Because of its unpredictable clinical course, treatment strategies for low-grade (grade II) astrocytoma vary from “wait and see” to gross tumour resection followed by immediate radiotherapy. Clinical studies on grade II astrocytoma show that 5-year-survival ranges from 27% to 85% of patients with very few consistent prognostic variables besides the patient’s age and the presence of neurological deficit. There is no universally recognised choice of therapy for patients with astrocytoma grade II, partly because of the shortcomings of histological classification systems. Routine microscopy tends to underestimate malignancy grading of astrocytomas and in most cases cannot distinguish between indolent and progressive subtypes. Recent studies suggest that proliferation and genetic markers can be used to identify subgroups of astrocytoma grade II with a rapid progressive clinical course. Therefore these markers should be included in ongoing and future clinical studies of patients with astrocytoma grade II.

Lancet Neurology 2003; 2: 395–403

Grade II astrocytoma—the commonest form of low-grade glioma—has an estimated incidence of 0.5–1.0 per 100 000 people/year. The incidence peaks in early adulthood and the mean age at diagnosis is 35–40 years. Only a small percentage of patients are younger than 18 years or older than 65 years of age. For unknown reasons there is a slight bias in the male/female sex ratio (1:2) of cases. Grade II astrocytoma is most commonly sporadic and is rarely the result of a familial tumour syndrome. Li-Fraumeni syndrome is a familial form of astrocytoma caused by an inherited mutation of the p53 tumour suppressor gene, in which astrocytomas may coexist with other solid tumours. The only well-documented environmental risk factor for astrocytoma of all grades is skull irradiation in young patients with haematological malignancies. Workers in some chemical industries (eg, synthetic rubber processing, petrochemical refineries, and pesticide and fertiliser manufacture) were found to have an increased risk of brain tumours, but the causative agents have not been identified. There is little evidence that the use of cellular telephones increases the risk of astrocytoma. Furthermore the low variation of incidence rates for CNS tumours across Europe does not support the existence of specific environmental causes of these malignancies. Epidemiological studies focusing on causal factors specific for grade II astrocytoma have so far not been presented.

Presenting symptoms and imaging of grade II astrocytoma

Epileptic seizure is the most common presenting symptom of grade II astrocytoma and occurs in about 80% of the patients; this is probably due to the superficial localisation and low growth rate of the tumour in many cases. Focal neurological deficit (30%) and mental changes (10–30%) are less common. Symptoms caused by raised intracranial pressure, such as headache, vomiting, and papilloedema (10%), are rare.

Before CT, focal neurological deficit and raised intracranial pressure were reported in a high percentage of patients with grade II astrocytoma. These percentages have declined in recent series because modern neuroimaging techniques and stereotactic-guided biopsies allow the diagnosis of the disorder at an earlier stage.

Grade II astrocytomas can arise anywhere in the hemispheres, but show a preference for the frontal and temporal lobes. On CT, the tumours are typically hypodense, poorly demarcated, and non-enhancing lesions, and their size is commonly underestimated. MRI is more sensitive than CT in detecting astrocytoma grade II.

Figure 1. T1-weighted MRI image showing a hypointense lesion (without gadolinium enhancement) in the frontal lobe of a 29-year-old patient (left); the same lesion is hyperintense in the T2-weighted MRI image (right).
MRI, the tumours are hypointense on T1 and hyperintense on T2-weighted scans (figure 1). T2-weighted images provide a more accurate estimation of size and of infiltration by neoplastic astrocytes. Calcifications and cysts are sometimes present. Despite being fairly typical of the disorder, these neuroimaging features are not diagnostic for grade II astrocytoma. Contrast-enhancement, for example, is seen in some cases of this malignancy. Furthermore, a third of high grade gliomas show no contrast enhancement and, therefore, have a typical appearance of grade II astrocytoma, despite being at a later stage of progression.

In the future, PET and proton magnetic-resonance spectroscopy might provide additional diagnostic precision. PET with fluorine-18-labelled fluorodeoxyglucose could be used to predict malignant transformation of low-grade glioma and PET with the amino-acid tracer carbon-11-labelled methionine may help to estimate survival of patients with low-grade glioma. PET seems to have potential in the detection of glioma recurrence: stable or decreased uptake of 11C methionine during follow-up after radiotherapy is a favourable sign. Magnetic-resonance spectroscopy, used to measure concentrations of lactate and choline in brain tumours, enables discrimination between radionecrosis and tumour recurrence.

### Clinical course and prognostic features

The course of grade II astrocytoma is still largely unpredictable for several reasons. First, proliferation and progression are highly variable. Studies are difficult to interpret, as they are mostly retrospective in nature and include other subgroups of low-grade gliomas. Furthermore, the use of different treatment strategies may be an important confounder in most studies.

Recent studies have used CT and MRI to predict the clinical course, and have tried to describe prognostic features of grade II astrocytoma (table 1). The survival rates of patients in these studies at 5 and 10 years range from 27% to 85% and 14% to 70%, respectively. Only four prospective randomised trials have been conducted in patients with low-grade glioma, two of which have only recently been published. All other studies are retrospective, and often include other variants of low-grade gliomas, such as pilocytic astrocytomas, oligodendrogliomas, and oligoastrocytomas, which all have a better prognosis than grade II astrocytoma. Apart from heterogeneity in

### Table 1. Studies of potential prognostic features in studies of patients with grade II astrocytoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Median age</th>
<th>5 year survival (%)</th>
<th>10 year survival (%)</th>
<th>Anaplastic change (Number reoperated)</th>
<th>Potential prognostic parameters</th>
<th>Age</th>
<th>Neuro-logical deficit</th>
<th>Performance score</th>
<th>Tumour volume</th>
<th>Contrast enhancement</th>
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<td>Lote*</td>
<td>258</td>
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<td>Karim**</td>
<td>343</td>
<td>38</td>
<td>47 vs 50 vs 50*</td>
<td>--</td>
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<td>N</td>
<td>N</td>
<td>P*</td>
<td>N</td>
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<tr>
<td>Karim*</td>
<td>290</td>
<td>--</td>
<td>63 vs 66 vs 66*</td>
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<tr>
<td>Shaw**</td>
<td>211</td>
<td>72 vs 64**</td>
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<td>N</td>
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*P=positive association with survival; N=negative association with survival; NS=no significant association with survival (p>0.05); only associated in univariate analysis. †Study also included patients in Philippin and Leighton. ‡Estimated from Kaplan-Meier curves. §low-dose versus high dose radiotherapy (EORTC I trial). ¶None versus postoperative radiotherapy (EORTC II trial). **Low-dose versus high-dose radiotherapy (US trial).
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The application of these classifications to individual patients has many limitations, because survival of patients with one grade may vary widely, whereas, survival for different grades may have notable overlap.

Histological heterogeneity within the tumour is another source of confusion when the diagnosis is based on small samples of the tumour. Diagnosis on the basis of stereotactic biopsy samples underestimates the histological grade in 10–25% of astrocytomas compared with resection specimens of the same tumour. This risk of underestimation is reduced by taking more (>6) stereotactic biopsies per tumour.

The differentiation between “pure” astrocytoma and mixed oligoastrocytomas is of clinical relevance, because the presence of oligodendroglioma increases the chance of chemosensitivity. However, this distinction can be difficult to make because some tumour cells have both astrocytic and oligodendroglial features, and the histological diagnosis is influenced by heterogeneity within the specimen.

Finally, a problem in clinical practice with stereotactic biopsy specimens is the differentiation between grade II astrocytoma and reactive gliosis (a proliferation of glial cells in response to neural tissue damage). Both tissue types may have only a mild increase in astrocyte cellularity and some nuclear atypia on routine microscopy; histological diagnosis is commonly inconclusive in such cases.

**Biological features of grade II astrocytoma**

Phenotype and genotypic differences underlie the variable clinical course seen in patients with grade II astrocytoma. The development of astrocytoma is associated with genetic instability and an imbalance between proliferation and apoptosis of astrocytes. Recent studies have suggested that markers for proliferation activity and certain cytogenetic changes may predict the malignant transformation from grade II to grade III or IV astrocytoma.

An established histological method for the estimation of proliferative activity in tumours is to measure the percentage of cells with mitotic features. However, because mitoses are absent by definition in astrocytoma grade II, other measurements of proliferative capacity have been sought, such as the bromodeoxyuridine (BrdU) incorporation assay, and immunostaining of the proliferating cell nuclear antigen.

The Ki-67 antigen is present in all active phases of the cell cycle, but absent in the G phase. Specific antibodies allow its detection in routinely processed glioma biopsy samples. The percentage of Ki-67-positive cells—expressed as the Ki-67-labelling index—has a positive correlation with histological grade in astrocytomas. In a series of grade II astrocytomas, a Ki-67 labelling index of more than 2% was predictive of shorter survival, independent of the patient’s age.

**Markers of proliferation**

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The Ki-67 antigen is present in all active phases of the cell cycle, but absent in the G phase. Specific antibodies allow its detection in routinely processed glioma biopsy samples. The percentage of Ki-67-positive cells—expressed as the Ki-67-labelling index—has a positive correlation with histological grade in astrocytomas. In a series of grade II astrocytomas, a Ki-67 labelling index of more than 2% was predictive of shorter survival, independent of the patient’s age.

**Molecular cytogenetics**

Various molecular techniques, including karyotyping, mutation analysis, allelotyping, in situ hybridisation, comparative genomic hybridisation, and expression profiling have been used to study astrocytomas.

In particular, in situ hybridisation and comparative genomic hybridisation are well suited to the analysis of numerical and structural chromosomal aberrations. The in situ technique uses chromosome specific DNA probes that allow the detection of chromosomal imbalances—losses, gains, and amplifications—in individual cells in paraffin-embedded brain tumour samples. In situ hybridisation is particularly well suited for the study of astrocytoma grade II, which is often surrounded by reactive, non-neoplastic cells, and from which only small stereotactic biopsy samples with a few cells are available.

When large and more homogeneous samples are available, comparative genomic hybridisation detects gains and losses of...
genetic material across the entire tumour genome. Typical chromosomal aberrations in grade II astrocytoma include loss or mutation of the p53 tumour suppressor gene and trisomy for chromosome 7. This technique simultaneously hybridises differently fluorescent labelled tumour DNA and normal reference DNA to normal metaphase chromosomes. Digital analysis of the fluorescence intensity ratios identifies chromosomal gains or losses of 2 Mbp or more (figure 6). Only a few of the target genes that are either lost or increased in number have been identified (table 2).

In grade IV astrocytoma two distinct genetic subtypes exist—primary (or de novo) and secondary (or progressive). In primary tumours there is no previous evidence for a low-grade precursor lesion. Typical aberrations in these tumours include amplification of the gene for epidermal growth factor receptor (EGFR) on chromosome 7 and loss of chromosome 10, on which the tumour suppressor gene phosphate tyrosine (PTEN or MMAC1) is located (figure 6). In both grade II and secondary grade IV astrocytoma, losses of chromosome arm 17p with mutation of the p53 tumour suppressor gene are often present. Other mutations are rarer in grade II than in grade IV tumours.

**Initiation of grade II astrocytoma**

About two-thirds of patients with grade II astrocytoma have mutated or deleted p53. Several protein regions of p53 play different parts in cellular processes, one of the most important being the regulation of gene transcription. Absence of functional p53 protein leads to deregulation of the cell cycle and absence of induction of the normal process of apoptosis, thereby causing genomic instability. Although loss or mutation of p53 have been suggested as early changes in the initiation of astrocytoma, additional genetic changes are necessary for astrocytoma carcinogenesis.

An important mechanism for growth stimulation of astrocytomas is the simultaneous overexpression of growth factors and their receptors, which leads to autocrine stimulation of the ras-signalling pathway. The platelet-derived growth-factor-receptor α (PDGFR-α) subunit is commonly overexpressed in grade II astrocytoma. A close association has been found between overexpression of PDGFR-α and loss of heterozygosity at 17p, the locus of p53, which suggests that growth stimulation and p53 mutation may have a synergistic effect in the initiation of astrocytoma.

Recent in situ and comparative genomic hybridisation studies have shown that other chromosomal mutations occur in astrocytoma grade II, such as gains of chromosome 7 or 7q, 8q, and general polyploidy. EGFR has been suggested as a target on chromosome 7p, but amplifications of this gene are very rare. Loss of regions on chromosome 22q has also been seen in grade II astrocytoma. In this region, neurofibromatosis 2 (NF2) has been ruled out as a candidate tumour suppressor gene by mutation analysis. Deletions of regions on chromosome 10 (ie, 10p14–15 and 10q25–26) have been found in a few studies.

**Malignant progression**

An important role in malignant progression of astrocytoma grade II has been suggested for cell-cycle regulator genes involved in the INK4A-CDK4-Rb pathway. INK4A (p16) and cycline dependent kinase (CDK4) regulate phosphorylation of the retinoblastoma (Rb) protein, which in turn regulates transition from the G1 to the S phase of the cell cycle. In about half of grade III tumours either one of these three genes is mutated, which leads to uncontrolled cell proliferation. Another frequent change in both grade III and secondary grade IV astrocytoma is chromosomal loss of 19q where an unidentified tumour suppressor gene is located that might play a part in progression.

Molecular allelotyping studies suggest secondary grade IV astrocytomas that have progressed from grade II have a
**Supratentorial grade II astrocytoma**

**Review**

**Table 2. Common genetic abnormalities reported for the different grades of astrocytoma**

<table>
<thead>
<tr>
<th>Astrocytoma subtype</th>
<th>Chromosome mutation</th>
<th>Percentage of tumours</th>
<th>Gene involved (focus)</th>
<th>Change to protein expression</th>
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<td><strong>PS3</strong> (17p13.1)</td>
<td><strong>PDGFRA</strong>†</td>
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<td></td>
<td>7gain</td>
<td>10–50</td>
<td><strong>EGFR</strong> (7p12–14)</td>
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<td>8q gain</td>
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<td>cMYC (8q22)</td>
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<td><strong>CDK4</strong> (12q13–14)</td>
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</tr>
<tr>
<td></td>
<td>19q deletion</td>
<td>50–60</td>
<td>Unknown (19q13)</td>
<td></td>
</tr>
<tr>
<td>Primary grade IV</td>
<td>10 deletion</td>
<td>70–80</td>
<td><strong>PTEN</strong> (10q23.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7gain</td>
<td>50–80</td>
<td><strong>EGFR</strong> (7p12–13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9p deletion</td>
<td>30–60</td>
<td><strong>INK4A/ARF</strong> (9p21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12q gain</td>
<td>10</td>
<td><strong>MDM2</strong> (12q14–15)</td>
<td><strong>MDM2</strong>†</td>
</tr>
</tbody>
</table>

*EGFR*=epidermal growth factor receptor; *NF*=neurofibromatosis; *DMBT1*=deleted malignant brain tumour; *PDGFRA*=platelet derived growth factor receptor; *CDK*=cycline dependent kinase; *RB*=retinoblastoma; *PTEN*=phosphatase tyrosine gene; *MDM*=murine double-minute; *DCC*=deleted in colon carcinoma; *PDGFR*=platelet derived growth factor receptor; *CDK*=cycline dependent kinase; *Rb*=retinoblastoma; *PTEN*=phosphatase tyrosine gene; *MDM*=murine double-minute; *DCC*=deleted in colon carcinoma; † increases, ‡ decreases.

The first cDNA expression-array study, which assessed upregulation and downregulation of different genes that have not previously been implicated in astrocytoma carcinogenesis, confirmed the complexity of genetic changes in the disease. A cDNA-array study in high-grade glioma suggested that this technique would enable a molecular—instead of a histological—classification of gliomas.

**Conclusions**

Because of the unpredictable clinical course of grade II astrocytoma, treatment strategies range from gross tumour resection followed by immediate radiotherapy to a “wait and see” approach. At present the best prognostic variable is the patient’s age; other indicators of poor prognosis include neurological deficit and a low performance score at time of presentation.

For young patients (under 35 or 40 years of age) with indolent grade II astrocytoma, the efficacy of surgical intervention and early radiotherapy has never been proven. Because histological confirmation through stereotactic biopsy does not change the treatment strategy, a “wait and see” policy is often recommended for these patients.

In patients over 40 years of age with astrocytomas that have a mass effect or progressive neurological deficit, gross tumour resection improves survival. The use of postoperative radiotherapy is still under debate; however, if it is used the fraction dose should not exceed 2 Gy, and a total dose of 45 Gy is probably as effective as 59·4 Gy. Routine chemotherapy is not indicated for patients with grade II astrocytoma, and at present serves only as a salvage therapy for recurrent disease.

Recent data suggest that biological and genetic features are closely related to the highly variable clinical course of astrocytoma. Of these, the Ki-67 proliferation marker should be included in routine pathology. Analysis of these tumours should look for genetic changes, in particular gain

common deletion of the 10q25–26 region. One of the candidate tumour suppressor genes in this region is the deleted in malignant brain tumour (*DMBT1*) gene, the product of which has been linked to processes of cell differentiation and migration of epithelial cells.

Important hallmarks of primary grade IV astrocytoma are loss of chromosome 10, *PTEN* mutation, and amplification or overexpression of *EGFR*. The p53 pathway is also disrupted, by deletion of *ARF* or, less frequently, by replication of *MDM2*.

**Clinical application of molecular markers**

In general, the higher the number of mutations, as detected by genetic hybridisation, the more rapid the malignant progression. By use of in situ hybridisation, trisomy of chromosome 7 was shown to be associated with shorter survival of patients with grade II astrocytoma.

An association of p53 mutations with survival has been suggested by some studies, but contradicted by others. A recent study suggested that mutation of codon 175 (“a hot-spot codon”) of the p53 gene is associated with short survival of patients with astrocytoma grade II.

Molecular analyses are also of potential interest when a (stereotactic) sample error is suspected. First, detection of trisomy for chromosome 7 might help to discriminate between non-neoplastic reactive gliosis and astrocytoma in cases of inconclusive histological diagnosis. Second, monosomy for chromosome 10—distinctly uncommon in grade II astrocytoma—may help to discriminate between grade II and grade IV tumours. Furthermore, loss of chromosomes 1p and 19q is frequently observed in a few grade II astrocytomas, which suggests that the detection of these mutations can also predict chemosensitivity of a subgroup of (histological) grade II astrocytomas with oligodendroglial genotype.
Supratentorial grade II astrocytoma

Search strategy and selection criteria
Data for this review were identified by searches of PubMed and Cancerlit (1980–2002) and from references of relevant articles. The search terms were "astrocytoma grade II", "astrocytoma grade 2", "low-grade astrocytoma", "treatment", and "prognosis". Inclusion criteria included "child" or "childhood" and "neurologist". Only papers published in English or German were reviewed. Only CT/MRI studies of 40 or more adult patients were included.

FCSR were responsible for the review of proliferation and genetic parameters. GR participated in the literature search. All authors read and approved the final version of the review.

Conflict of interest
We have no conflicts of interest.

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References


