and fused with the pre-operative localized CT to control the seed positions. Treuer *et al.* have assessed the accuracy of the stereotactic implantation procedure and

Table 2. *Treatment parameters brachytherapy: temporary and permanent seeds*

	Temporary	Permanent
Prescription dose	50–60 Gy at the tumour margin	70–100 Gy at the tumour margin
Dose rate	~10 cGy/h	
Number of seeds	1–5	1–5
I-125 seeds	Activity: <20 mCi	Activity: <10 mCi
Duration of implantation	20–30 days	Permanent

observed a mean spatial target point deviation of 2 mm. Target point deviations less than 1.5 mm were found to have only minor influence on surface dose and conformity [100]. Figure 1B shows a postoperatively performed CT scan and a sagittal reconstruction with four implanted seeds. A hospital stay of no longer than three days is required for the implantation procedure. The level of radiation upon discharge is checked and documented by the physicist. A flow chart of modern mutimodally imaging guided stereotactic biopsy and implantation is given in Table 3.

A prerequisite for stereotactic brachytherapy is that the treatment volume matches the tumour volume. Usually one to five seeds are used to achieve a conformal interstitial irradiation even of complexly shaped tumour volumes. Care has to be taken that the high dose zones (>150 Gy) always lie within the tumour tissue (to avoid radiation injury of the non-neoplastic tissue) and vessels are not adjacent to these zones [8]. Tri-planar treatment-planning using stereotactic CT and MRI ($\pm$ PET) data and an adequately equipped workstation must be considered indispensable [2, 60]. The isodoses are calculated by a computer program specially adapted for this purpose (e.g. @Target® or i-plan stereotaxy® (Brainlab®)). The importance of a low-dose rate radiation (in the range of 10 cGy/h) has been emphasized: The higher the dose rate the more pronounced are the biological effects and the side effects of the therapy [34]. Higher dose rates (30–60 cGy/h) alone or in combination with external beam radiation have been shown to be associated with a high frequency of radiogenic complication (30–50%) as demonstrated after stereotactic brachytherapy of malignant glioma [29, 59, 89]. There is no place of afterloading brachytherapy for treatment of low-grade gliomas [6, 28]. Steroids should be administered routinely on the day of implantation and for three days postoperatively at a daily decreasing dose of 24, 12, 8, and 4 mg dexamethasone, respectively.

Imaging changes after stereotactic brachytherapy

Typical imaging changes in the follow-up MRI/CT-scan can be detected in over 80% of the patients after interstitial irradiation of low-grade glioma [53, 56]:

Table 3. *Brachytherapy procedure*

- Fixation of the stereotactic frame
- Image fusion (CT-, MRI-, FET-PET-data)
- Stereotactic biopsy (2 mm burr hole)
- 3-D Treatment planning
- Stereotactic implantation of the seed catheters (2 mm burr hole for each catheter)
- Image fusion of pre- and postoperative CT-scan
- Duration of surgery: 2–2.5 h
- Duration of hospital stay: 3 days

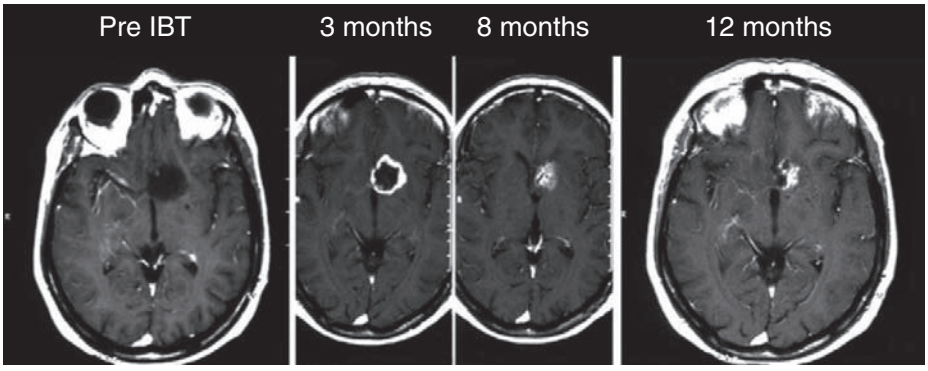

Fig. 2. *Typical imaging changes after stereotactic brachytherapy of a circumscribed hypothalamic WHO grade II astrocytoma.* A ring enhanced lesion was seen three months after implantation which resolved slowly during one year. No new clinical symptomatic occurred and no steroids were given. Complete response was finally achieved and the patient has a progression free survival of more than 9 years

An enhanced ring-formation can be observed – usually as early as four weeks after implantation – that develops gradually from the center to the periphery of the treatment volume and then slowly resolves over time (see Fig. 2). The inner zone of this so called "triple ring" formation represents necrotized tumour, which is surrounded by a small rim of still viable tumour tissue with increased permeability; the outer zone refers to treatment induced edema. Elimination of the necrotic tumour tissue is performed by macrophages, which is usually associated with renormalization of capillary permeability during a time period of approximately one year after treatment [27, 40, 79, 108]. These typical benign imaging changes of stereotactic brachytherapy should not be confused with tumour progression and/or malignant transformation at the time of follow-up MRI evaluation. First clinical and neuroradiological (MRI, T1/T2 with/without contrast) follow-up should be performed three months postoperatively. Thereafter, six months' intervals are sufficient.

Stereotactic brachytherapy in adult glioma patients

The literature on the role of open tumour resection, stereotactic brachytherapy, and chemotherapy only consists of retrospective data. Results of brachytherapy studies for low-grade gliomas have been already summarized by Vitaz *et al.* [104]. The most recently published long term study – conducted within the CT-era – concerned stereotactic Iodine-125 brachytherapy as initial treatment concept for 239 patients with eloquently located, circumscribed, supratentorial WHO Grade II glioma [56]. Interstitial irradiation was initially considered indicated for tumours with a diameter not exceeding 5 cm on CT or MRI scan;

with growing clinical experience treatment volumes became smaller. Patients had to have either clinical or radiographic progression to be considered candidates for interstitial irradiation. At the beginning of the experience permanent implants were used (103 patients), since 1985 temporary implants were preferred. The median follow-up was 10.3 years for the survivors. Five-, 10-, and 15-year progression free survival was 45%, 21%, and 14%, respectively. The corresponding survival rates were 51%, 32%, and 22%, respectively. High performance scores (median Karnofsky score: 80) were generally maintained throughout the follow-up period [42]; tumour progression, however, was associated with a decline on the Karnofsky scale. No levelling off of the Kaplan-Meier curves was observed and patients experienced tumour progression even 10 years after treatment. Long-term progression free survival of more than 10 years was seen in 31 out of 239 patients. The "best" treatment response after brachytherapy was achieved after 14 months (median). Complete response was seen in 18 patients, partial response in 33 patients, tumour control in 146 patients, and unrestrained tumour growth in 42 patients (non-responder group). Patients of the non-responder group were older and had larger tumours. Patients with complete to partial response did significantly better than those showing tumour control but did not differ in terms of histology, age, performance score, or tumour size. Perioperative mortality was 0.8% and perioperative transient morbidity 1.2%. Transient radiogenic complications occurred in 19 patients and progressive clinical symptoms in eight patients. The large range of treatment responses after brachytherapy, which is associated with a distinct prognostic profile, deserves further evaluation, e.g. on the molecular level, in order to improve selection criteria and to define the role of brachytherapy within the network of available treatment concepts more precisely. Voges *et al.* have reported slightly longer survival times after stereotactic implantation of low-grade gliomas. The sample size, however, was much smaller and the follow-up period less than 5 years [105]. In a retrospective analysis, Warnke *et al.* observed a significant reduction of seizure incidence and increase of benzodiazepine receptor density (as demonstrated by single photon emission computed tomography in a subset of 20 patients) after brachytherapy of 80 patients with temporal WHO grade II astrocytomas. Due to combined treatment by brachytherapy and anticonvulsive medication 79% of patients became seizure free after six months. The median follow-up observation period of the study was 4.1 years, but no data were presented beyond the six months interval [107].

The development of individualized, risk adjusted treatment concepts might be supported either by the assumption that different treatment strategies are considered similarly effective but differ significantly with regard to their risk profile or that modern treatment strategies will probably influence survival only if appropriate patients subgroups can be identified. Available preliminary data

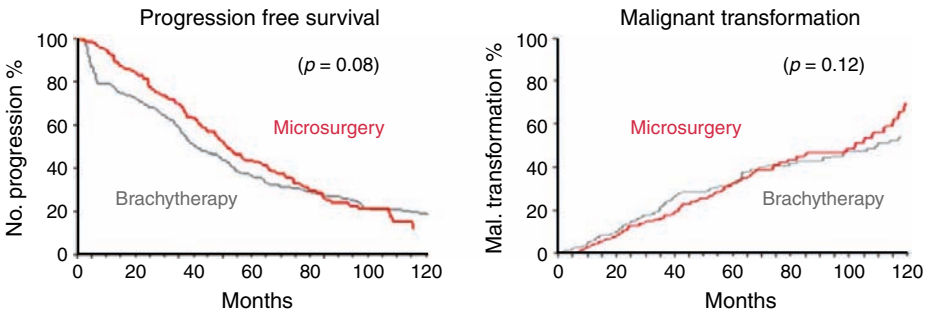

Fig. 3. *Efficacy of microsurgery versus brachytherapy*. Kaplan-Meier curves show similar outcome scores with respect to progression free survival and the malignant transformation rate in both treatment groups even after adjustment for the effects of age and Karnofsky score. Brachytherapy was initiated in 239 and microsurgery in 108 adult patients with so far untreated supratentorial WHO grade II gliomas (unpublished data of the authors)

seem to be in accordance with the former assumption: Progression free survival and the risk of malignant transformation after stereotactic brachytherapy alone of supratentorial WHO grade II glioma was not significantly different as compared to open tumour resection alone (Fig. 3). These findings remain true even after the adjustment for the effects of age and Karnofsky score. Patients in the surgery group, however, had significantly more often larger tumours, whereas patients of the brachytherapy group exhibited more often left-sided and deep-seated non-lobar tumours, indicating different risk profiles of the applied treatment strategies. Moreover, a comparison of 5-year survival after brachytherapy and external beam radiation (after various extent of open tumour resection) as conducted in the randomized trial on dose-response by the European Organization for Research and Treatment of Cancer (EORTC) Study 22844 revealed nearly identical results (Fig. 4) [41]. Long-term data analysis and risk assessment of comparable or alternative treatment strategies for well-defined subpopulations are an indispensable prerequisite for further development of individualized treatment concepts.

Precise high-dose application within the tumour, maximal sparing of the surrounding normal tissue, and therefore, preservation of the whole therapeutic spectrum for the future in case of tumour progression (e.g. re-implantation, external beam radiation) are the hallmarks of stereotactic brachytherapy [53, 56]. In the long-term analysis of Kreth *et al.* conventionally fractionated external beam radiation with a tumour dose between 50–60 Gy has been shown to be a possible treatment strategy in case of tumour progression or malignant transformation and was initiated in 109 out of 239 patients; Iodine-125 re-implantation was done in additional 21 patients because of small tumour

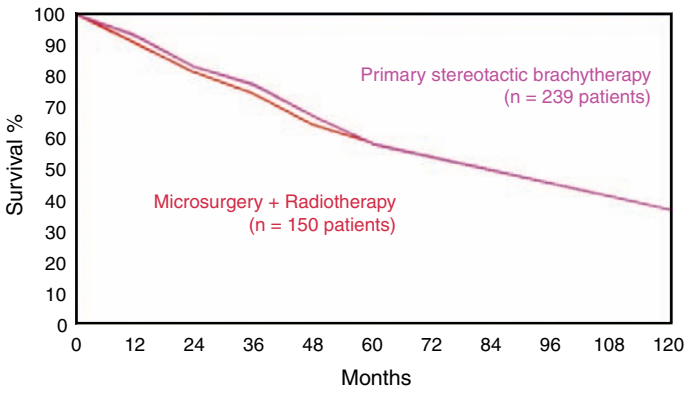

Fig. 4. *Overall survival after stereotactic brachytherapy versus microsurgery and radiotherapy.* Graph showing the overall survival after primary stereotactic brachytherapy as the pink plot [56] and after conventionally fractionated external beam radiation in combination with various degrees of tumour resection or biopsy as the red plot ([41]; EORTC study 22844) in patients with WHO grade II gliomas

recurrences. Additional irradiation was not associated with a higher incidence of radiogenic complications. The estimated probability to receive external beam irradiation after 5 and 10 years was 39% and 59%, respectively [56].

Stereotactic brachytherapy in paediatric glioma patients

The treatment results of pilocytic astrocytomas must not be mixed with those of WHO grade II gliomas. Patients with pilocytic astrocytomas represent a separate entity with a significantly younger age and a higher frequency of a non-lobar tumour location [52]. Notwithstanding a favourable overall prognosis after open tumour resection, which still remains the first-line treatment, poor physical, cognitive, and psychosocial outcome scores have been reported after long-term follow-up evaluation, and particularly patients with deep-seated tumours (diencephalon, optic chiasm, etc.) were concerned. Unfavourable outcome scores were at least partly attributed to side effects of surgical treatment [1, 94, 95]. Retrospective data indicate that stereotactic Iodine-125 brachytherapy is a safe, minimally invasive, and effective first-line treatment strategy for selected patients with highly eloquently located circumscribed glioma even in the paediatric subpopulation. In a series of 45 hypothalamic pilocytic astrocytomas (as part of a large series of 97 pilocytic astrocytomas) Kreth *et al.* [52] showed the treatment modality to be associated with low risk and high efficacy for this tumour entity. The 5- and 10-year survival rates for all 97 patients with pilocytic astrocytomas in that series were 84.9% and 83%, respectively. Unfortunately, detailed functional outcome data were not given and the median follow-up was only 5 years. Thus, not surprisingly, stereotactic brachytherapy is

seldom mentioned or discussed as a valuable treatment option for selected paediatric patients. In a pilot study of Peraud *et al.* it was hypothesized that the favourable radiobiology with effects of superfractionation at the boundary of the treatment volume predestine stereotactic brachytherapy for minimal invasive low risk treatment of complex located glioma (WHO Grade I or II) either as initial treatment or after previously performed partial tumour resection [83]. Tumour location was lobar (three patients), hypothalamic/suprasellar (four patients), thalamic/pineal (two patients), and mesencephalic/pontine (two patients). A hemiparesis was seen in three, hypothalamic insufficiency in two, and impaired visual function in three patients before the therapy. A complete response after brachytherapy was seen in four patients, and a partial response in seven patients. An example of stereotactic brachytherapy of a deep-seated WHO grade II astrocytoma is given in Fig. 5. None of the patients exhibited tumour progression or tumour recurrence at the time of last follow-up evaluation (median follow-up: 31.5 months), and no radiogenic complications (including cyst formation) occurred. Functional outcome scores were

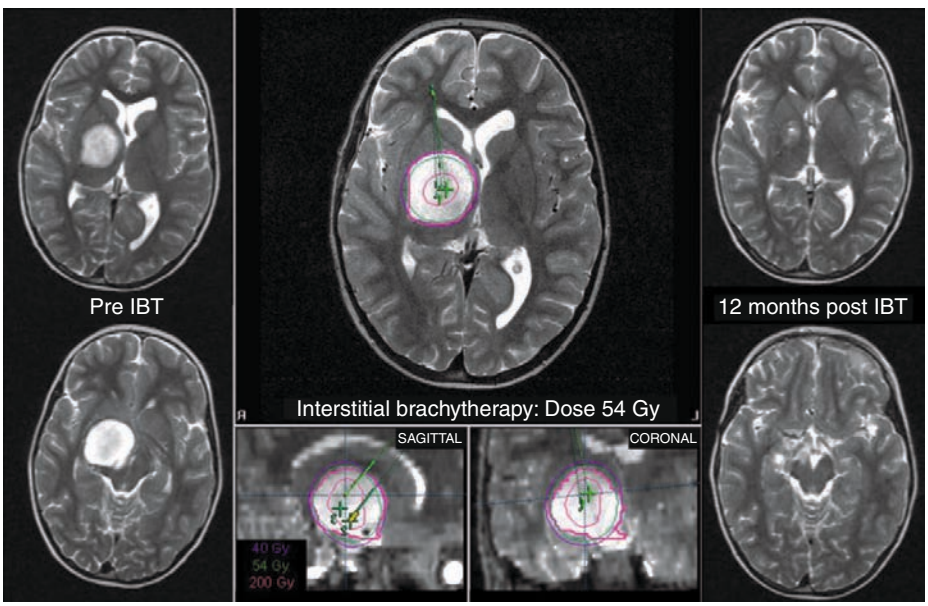

Fig. 5. *Radiologic follow-up after stereotactic brachytherapy*. WHO grade II astrocytoma of the left sided basal ganglia. The tumour was treated with stereotactic brachytherapy after histological assessment exhibiting complete tumour regression within 12 months. Dosimetry was performed on the basis of T2-weighted images (after image fusion with the stereotactically localized CT). Implantation of three Iodine-125 seeds revealed a conformal irradiation. The applied reference dose (calculated to the outer rim of the tumour) was 54 Gy. The dose rate was 10 cGy/h. The young patient exhibited a hemiparesis before treatment, which completely resolved within 6 months

favourable: Significant improvement of hemiparesis (three of three patients), improvement of endocrine deficits, and improvement of visual function. Visual and endocrine deficits remained unchanged in two patients and in one patient, respectively, and no child exhibited functional deterioration during the follow-up period. Preliminary retrospective data published by Herrera *et al.* are in line with the Peraud study [36]. More prospective data are necessary for further validation.

Radiogenic complications

In a small percentage of patients imaging changes can be progressive with subsequent increased edema and mass-effect associated with clinical deterioration. Those patients with transient symptoms (commonly headache) can usually be rapidly stabilized with steroids (dexamethasone, dose range between 2 and 12 mg per day) within 4–8 weeks. Very rarely, an expanding space occupying radiation necrosis that cannot be controlled with steroids might occur, making surgical decompression necessary. The estimated rate of radiogenic complications two years after brachytherapy in a series of 515 Grade I and Grade II glioma patients was 7.5% [53]. It was further demonstrated that radiogenic complications – if they occurred – typically were observed within the first two years after treatment, beyond that time interval further complications were usually not seen (only in one out of 515 patients a severe complication was noted 50 months after treatment) [53]. Long-term evaluation revealed that this estimation still remained true after a median follow-up period of more than 10 years [56], which indicates an important difference as to the risk profile of external beam radiation [47, 70].

Risk estimation of stereotactic brachytherapy

Taking into account the physical advantage of an accurate dose distribution of an intratumoural Iodine-125 implant, the rapid dose decrease from the centre of the treatment volume towards the periphery, and the very favourable biologically effective dose for the late responding tissue at the boundary of the target volume (due to effects of superfractionation), the possibility of radiation injury outside the target volume must be considered unlikely for interstitial low-dose rate irradiation for a large range of applied reference doses (60–100 Gy) [53]. Very seldom, however, radiation injury of non-neoplastic tissue outside the treatment volume might occur in case of rapid tumour shrinkage during the course of irradiation, thereby bringing normal tissue in the vicinity of the high dose zone. This mechanism has been shown to be important after implantation of permanent seeds [14, 53, 111]. An available risk analysis has indicated that radiogenic complications are predominantly generated inside the treatment

volume and are positively correlated with the volume of the intratumoural high dose zone (200 Gy isodose). Extrapolating the volume of the high dose zone to the corresponding treatment volumes for a given reference dose of 60 Gy, Kreth *et al.* demonstrate that beyond a cut-off of approximately 3.5 cm in tumour diameter (tumour volume 22.4 ml) an exponential increase of radiogenic complications can be expected. These results were further supported by long-term analysis: Median tumour diameter was 4.2 cm in patients with radiogenic complications and 3.4 cm in patients without complications. The estimated risk for a radiogenic complication for a tumour diameter < 4 cm and a diameter ≥ 4 cm was 9% and 25%, respectively (Fig. 6). Remembering (i) tissue effects of brachytherapy such as the increase of capillary permeability in the vicinity of the high-dose zone and (ii) the exponential increase of the damaged capillary surface area product with the square of the radius of the high-dose zone, the steep increase of radiogenic complications beyond a critical threshold is not surprising [27, 108]. As a consequence of these estimations the indication for low-risk interstitial irradiation of low-grade gliomas should be limited to small circumscribed tumours with a maximum diameter of 4 cm [56]. In case of larger tumours, which could not be treated with open tumour resection, the reference dose has to be decreased and care has to be taken to minimize the volume of the high-dose zone by implantation of multiple seed catheters (e.g. 4–6 catheters), which results in a more homogeneous dose distribution. Notably, the risk of stereotactic brachytherapy is not influenced by tumour location, re-implantation, and/or in addition to performed external

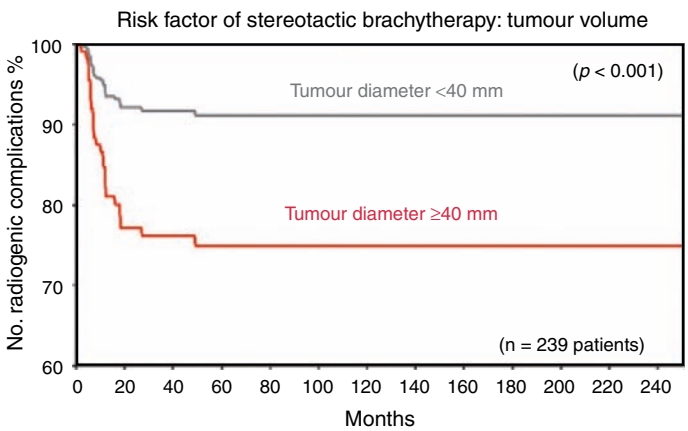

Fig. 6. *Prognostic factor in stereotactic brachytherapy: tumour volume*. Graph showing the incidence of radiogenic complications as a function of time. No long-term complications were observed. The impact of the tumour volume is emphasized: The estimated risk of a radiogenic complication for a tumour diameter < 4 cm and ≥ 4 cm was 9% and 25%, respectively (unpublished data of the authors)

beam irradiation, which underscores the protective effects of continuous irradiation for the non-neoplastic, late responding tissue [53, 56].

Microsurgery in combination with stereotactic brachytherapy

The complementary use of another highly localized neurosurgical/radio-oncological treatment option, such as stereotactic Iodine-125 brachytherapy, which is not so strongly limited by tumour location, might improve the risk/benefit ratio for a considerable number of patients even in case of large and complex located glioma. This combined approach might spare the patient from the increased risk of suffering a neurological deficit due to attempted radical resection as well as the increased risk of a radiogenic complication linked to interstitial irradiation of tumours with diameters >4 cm [71, 83, 90]. Two recently published pilot studies have focused on the feasibility, risk, and outcome of this combined treatment concept in paediatric and adult patients with complex located supratentorial low-grade glioma. Microsurgery plus stereotactic brachytherapy was considered to be indicated for patients with an untreated circumscribed, eloquently located supratentorial low-grade glioma with a diameter of more than 4 cm harbouring progressive clinical signs and symptoms and/or an increase in tumour size as indicated by follow-up magnetic resonance imaging (MRI) and/or risk factors for tumour progression/malignant transformation (e.g. age >40 years) [83, 90] (a typical example is given in Fig. 7). A planned partial tumour resection was intended using neuronavigation (BrainLAB AG, Feldkirchen, Germany) and intraoperative stimulation techniques in all cases. Extent of resection was preoperatively determined by the attending microsurgeon and stereotactic neurosurgeon taking into account the advantage and limitation of each treatment modality. Extent of resection was also influenced by the results of the intraoperatively performed stimulation/mapping procedures, and a distance in the range of 10 mm from detected functional areas (e.g. motor cortex, speech area) was considered a safe working margin for the microsurgeon. The usefulness of this distance has already been found by other groups [33, 77]. Tumour remnants located nearby or in the motor cortex or speech areas were intentionally left in place. Extent of resection was further modified in the case of an interrelation between the tumour and perforating arteries (e.g. in patients with insular glioma). Prospective evaluation revealed a transient morbidity rate of 27.8% after a planned partial tumour resection in the adult and 0% in the paediatric population; there was no permanent morbidity and no mortality. Paediatric patients had smaller tumours and more often pilocytic astrocytoma, which might explain the lower morbidity rate. The determination of the extent of resection by the microsurgeon and the attending stereotactic neurosurgeon before treatment enabled low-risk surgical treatment of complex located glioma; moreover, a clear tumour volume reduction (from 66 ml to 9.3 ml in the adult population, from 52 ml to 14.9 ml in the paediatric

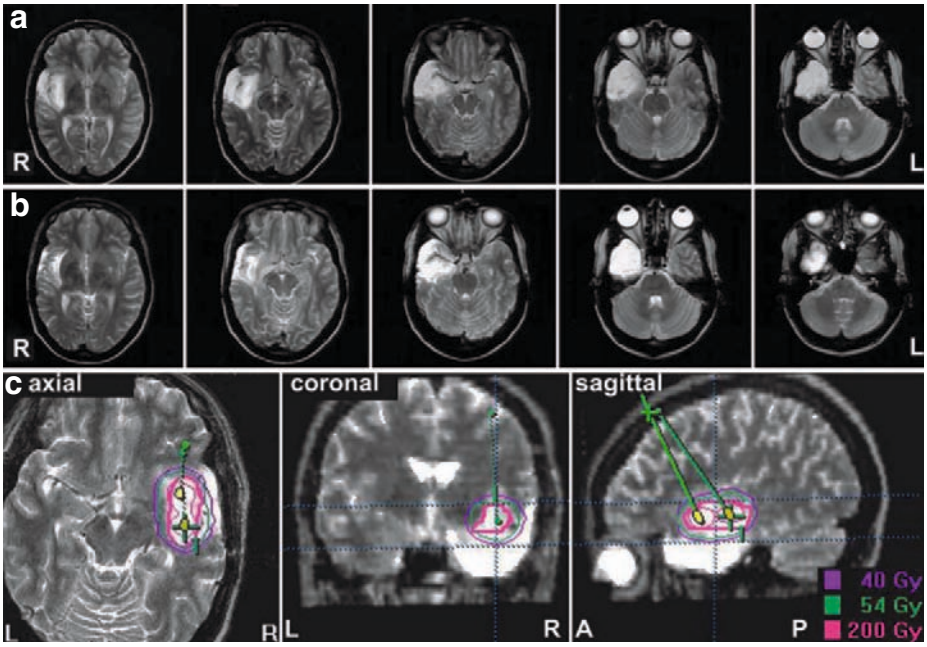

Fig. 7. *Microsurgery in combination with interstitial brachytherapy in complex located glioma:* MRI scans of a 27-year-old female patient harboring a right temporal WHO grade II astrocytoma infiltrating the insula of Reil before (a) and two years after (b) combined microsurgical/stereotactical brachytherapeutical treatment. The temporal part of the tumour had been removed microsurgically. The insular part of the tumour has been implanted with two Iodine-125 seeds and shows partial response according to the modified MacDonalds criteria for low-grade glioma. Radiation treatment plan (c) for the same patient after microsurgical resection of the temporal part. Axial, coronal and sagittal planes show trajectories as well as isodoses (40, 54 and 200 Gy) for implantation of two Iodine-125 seeds (with authors permission from Schnell *et al.* [90])

population) could be achieved and enabled safe treatment of the residual tumour volume by stereotactic brachytherapy in each patient. There was no radiogenic complication in these series so far. No patient of the paediatric population had received external beam radiation and/or chemotherapy at the time of the closure of the study and the overall 5-year probability to receive additional radiotherapy and/or chemotherapy was 18% in the adult population. The combination of two highly localized treatment modalities enabled the treatment of the whole tumour volume in all cases as defined by MRI evaluation. These preliminary results compare favourably with those reported in the literature after open tumour resection or stereotactic brachytherapy alone [18, 43, 71, 81, 82, 88, 101]. For example, gross total resection of low-grade glioma of the insula of Reil was aimed for in two recently published studies, but

could only be achieved in approximately 40% of the patients; early postoperative deficits were seen in 40–70% (permanent morbidity: 5–10%) [17, 61]. Complex tumour/vessel interrelations have been considered the major cause for high rate of incomplete resections and surgery-associated complications in these series.

Radiosurgery

Background

Radiosurgery is a term coined by Leksell in 1951 to describe the closed-skull destruction/devitalizing of a stereotactically defined target volume with a single high dose of ionizing radiation. Normal tissue radiation can be minimized due to stereotactic definition of the target and a sharp dose gradient, which is achieved by precise multiple beam shaping adjusted to virtual target volumes that have been defined by multimodally imaging data [51, 65, 66]. Classic stereotactic frame-based (Gamma Knife® or LINAC system) as well as a novel frame-less setup (based on a proprietary image-guidance system [Cyberknife® technology]) ensure high precision so that the virtually planned target volume closely coincides with the treatment volume of conformal radiation in situ.

Rationale for radiosurgery

The goal of radiosurgery is to arrest the cell-devision capability of target cells irrespective of the individual cells' mitotic activity and radiosensitivity [32, 51]. The predominant radiobiological effects of stereotactic radiosurgery, as described in animal models [48] and in vitro cell culture studies [35, 97], are the induction of apoptosis, modulation of cell motility, irreparable cellular damage, and delayed vascular occlusion causing tissue necrosis [48, 50, 91, 97] as being similarly observed after stereotactic brachytherapy [78]. Compared to the complex nexus of radiosurgical effects within the high-dose zone (aiming for the solid tumour mass) and protective effects of fractionation at the boundary of the target in stereotactic brachytherapy, stereotactic radiosurgery is characterized by less dose inhomogeneity within the target volumes [9, 15, 99] and the absence of any effects of fractionation. This has been recently pointed out by Viola *et al.*, who have theoretically compared some radiobiological aspects of LINAC radiosurgery and Iodine-125 stereotactic brachytherapy. With some critical methodological limitations in extrapolating theoretical considerations to a clinical setup the authors suggest that LINAC-based radiosurgery enables a more homogeneous dose distribution within the target volumes while stereotactic brachytherapy seems to be less damaging to

surrounding normal tissues, probably due to protecting effects of superfractionation [103]. Thus, ideal targets for radiosurgical treatment have been shown to be singular/multiple circumscribed lesions, with sharply delineated edges to the surrounding healthy brain tissues such as brain metastases, meningeomas, acoustic schwannomas, and arteriovenous malformations, particularly in eloquent locations not suitable for open tumour resection [98].

Risk factors of radiosurgery

Even though normal tissue irradiation can be minimized to a thin shell around the treatment volume, which is realized by stereotactic definition of the treatment volume and the sharp focus of multiple radiation beams, the volume of this shell is directly proportional to the treatment volume, which turned out to be the most important risk factor in radiosurgery; accordingly the amount of normal tissue that lies within the prescription dose has been shown to be positively correlated with the risk of the radiosurgical procedure [92, 102, 106]. As a consequence of these estimations the prescription dose has to be adjusted to the size of lesion [76]. For lesions in the range of 4 cm in diameter, for example, prescription doses of 13 Gy or less are believed to be safe, as predicted by Kjellberg's one percent dose-volume isoeffect line and the integrated logistic formula of Flickinger [20, 46]. A dose in that range, however, has limited or no biological advantage as compared to conventionally fractionated external beam radiation. Thus, treatment volumes suitable for radiosurgery should be smaller and, ideally, lie in the range of 3 cm in diameter or less. Complications were also found to be correlated with tumour dose inhomogeneity, maximum tumour dose, and number of isocenters; all these parameters, however, were usually intercorrelated with the treatment volume and underscore its prognostic importance in radiosurgery. Even though the treatment volumes were also considered the essential risk factor in brachytherapy, its influence is – in contrast to radiosurgery – not explained by radiation injury of normal tissue in case of larger tumour volumes, which indicates important radiobiological differences between brachytherapy and radiosurgery. It is important to note that risk factors of radiosurgery have been obtained from retrospective analyses of different, mostly sharply delineated lesions (such as metastases) and could therefore not be extrapolated to infiltrative tumours such as low-grade gliomas, which represent a completely different target.

Radiosurgery in low-grade gliomas

Radiosurgical treatment is seldom used in low-grade gliomas. Available retrospective, single institutional studies suffer from major limitations such as small study populations (in the range of 10–30 patients), absence of any control

group, short follow-up periods (in the range of 28–78 months), intermingled analysis of Grade I and Grade II gliomas (including brainstem gliomas, predominant inclusion of recurrent/progressive tumours (frequently after previously performed external beam radiation), highly variable treatment volumes (range: 1–44 ml) and applied tumour doses (range: 8–24 Gy).

The Pittsburgh group, for example, has examined the role of stereotactic radiosurgery in the management of 37 pilocytic astrocytomas WHO grade I and 12 circumscribed WHO grade II astrocytomas [30–32]. Stereotactic radiosurgery was considered indicated in patients with tumour recurrences after previously performed external beam radiation (pilocytic astrocytomas: 9/37 pts, grade II astrocytomas: 4/12 pts), and in those with eloquently located tumours (after previously performed biopsy or various degrees of tumour resection). Tumour size was highly variable (range: 0.9–45.1 cm^3) and the same remained true for tumour location including 18 pilocytic astrocytomas and four fibrillary astrocytomas of the brainstem. The median radiation dose to the tumour margin was 15 Gy (range: 9–22.5 Gy). Median follow-up was shorter for pilocytic astrocytomas (25 months versus 52 months, respectively). The 2-year tumour control rate for pilocytic astrocytomas was 68%; diffuse tumours, previous fractionated radiation therapy, increased age (>18 years of age), and applied treatment doses of less than 15 Gy were significantly associated with a worse prognosis [30]. For 12 patients with WHO grade II astrocytomas 4-year progression free survival was in the range of 67%. One out of 49 radiosurgically treated patients developed a symptomatic edema with worsening of his hemiparesis six months after the therapy. No risk analysis was possible due to the small sample size.

Boethius *et al.* [10] reported a more favourable outcome after radiosurgery in 19 children suffering from pilocytic astrocytomas (16/19 patients had residual tumours after surgery), which were predominantly located within the brainstem (12 tumours). Indication for radiosurgical treatment, however, was not defined and a detailed analysis of the tumour location within the brainstem was not given. Presumably, small, circumscribed, unifocal lesions were considered eligible. The authors used lower tumour doses (10–12 Gy) and achieved higher tumour control rates (100% after a median follow-up period of 7 years) than the Pittsburgh group [31, 32]. Two patients in the Boethius series suffered from severe radiogenic complications; one of them had been treated with external beam radiation before radiosurgery. Whether the favourable outcome data should be related to smaller tumour volumes (range: 0.3–11.5 vs. 0.9–45.1 cm^3 in the Pittsburgh studies), or to patients with a more benign natural course of the disease remains unknown [86, 87].

Heppner *et al.* presented outcome data of 49 patients with low-grade gliomas (including 21 pilocytic astrocytoma) after Gamma knife surgery with a median follow-up period of 63 months [37]. Radiosurgery was felt to be indi-

cated for eloquently located small residuals or recurrences after microsurgery. Five out of 49 patients received external beam radiation before radiosurgery, tumour location was extremely variable (e.g. brainstem: 11 tumours, non-lobar: 14 tumours, lobar: 17 tumours) and the applied tumour dose and the treatment volume were comparable with those of the Pittsburgh protocol (median tumour margin dose: 15 Gy, tumour size: range 0.5–36 cm^3). Median progression free survival was 37 months and not influenced by histology, treatment volume, previously performed external beam radiation, and the applied tumour dose. Four patients suffered from symptomatic radiogenic complications. No risk factors could be identified. Kida *et al.* [44] addressed Gamma knife radiosurgery in a series of 12 patients with pilocytic astrocytomas and 39 patients with apparently untreated grade II astrocytomas. Radiosurgery was indicated for circumscribed eloquently located tumours with a maximum diameter of 3 cm. The majority of pilocytic astrocytomas were located in and round the optic pathways and hypothalamus. The margin dose for grade I astrocytomas was comparable to the Boethius study (mean 12.5 Gy) and similar to the Pittsburgh and Heppner study for grade II glioma. A short follow-up prevents valid analysis of outcome data at this moment. Symptomatic radiogenic edema was seen in 18 out of 51 patients and was more often seen in Grade II glioma. No risk factors were identified. A summary of the mentioned studies with regard to the analyzed sample size, applied treatment strategies and outcome measurements is given in Table 4.

Taking into account both the radiobiological characteristics and favourable clinical outcome scores of stereotactic brachytherapy and the inconclusive data on radiosurgery of low-grade glioma, the authors do not use the latter treatment option at this moment although Cyberknife® radiosurgery is available at their own institution. However, future studies offering more versatile risk/benefit analyses will clarify whether there is a place for radiosurgery e.g. in the treatment of well-delineated pilocytic astrocytomas.

Summary of important facts

To further establish stereotactic brachytherapy as an effective first-line treatment strategy for selected patients with eloquently located and/or deep-seated low-grade glioma, that are not suitable for low risk gross open tumour resections, following important facts should to be considered: (I) Stereotactic brachytherapy aims for the devitalization of a well-defined treatment volume with minimal damage to the surrounding tissue. (II) Patients suffering from symptomatic/progressive circumscribed glioma with less than 4 cm in diameter and with no infiltration of the corpus callosum qualify for stereotactic brachytherapy. (III) In larger tumour volumes a

Table 4. *Summary of studies addressing stereotactic radiosurgery in WHO grade I/II gliomas*

Reference	No. of patients	Tumor location	Pathology	Follow up	Prior treatment modality	Treatment volume	Mean dose at tumor margin	Treatment outcome (No. of patients)	Complications
[30, 31]	37	Supratentorial: 21 Infratentorial: 16 (Incl. brainstem: 18)	Grade I: 37	28 months	Surgical resection: 24 Fractionated radiotherapy: 9	0.42–25 cm^3	15 Gy	Complete resolution: 10 $>50\%$ reduction in volume: 8 Unchanged: 7 Progression: 12	
[32]	12	Supratentorial: 7 Brainstem: 4 Cerebellum: 1	Grade II: 12 (Fibrillary astrocytomas)	52 months	Surgical resection: 7 Fractionated radiotherapy: 4	1.2–45.1 cm^3	15 Gy	Complete resolution: 1 Reduced tumor volume: 4 Unchanged: 3 Progression: 4	
[10]	19	Brainstem: 12 Cerebellum: 3 Supratentorial: 4	Grade I: 19	5.9 years	Surgical resection: 17 Brachytherapy: 1 Conventional radiotherapy: 2	0.3–11.5 cm^3 (spheroids)	10–12 Gy	Complete resolution: 4 Unchanged: 15	Adverse radiation effects: 5 Temporary neurol. decline: 2
[37]	49	Lobar: 17 Non-lobar: 16 Brainstem: 11	Grade I: 21 Grade II: 28	63 months	Surgical resection: 24 Conventional radiotherapy: 2	0.5–36.0 cm^3	15 Gy	PFS (months): 37 Stable desease: 37 Progression: 12	Temporary neurol. Decline: 3 Radiological changes: 7
[112]	20	Brainstem: 20 (Incl. Tectum: 13)	Grade I: 5 Grade II: 5 (unknown: 10)	78 months	Surgical resection: 5	0.4–9.7 cm^3	12.8 Gy	Complete resolution: 4 Reduced tumor volume: 12 Progression: 4	Neurol. Decline: 3 Death due to progression: 1
[44]	51	Optic pathways: 11	Grade I: 12 Grade II: 39	27.6 months	none	<3 cm diameter	Grade I: 12.5 Gy Grade II: 15.7 Gy	Grade I: Regression 6 Stable desease 5 Grade II: Regression 5 Stable desease 13	Radiol. changes: 18 Temporary neurol. decline: 9

combined microsurgical/brachythera-peutical approach should be considered a treatment option. (IV) Institutional and technical prerequisites include a comprehensive network of neurosurgeons, radio-oncologists, neuro-radiologists, and radiation physicists. (V) Versatile histopathological and molecular genetic characterization of tumour probes harvested from advanced stereotactic biopsy procedures, that include modern multimodal (including metabolic) imaging techniques, are a fundamental prerequisite in a risk-adjusted individualized treatment planning and should be achieved prior to stereotactic brachytherapy in a staged fashion. (VI) Treatment planning should be done with a low-dose rate (10 cGy/h) and a reference dose of 50–60 Gy calculated to the tumour margin. (VII) The postoperative routine includes steroid treatment for three days and a post-surgical CT-scan to control seed position before discharge. (VIII) A first clinical and neuroradiological follow-up evaluation is scheduled three months after seed removal and every six month thereafter. (IX) Typical imaging changes after brachytherapy include various degrees of focal contrast enhancement and/or edema and should not be confused with tumour progression or malignant transformation. (X) The use of radiosurgery for low-grade gliomas is not yet well defined.

Conclusion

Overall survival and progression-free survival of adult patients harbouring circumscribed, supratentorial WHO grade II astrocytomas and oligoastrocytomas and a progression of their disease at the time of presentation is mainly determined by treatment-independent prognostic factors such as age, Karnofsky score, and tumour volume. Risk minimization must be considered the hallmark of any modern treatment strategy, and stereotactic Iodine-125 brachytherapy fulfills this requirement for selected patients with circumscribed, supratentorial astrocytoma or oligoastrocytoma with a tumour diameter of less or equal 4 cm in any location of the brain as initial treatment or as combined treatment concept in combination with microsurgery for highly selected eloquently located larger glioma. The absence of long-term complications (as demonstrated in the adult population) also allows the application of stereotactic Iodine-125 brachytherapy alone or in combination with a planned partial tumour resection for treatment of complex located, circumscribed WHO grade I and II glioma in the paediatric patient population. This still new combined approach deserves further prospective evaluation. Long-term data analysis and risk assessment of comparable or alternative treatment strategies for well defined subpopulations are an important prerequisite for further development of individualized treatment concepts. The role of radiosurgery for treatment of low-grade glioma is still debated; due to the absence of sufficient selection

criteria, treatment protocols, risk analysis and follow-up data, radiosurgical treatment cannot not be recommended for low-grade glioma at this moment in daily clinical practice.

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Health-related quality of life aspects in patients with low-grade glioma

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Contents

Abstract

Standard therapeutic options for brain tumors include surgery, radiotherapy, and chemotherapy. Unfortunately, these same therapies pose risks of neurotoxicity, the most common long-term complications being radiation necrosis, chemotherapy-associated leukoencephalopathy, and cognitive deficits. Currently, there is no consensus on the treatment strategy for these tumors. Because of the relatively slow growth rate of low-grade gliomas, patients have a relatively long expected survival.

Compared to traditional outcome measures like (progression-free) survival, evaluation of health-related quality of life may be time-consuming and burdensome for both the patient and the doctor. Besides, given the relatively low incidence of brain tumors and the ultimately fatal outcome of the disease, the interest in HRQOL emerged relatively late in these patients. Moreover, the notion that the disease itself may affect the patient's ability to judge his or her own functioning may hinder the use of patient self-reported measures.

The studies presented in this chapter describe outcomes of both single dimensional and multidimensional methods of studying HRQOL. Although only few studies incorporated HRQOL as outcome measure, most studies have embraced the notion that an accurate assessment of HRQOL must be based on patient self-report. HRQOL instruments from other cancer groups are adapted for use with brain tumor patients. The multidimensional scales used to study changes in HRQOL studies in brain tumor patients provide a more comprehensive view of what is important to the patient concerning living with their disease and receiving treatment.

In future trials, more sensitive measures of long-term cognitive, functional, and HRQOL outcomes on LGG patients at important time points over the disease trajectory are needed to better understand the changing needs that take place over time.

Keywords: Health-related quality of life; cognitive functioning; neurosurgery; radiotherapy; chemotherapy; mood.

Introduction

Diffusely infiltrating low-grade gliomas (LGGs) include astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas (WHO grade 2). Supratentorial LGGs account for 10–15% of all adult primary brain tumors [34]. Most patients present between the second and fourth decades of life, and a seizure is the presenting symptom in 72–89% of patients [89]. Mental status changes are present in 3–30% of patients at the time of presentation [50, 93, 95]. Ten to 44% have signs of increased intracranial pressure, such as headache and nausea, when first diagnosed [61, 93, 95]. Focal neurological deficits are present in 2–30% of patients [69, 95]. However, patients may also have normal neurological examinations.

Although their name might imply otherwise, most LGGs result in considerable morbidity and inevitable death. Management of LGG is controversial because these patients are typically younger, with few, if any, neurological symptoms. Historically, when LGG was diagnosed in a young, healthy adult, a commonly accepted strategy was a "wait and see" policy because of the indolent nature and variable behavior of these tumors. The support for this practice came from several retrospective studies showing that, when therapy

was deferred, patients had no difference in outcome (survival, health-related quality of life [HRQOL]) from time of radiological diagnosis [12, 61, 69]. There was also a belief that LGGs did not necessarily transform into malignant tumors over time. However, the latter notion has been refuted. In retrospective studies of the kinetics of glioma growth, continuous growth was seen in the premalignant phase before anaplastic transformation [56]. The majority of LGGs are now known to progress to malignant gliomas with time. A better understanding of the natural history of LGGs has led to an interest in earlier treatment. The decision as to whether a patient with LGG should receive resection, radiotherapy, or chemotherapy is based on a number of factors including age, performance status, location of tumor, and patient preference. Since LGGs are such a heterogeneous group of tumors with variable natural histories, the risks and benefits of each of the three therapies must be carefully balanced with the data available from limited prospective studies.

The incidence of treatment-related late-delayed encephalopathy in these patients is steadily increasing, not only because of increased survival but also because of improved detection (neuroimaging and extensive cognitive function testing) and raised awareness among both physicians and patients [19]. The information on treatment options and their side-effects in brain tumor patients that is readily available on the internet has substantially added to this awareness.

With 5-year and 10-year progression-free rates of 50% and 12%, respectively, for supratentorial low-grade astrocytomas, low-grade oligodendrogliomas, and mixed gliomas [51], and a median better survival of 16.7 years for the latter two groups [61], patients with LGGs can survive in a stable state for several years after diagnosis. The long-term effects of the disease and its treatment on cognitive functioning and HRQOL of these long-term survivors are especially salient.

Health-related quality of life assessment

The definition of health-related quality of life (HRQOL) is the level of performance in the major domains of life function as measured from the patient's perspective [30, 32]. The concept of HRQOL is not unidimensional, but instead covers a number of life domains. For each domain, HRQOL may be perceived differently and be differentially weighted. Changes in one domain can influence perceptions in other domains. Thus, disruption in the physical domain is likely to affect the individual's psychological or social well-being. While many different domains have been described [14], most generally HRQOL is defined as including physical, psychological, social, and spiritual domains [2, 15, 28]. No "gold standard" of measurement, however, currently exists to assess HRQOL, but there are several frequently used scales employed to monitor function and the effects of treatment.

Interest in HRQOL grew after 1984, when the U.S. Food and Drug Administration (FDA) demanded that the efficacy of new anti-cancer agents be demonstrated by improved survival or evidence of enhanced HRQOL. Coupled with patients' involvement in their treatment decisions and concerns about informed consent, issues regarding HRQOL with one treatment versus another led to heightened interest in finding wars to measure this variable. Karnofsky and Burchenal actually described in 1949 that in addition to survival, subjective improvement was equally important in the evaluation of patients' responses to treatment [40]. Despite that early observation, however, today only selected trials assess HRQOL, usually when there is a small likely treatment advantage (e.g., trials of chemotherapy agents in pancreatic cancer) or when a highly effective new treatment has significant side effects (e.g., stem cell transplantation [46]).

Initially, the most widely used was the functional living index-cancer ([FLIC] [76]). A 22-item scale with physical well being and emotional subscales, the FLIC has largely been replaced by scales specifically for use with cancer that provide broader information. The cancer rehabilitation evaluation system (CARES) is a scale that consists of 139 items concerning cancer problems across the six HRQOL domains [74]. A series of HRQOL measures were developed and tested by the European Organization for Research and Treatment of Cancer ([EORTC] [1]). The scales have a core of questions that are applicable to the HRQOL for all patients with cancer and modules which are attached to query the specific issues related to a disease site (e.g., prostate, breast, lung cancers).

A similar approach has been used by Cella *et al.* [16] in the development of the functional assessment of cancer therapy (FACT), which adds an aspect of patient assessment regarding the discrepancy between prior and present functions. In addition to the FACT-G, the core questions, Cella has developed modules for major cancer sites and common problems requiring subjective assessment, such as nausea, vomiting, and pain. Aside from the Karnofsky performance rating scale, Spitzer and colleagues' quality of life index (QL-index) is the only observer-rated measure of HRQOL that is used with any frequency [80].

Additional scales, not developed specifically for cancer but widely used, are the psychosocial adjustment to illness scale (PAIS) and the sickness impact profile ([SIP] [9, 21]). The PAIS, in particular, has been used extensively with several chronic illnesses, including cancer. The SIP scale is similar in format to CARES, in that it lists 136 problems that can result from illness that affect HRQOL.

Most HRQOL scales presently being developed are designed for self-report or to be completed in response to structured interview questions [17, 81]. Traditionally, such forms were administered at the time of clinic visits;

however, the use of trained telephone interviewers in co-operative group trials in the CALGB has been found to be not only a more practicable approach but more effective because it takes the collection of HRQOL data away from the rushed clinic setting [46]. The method ensures consistency in terms of evaluation and promotes better compliance as well as patient satisfaction. There are fewer missing data points because answers can be clarified immediately with the patient by the interviewer. Using this type of telephone approach, in which the patient has the written questions and responds to them at the interviewer's request, findings were comparable with those attained using face-to-face interviews.

Efforts in HRQOL research have also concentrated on the development of a unitary measure that might combine length of survival and HRQOL, referred to as "quality-adjusted life years" or QALY. "TWIST" (time without symptoms or toxicity), is another QALY method developed by Gelber and Galdhirsch [29] and by Goldhirsch *et al.* [31]. In this method, the number of months in which the patient experienced symptoms (weighted as to toxicity) or was in relapse is subtracted from overall survival time, yielding a QALY score. In QALY research, weights, which are either empirically derived or chosen arbitrarily, are assigned equally to disabilities and symptoms in the two treatment arms. In this manner, the effects of difference between symptoms on HRQOL can be mathematically taken into account. These methods, coupled with economic analysis, are providing increasing information to assist patients in making decisions about cancer treatments.

In summary, patient-oriented outcome measures, such as symptoms, physical functioning, and HRQOL, are most relevant for patients who cannot be cured of their disease. This is the case for most brain tumor patients for whom palliation of symptoms and the maintenance or improvement of HRQOL may become important goals early or late in the disease trajectory. Evaluation of treatment in brain tumor patients should therefore not only focus on survival improvement, but should be aimed at neurological functioning and at adverse treatment effects on the normal brain. In this respect, cognitive functioning is a highly critical outcome measure for brain tumor patients [86].

Treatment and quality of life in low-grade glioma

Health-related quality of life in LGG patients has not been studied extensively, although the impact of being told the diagnosis of brain tumor is great. The diagnosis of having a brain tumor carries the stigma of losing mental capabilities and a common thought is that patients diagnosed with brain tumors shortly die, which certainly does not have to be the case in patients with LGGs.

Major symptoms related to having a LGG are the cognitive and physical changes that may be due to effects of tumor and treatment. Frequent symp-

toms are headache, nausea, vomiting, seizures, fatigue, and sleepiness [65, 85, 87]. Most patients have cognitive dysfunction of various degrees, from mild dysfunction with good information processing and good performance to severe dysfunction with problems in most cognitive domains [64, 70, 86]. Neurological deficits also occur; in most cases, motor impairment limited to difficulties with function in the upper limbs [64, 65]. Many of these changes may alter the patient's ability to function in a work or home environment. In addition, the roles of the people closest to them usually change to adjust to the neurological deficits and treatment requirements. Because of these changes, the patient may experience a decrease in HRQOL. Health-related quality of life in LGG patients can be affected by the tumor, by tumor-related epilepsy and its treatment (surgery, radiotherapy, antiepileptics, chemotherapy, or corticosteroids), and by psychological distress. Therefore, the remainder of this chapter will discuss the tumor and treatment effects on HRQOL of low-grade glioma patients.

Brain tumor effects on health-related quality of life

In addition to seizures, motor or sensory deficits, and increased intracranial pressure, LGG patients can present with cognitive complaints and deficits that negatively affect HRQOL [45]. With this respect, it is important to note that patients with tumors in the dominant hemisphere tend to have more symptoms than those with lesions in the non-dominant hemisphere [35, 37]. Patients with LGG furthermore tend to have more global cognitive deficits, unlike patients with stroke who tend to have lesion site-specific deficits. This may be explained by a diffuse growth of tumor cells infiltrating normal brain tissue [5]. Additionally, acute neurotransmitter changes and chronic degeneration of fiber tracts [94] caused by damage to certain brain areas may impair neuronal responses in remote undamaged cortical regions (i.e., diaschisis). Diaschisis in brain tumor patients might be attributed to both tumor and treatment effects. However, given the brain plasticity and functional compensation seen after stroke, congenital malformations, or brain injury, infiltration by LGG might lead to reshaping or local reorganization of functional networks [24]. Evidently, deterioration in functioning may also occur at the time of anaplastic transformation, which occurs in the majority of LGG patients [56].

With regard to LGGs a single study [72] used the Karnofsky Performance Scale (KPS) as the only measure of HRQOL. The KPS was designed by Karnofsky *et al.* [39] in an attempt to evaluate survival and provide information about the patient's functional status. The KPS is an 11-point scale (ranging from 100 to 0) that is often used by physicians or health care providers. The problem with using the KPS as a measure of HRQOL is that it is a unidimensional scale. Psychological and social dimensions of HRQOL are not included

in the KPS. However, for many years KPS has been used a as proxy measure for HRQOL in studies with cancer patients. In a study on brain tumor patients who had surgery, the KPS score was evaluated at 3 month intervals for a total of up to 36 months [72]. The sample included patients with grade III and IV (Kernohan classification) astrocytomas (n = 132), low-grade I and II astrocytomas (n = 72), brain metastasis (n = 42), and meningiomas (n = 144). For patients with grade I and II astrocytomas, improvement in KPS scores (mean 75) was seen during the 12 months following therapy. However, only 25% of the patients were able to work. The major disadvantage of the use of the KPS is the fact that the KPS is rated by the health care provider rather than the patient, which has been shown to yield higher ratings than patient's subjective ratings [78].

With regard to the effect of tumor lateralization on HRQOL, the clinical trial by Trojanowski *et al.* [88]. Conducted to evaluate the differences between radiotherapy alone and radiotherapy with lomustine is of interest. The sample consisted of 198 patients with supratentorial tumors, 149 patients with high-grade tumors, and 49 patients with low-grade tumors. The mean age of the participants was 47.2 years (range 18 to 71 years). HRQOL was evaluated through physical (KPS) and mental (i.e., neuropsychological) testing. The neuropsychological life-quality coefficient (NLQC) is a neuropsychological evaluation tool with 28 tests focusing on higher functions, such as gnosis, praxis, thinking, speech, and memory. Each higher function was weighted by a panel of neuropsychologists by importance for a good HRQOL. Using a mathematical formula, the investigators derived a single value representing the status of higher brain functioning for each of the patients. Persons with normal cognition received a score of 100%. The patients in this study were followed over a 24-month period. Results showed that the mean baseline KPS score was 65. In 6 to 12 months following treatment, the KPS scores increased to between 70 and 90. In patients who survived for 24 months, the KPS scores remained high (70 to 100). The highest KPS scores were found in patients with right hemisphere and frontal lobe tumors. The mean baseline NLQC value (before the brain tumor surgery and treatment) was 69.5%. By 12 months after diagnosis, the NLQC had increased by 10% ($p < 0.05$). A 3% decrease from the increase in 10% was observed 24 months after baseline, but this change was not significant. The NLQC scores were the same for each treatment group. Completely contradictory findings came from a more recent study [73] specifically aimed at determining the effect of the volume, location, and histological grade of brain tumors on preoperative HRQOL of 101 successive brain tumor patients. The Nottingham health profile (NHP) and Sintonen's 15D scale (2001) were used at that time to measure HRQOL. Analyses showed tumor size not to be related to HRQOL scores. However, large tumors (> 25 ml) were associated with poorer HRQOL than small tumors (≤ 25 ml).

Surprisingly, patients with tumors located on the right side or in the anterior region reported a poorer HRQOL than those with tumors on the left side or posteriorly. Quality of life assessments made by doctors using the Karnofsky performance scale showed no differences between the two hemispheres. From this study the authors [73] conclude that large tumors apparently damage several parts of the brain and/or raise intracranial pressure to a level that exceeds the brain's compensatory capacity. Contrary to earlier understanding, tumors in the right hemisphere seemed to be related to poorer HRQOL. This effect was especially clear in the patients' subjective evaluation of their HRQOL. As the location of the brain tumor thus affects perceived HRQOL, HRQOL measurements should take into account the location and laterality of the tumor. There could be a number of reasons for the discordant findings between the study by Trojanowski *et al.* [88] and Salo *et al.* [73]. One reason may be a cognitive inability to evaluate one's condition and to reply to questions coherently. According to some researchers [22, 66], the human ego and consciousness are mostly located in the left hemisphere, which implies that injury to this hemisphere could impair the patient's ability to evaluate their HRQOL and functional capacity. Another explanation could be that a pathologically positive mood gives rise to an unrealistic understatement of problems and complaints.

In a cross-sectional study by Weitzner [91] the diagnosis-to-test interval for the 50 patients in the study was a mean of 30.7 months (range 1 to 154 months). The predominant diagnosis was astrocytoma grade II or III (60%) and glioblastoma (30%). Patients undergoing treatment for primary brain tumors were given two multidimensional HRQOL measures: the Ferrans Powers-Quality of Life Index ([FP-QLI] [27]) and the Psychological Assessment to Illness-Self Report ([PAIS-SR] [21]). Results of the FP-QIL showed better HRQOL scores for married patients in contrast to divorced patients. The PAIS-SR showed that divorced patients were more impaired in the domain of the domestic environment. In addition, lower overall HRQOL on the PAIS-SR was associated with not working because of the illness, in contrast to patients who were either working or not working because of other reasons. In certain domains women presented lower scores on family environment and psychological distress. Age and radiotherapy did not relate to changes in HRQOL scores.

Giovagnoli *et al.* [30] stratified patients into five stages of their disease: before surgery, after surgery with chemotherapy alone, after surgery receiving radiotherapy and chemotherapy, having stable disease with no recurrence, and having had a recurrence of the disease. The patients ($n = 101$) filled out the Functional Living Index-Cancer ([FLIC] [76]), the KPS, the State-Trait Anxiety Inventory ([STAI] [79]), and the Self Rating Depression Scale [96]. Results showed that patients who were disease free or were receiving radiotherapy

and chemotherapy had the highest HRQOL scores. Not surprisingly, patients with recurrent disease had the lowest HRQOL scores.

The principal aim of the study by Gustafsson *et al.* [33] was to describe function, HRQOL and coping with illness-related problems in low-grade glioma patients and to evaluate the need of support. A second aim was to investigate how function, HRQOL and coping were related. Thirty-nine low-grade glioma patients answered the EORTC-QLQ-C30 quality of life questionnaire and the Ways of Coping Questionnaire (WCQ). The patients' level of function was assessed in accordance with the WHO performance status scale. Nearly all patients were capable of self-care, but less than half were able to carry out normal activities without restriction. Problems with fatigue, sleep disturbances and pain were most frequent. Most difficulties were reported in the domains, Role, Cognitive and Emotional functioning. Seventeen patients (45%) had scores indicating low overall HRQOL. Ratings of overall HRQOL and fatigue had the strongest relationship. The trend in the results suggested that mental problems have a stronger impact on HRQOL than physical ones.

None of the aforementioned HRQOL studies have employed a healthy population control group, matched on key background characteristics such as age, sex and education. Such a control group is needed in order to place the self-reported levels of HRQOL of LGG survivors in an appropriate, interpretable context. In a study [3] related to a study by Klein *et al.* [45] 195 LGG patients were compared with 100 hematological (non-Hodgkin lymphoma and chronic lymphatic leukemia cancer survivors (NHL/CLL) and 205 healthy controls, matched on age, sex and educational level. Generic HRQOL was assessed with the SF-36 Health Survey; condition-specific HRQOL with the Medical Outcomes Study Cognitive Function Questionnaire and the EORTC Brain Cancer Module. Objective cognitive functioning was assessed with a battery of neuropsychological tests. No statistically significant differences were observed between the LGG and NHL/CLL groups in SF-36 scores. The LGG group scored significantly lower than the healthy controls. Approximately one-quarter of the LGG sample reported serious cognitive symptoms. Problems with vision and motor function were uncommon. Age (older), sex (female), number of objective cognitive deficits, and epilepsy burden were associated significantly with both generic and condition-specific HRQOL. Clinical variables, including time since diagnosis, tumor lateralization, extent of surgery, and radiotherapy, were not related significantly to HRQOL. From this the authors conclude that LGG survivors experience significant problems across a broad range of HRQOL domains, most of which are not condition-specific. However, the cognitive deficits that are relatively prevalent among LGG patients are associated with negative HRQOL outcomes, and thus contribute additionally to the vulnerability of this population of cancer survivors.

The prognostic value of HRQOL was determined in a study by Mainio *et al.* [55]. The postoperative survival of 101 brain tumor patients was followed from surgery (1990–1992) until the end of the year 2003. Depression was evaluated by the Beck Depression Inventory (BDI) and HRQOL with Sintonen's 15D scale (2001) before operation and at one year as well as at five years after operation. The mean survival times in years were significantly related to tumor malignancy, being the shortest, 1.9, for patients with high-grade gliomas, while patients with LGGs or a benign brain tumor had mean survival times of 9.1 and 11.6, respectively. At all follow-ups, depressed LGG patients had a significantly shorter survival time, 3.3–5.8 years, compared to non-depressed LGG patients, 10.0–11.7 years. A decreased level of HRQOL in LGG patients was significantly related to shorter survival. These results suggest that depression and decreased HRQOL among LGG patients are related to shorter survival at long-term follow-up. Decreased HRQOL may therefore serve as an indicator for poor prognosis in LGG patients.

Surgery effects on health-related quality of life

Surgery for brain tumors is used to establish the histological diagnosis and to alleviate neurological symptoms through the reduction of tumor mass. Currently, the standard approach is to perform a gross total resection if technically possible [53, 90]. The risks and benefits must be weighed carefully because the surgical intervention itself may result in a transient or permanent decline in neurological function [63]. Where the tumor involves critical functional regions of the brain (e.g., motor cortex or Wernicke's area), complete tumor removal would directly affect the patient's functioning and is thus not feasible. Surgical debulking is often recommended for any patient with increased intracranial pressure, neurological deficits related to mass effects, or uncontrollable seizures. It is important for the patient to understand that gross total resection does not mean the tumor has been completely removed [84]. Surgery and perioperative injuries may cause (mainly transient) neurological deficits owing to damage of normal surrounding tissue. Many neurosurgeons are therefore hesitant to operate on patients with tumors in eloquent brain areas. According to Scheibel *et al.* [75], surgery in patients with glioma leads to focal cognitive deficits, in contrast to more diffuse cognitive disturbances caused by radiotherapy and chemotherapy. Studies that use intraoperative image guiding and functional mapping in patients with LGG in eloquent brain locations showed a high percentage of postoperative cognitive deficits [24, 25]. However, most of these deficits resolved within 3 months, presumably owing to the plasticity of the normal brain [24].

Specifically with regard to the effects of surgery, functional status (KPS), HRQOL, and cognitive status of 24 patients suspected of having a LGG, in

whom treatment was deferred, and 24 patients with proven LGG, who underwent early surgery were compared [70]. These patients were matched with healthy control subjects for educational level, handedness, age, and gender. The two patient groups were also matched for tumor laterality, use of anticonvulsants, and interval between diagnosis and testing. Functional status (KPS) was determined in both patient groups. HRQOL and cognitive status were compared between the three groups. Both patient groups scored worse on HRQOL scales than healthy control subjects. Unoperated patients with suspected LGG scored better on most items than patients with histologically proven LGG. Cognitive status was worse in both groups than in healthy control subjects, but, again, patients with suspected LGG performed better than patients with proven LGG. These data suggest that a wait-and-see policy in patients with suspected LGG has no negative effect on cognitive performance and HRQOL.

Radiotherapy effects on health-related quality of life

The risk of permanent central nervous system toxicity owing to radiotherapy, which typically becomes detectable after an asymptomatic latency period, continues to influence clinical treatment decisions. Interindividual differences in sensitivity result in a certain variability of the threshold dose and preclude administration of a guaranteed safe dose, even in the current era of high-precision image-guided radiotherapy. The therapeutic index in the nervous system is low, because the radiation dose required for tumor control is very close to, if not higher than, the toxic dose for neighboring tissues. In order to describe neurotoxicity caused by radiotherapy a distinction is made between acute encephalopathy, early-delayed encephalopathy, and late-delayed encephalopathy.

Acute radiation encephalopathy develops within 2 weeks of the start of radiotherapy, caused by vasogenic edema after disruption of the blood–brain-barrier. This may result in headache, somnolence, and worsening of pre-existing neurological deficits. Corticosteroids rapidly ameliorate this reversible disorder.

One to six months after completion of radiotherapy, early delayed radiation encephalopathy may occur. This encephalopathy may be difficult to distinguish from early tumor progression. Apart from drowsiness and worsening of the neurological disorder, a transient impairment in cognitive functioning may occur [18]. A return to normal baseline results normally occurs within 12 months. A reversible demyelination associated with blood–brain-barrier disruption is supposed to explain this disorder. There is no indication that this encephalopathy is a harbinger of the more severe late-delayed encephalopathy.

In contrast to the early complications, late-delayed encephalopathy is an irreversible and serious disorder. This complication follows radiotherapy by several months to many years and may take the form of local radionecrosis or diffuse leukoencephalopathy and cerebral atrophy. Cognitive disturbances are the hallmark of the diffuse encephalopathy [8]. The severity of cognitive deficits ranges from mild or moderate cognitive deficits all the way to cognitive deterioration leading to dementia. It is not hard to imagine that these limitations in functioning have profound effects on HRQOL.

A commonly overlooked late complication of cranial radiotherapy in adults is endocrine dysfunction caused by damage to the hypothalamic–pituitary axis. Only a few studies have been done in adults, and these indicate that most patients who have clinical or subclinical endocrine dysfunction also show a significant decrease in well-being [7, 26].

Taphoorn *et al.* [87] described HRQOL in 20 patients who had been treated with early radiotherapy and 21 patients who had undergone surgery or biopsy only. In addition, 19 patients with hematological malignancies were included as a control group. The patients were evaluated for HRQOL through an interview, a multidimensional questionnaire that included physical status, social status, overall well-being, and treatment experiences and through the Profile of Mood States (POMS). Results showed that patients with brain tumors, regardless of whether they had received radiotherapy, had greater fatigue, memory loss, lack of concentration, and speech disorders than the control group. Patients were less satisfied with their condition and felt more restricted in daily activities than the control groups.

In view of the long survival of patients with LGG and retrospective data suggesting a decline in cognitive function after radiotherapy in these patients, both the EORTC and the NCCTG did companion studies assessing quality-of-life outcomes [11, 43, 45, 47]. In the companion study EORTC 22844 [43], a subset of patients answered questionnaires on physical, psychological, social, and symptom domains before radiotherapy and at various times after treatment. Compliance on this study was poor, with fewer than 50% of patients completing at least one questionnaire. Thus, insufficient data were available for comparison of baseline scores and those after radiotherapy. Comparisons between the high-dose and low-dose radiotherapy groups could be made for two time points: from the completion of radiotherapy to 6 months, and from 7 months to 15 months after radiotherapy. During the initial postradiotherapy interval of 6 months, patients in the high-dose group reported poorer functioning and more symptoms than patients in the low-dose group. Significant differences were noted between the high-dose and low-dose groups for the symptoms of fatigue, malaise, and insomnia. During the 7–15-months after radiotherapy, significant differences favoring the low-dose group were noted in leisure time activity and emotional functioning. No significant differences be-

tween the baseline scores were seen. This quality-of-life study did not show any major differences between the high-dose and low-dose groups or between early and late radiotherapy. Although the study had substantial methodological and logistical problems, the investigators should be credited with prospectively assessing patient's HRQOL as part of a multinational cooperative oncology trial.

Effects of medical therapy on health-related quality of life

Antiepileptic drugs

Epileptic seizures are the first symptom of an intracranial tumor in 30–90% of patients and can substantially affect daily life, even if the tumor is under control. Apart from tumor type, tumor location, and peritumoral and genetic changes affect the mechanism of seizures in brain tumor patients [89]. In a large study one or more antiepileptic drugs were taken by 71% of patients with low-grade glioma to prevent seizures [44]. Risks of side-effects of antiepileptic drugs can add to previous damage by surgery or radiotherapy, and therefore appropriate choice and dose of antiepileptic drug is crucial. The older antiepileptic drugs (phenytoin, carbamazepine, and valproic acid) are known to have behavioral effects [23]. Several newer AEDs (e.g., gabapentin, lamotrigine, levetiracetam) appear to have fewer adverse effects than the older agents, though additional comparisons between new AEDs are required to fully assess the cognitive side effect profile of these newer anticonvulsant agents. Of the newer agents, topiramate is associated with the greatest risk of cognitive impairment, although this risk is decreased with slow titration and low target doses [58, 59].

The purpose of a study by Klein *et al.* [44] was to determine the impact of epilepsy and antiepileptic drug (AED) treatment on cognitive functioning and HRQOL in LGG patients. One hundred fifty-six patients without clinical or radiological signs of tumor recurrence for at least 1 year after histological diagnosis and with an epilepsy burden (based on seizure frequency and AED use) ranging from none to severe were compared with healthy controls. The association between epilepsy burden and cognition/HRQOL was also investigated. Eighty-six percent of the patients had epilepsy and 50% of those using AEDs actually were seizure-free. Compared with healthy controls, glioma patients had significant reductions in information processing speed, psychomotor function, attentional functioning, verbal and working memory, executive functioning, and HRQOL. The increase in epilepsy burden that was associated with significant reductions in all cognitive domains except for attentional and memory functioning could primarily be attributed to the use of AEDs, whereas the decline in HRQOL could be ascribed to the lack of complete seizure

control. The authors concluded that LGG patients suffer from a number of neuropsychological and psychological problems that are aggravated by the severity of epilepsy and by the intensity of the treatment.

A recent study by Struik [83] aimed at determining the prevalence and severity of fatigue in long-term survivors with a LGG, and at analyzing the relationship between fatigue and demographic variables, disease duration, tumor characteristics, former tumor treatment modalities, antiepileptic drug (AED) use, self-reported concentration, motivation, and activity. Therefore, 54 patients with stable disease (age range, 25–73 years) who were diagnosed and treated more than 8 years ago were included in this study and completed the Checklist Individual Strength (CIS) which is a questionnaire measuring fatigue. Thirty-nine percent of the LGG patients were severely fatigued, with older patients being most affected. Severe fatigue was associated with use of antiepileptic drugs, and with reduced self-reported concentration, motivation, and activity. No relation was found between fatigue and gender, histology, tumor laterality, disease duration, type of neurosurgical intervention and radiation treatment. Fatigue is perhaps the most common and potentially debilitating symptom experienced by cancer patients, including those with brain tumors, that have a significant negative impact on routine activities of daily living and diminish HRQOL.

Chemotherapy

Most chemotherapeutic agents that are active against anaplastic gliomas also have activity against LGG. A major advance relevant to the chemotherapeutic treatment for LGG was the discovery of the chemosensitivity of anaplastic oligodendroglioma based on chromosomal markers. Cairncross *et al.* [13] observed that 100% of tumors with chromosome 1p loss (24 patients) were chemosensitive and that 100% of those with loss of both 1p and 19q (22 patients) also responded to chemotherapy. The patients with the chromosomal losses also had significantly longer progression-free and overall survival times. Renewed interest in the use of chemotherapy in LGG patients has resulted in a number of promising studies [38, 49, 67, 71] but only a few also incorporated HRQOL as secondary outcome measure [10, 57, 62].

Potential late CNS neurotoxic side-effects of chemotherapy may be difficult to discern from radiotherapy, because a substantial number of LGG patients treated with chemotherapy have already been treated with radiotherapy [42, 92].

One of the oldest studies in LGG patients under chemotherapy has been performed by Mackworth *et al.* [54]. The sample, in which HRQOL self-reports with the KPS were collected, consisted of 195 patients seen in a neuro-oncology clinic. Most patients had undergone surgery and radiotherapy,

and were presently receiving chemotherapy. The mean age of the patients was 41 years (range 12 to 75 years). The patients filled out a questionnaire before meeting with the physician. The physician rated patient's performance using the KPS. The multidimensional questionnaire evaluated energy, social life, physical symptoms, cognitive and memory skills, freedom from depression, work, sex, and well-being. A composite HRQOL score was determined by using the areas that were significantly correlated with well-being. These areas were freedom from depression, good social life, energy, and freedom from symptoms. In this sample two thirds of the patients had a KPS score of 90 to 100. No relationship was found between the HRQOL scores and the KPS score of 90 to 100. Mean HRQOL scores decreased with a KPS score of <90. However, this relationship was not significant. Age was noted to be inversely related to the KPS score, yet age was not related to well-being. The patients who lived more than 1 year had significantly higher HRQOL and KPS scores than those who died within a year. Correlating the KPS scores to the HRQOL scores in this study was helpful because the KPS is used in daily clinical practice to assess functional status and crudely measure HRQOL. This study showed that patients with no disease symptoms, or patients who have only minor signs or symptoms of disease had a strong sense of well-being.

Chemotherapy in standard and intensified formulations of procarbazine, lomustine (CCNU), and vincristine was administered to nine symptomatic patients with low-grade oligodendrogliomas [57]. Eight patients were treated with chemotherapy at presentation and one was treated for a recurrence after radiotherapy had failed. All patients improved in seizure frequency and other neurologic symptoms or MRI criteria, or both. No patient deteriorated while in therapy and the responses were sustained without radiotherapy for a median of 35 months (range, 22–45) in all surviving patients treated at presentation. Chemotherapy was well tolerated; all patients developed myelosuppression, but only those receiving the intensified regimen required dose reduction or premature discontinuation of treatment. As with recurrent and anaplastic oligodendroglioma, low-grade oligodendroglioma responds to chemotherapy.

Brada [10] studied the efficacy of temozolomide in LGG patients treated with surgery alone using MRI and clinical criteria. Following surgery, 30 LGG patients received temozolomide 200 mg/m^2/day for 5 days at a median of 23 months after initial diagnosis, on a 28-day cycle, for a maximum of 12 cycles or until tumour progression. Median age was 40 years and median follow-up from entry into the study was 3 years. Objective response was assessed by 3-monthly MRI and monthly HRQOL and clinical assessment. Three patients had a partial response, 14 minimal response, 11 stable disease and one progressive disease. Of the 29 evaluable patients, three discontinued after four, five and six cycles and two after 10 cycles. Nine patients progressed,

five had evidence of transformation. The 3-year progression-free survival was 66%. Ninety-six per cent of patients with impaired HRQOL had modest improvement in at least one HRQOL domain. Fifteen of 28 patients (54%) with epilepsy had reduction in seizure frequency, of whom six became seizure free.

Forty-three patients with LGG (29 astrocytoma, 4 oligodendroglioma and 10 mixed oligo-astrocytoma) were treated with temozolomide at the time of clinical and radiological progression [62]. Thirty patients (69.7%) had previously received radiotherapy; 16 (37.2%) had received prior chemotherapy. Clinical benefit was evaluated measuring seizure control, reduction in steroid dose and modification of KPS and Barthel index. Quality of life was assessed with the QLQ-C30 questionnaire. A complete response was observed in four patients, 16 partial responses, 17 stable disease and six progressive disease. Median duration of response was 10 months, with a 76% rate of progression free survival at 6 months, and a 39% rate of progression free survival at 12 months. A relevant clinical benefit was observed particularly in patients presenting with epilepsy.

Newer agents, such as signal transduction inhibitors, angiogenesis inhibitors, monoclonal antibodies, immunotoxins, and gene transfer therapies, as well as new approaches to drug delivery, such as drug-impregnated sustained- release polymers and convection-enhanced delivery, remain to be investigated in LGGs.

Steroids

Brain edema is a common occurrence in brain tumor patients. The swelling is caused by the accumulation of fluids in the tissue around the tumor. This exerts pressure on the brain that can lead to additional symptoms including headaches, seizures, and focal neurological deficits. Brain edema may initially be due to the tumor itself or it may occur as a result of surgery or radiotherapy. The first-line treatment for brain edema is the administration of steroids. Corticosteroids – of which prednisone and dexamethasone are most commonly used to treat brain tumors – may cause mood disturbances and (infrequently) psychosis [36]. Steroid dementia is a reversible cause of cognitive deficits even in the absence of psychosis. Both short-term and long-term use of steroids have been associated with neurobehavioral effects [41]. More likely, however, cognitive and neurological deficits in brain tumor patients will be alleviated by steroids owing to the resolution of brain edema.

Effects of mood disorders on health-related quality of life

It comes as no surprise that brain tumor patients have feelings of anxiety, depression, and future uncertainty as psychological reactions to the disease

[20, 82, 85]. Patients with high-grade glioma report higher levels of panic, depression, anxiety, and fear of death than patients with low-grade glioma [52]. Mood changes are more common in brain tumor patients than in patients with other neurological diseases [6] and might be related to tumor location [60, 68]. These mood disturbances may lead to deficits in attention, vigilance, and motivation that subsequently affect HRQOL [4].

The consequences of the tumor for everyday life and the uncertainty of the future make great demands on the patients' ability in coping. Coping may be defined as cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or as exceeding the resources of the person ([48] p. 141). Coping has two basic functions, either to manage or alter the problems causing distress or to regulate the emotions caused by these problems. In LGG patients, there is a significant relationship between coping by escape-avoidance (i.e., wishful thinking and behavioral efforts to escape or avoid the problem) and lower level of emotional functioning [33].

Conclusion

The studies presented in this chapter described outcomes of both single dimensional and multidimensional methods of studying HRQOL. Initially, the HRQOL scores were assigned to the patient by the physician or neuropsychologist. Although only few studies incorporated HRQOL as outcome measure, current studies have embraced the notion that an accurate assessment of HRQOL must be based on patient self-report. HRQOL instruments from other cancer groups are adapted for use with brain tumor patients. The multidimensional scales used to study changes in HRQOL studies in brain tumor patients provide a more comprehensive view of what is important to the patient concerning living with their disease and receiving treatment.

In future trials, more sensitive measures of long-term cognitive, functional, and HRQOL outcomes on LGG patients at important time points over the disease trajectory are needed to better understand the changing needs that take place over time.

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