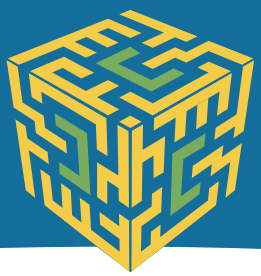

On High-Risk, Low-Grade Glioma: What Distinguishes High From Low?

Marjolein Geurts, MD, PhD
Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

Martin J. van den Bent, MD, PhD
The Brain Tumor Center at Erasmus Medical Center Cancer Institute, Rotterdam, The Netherlands

Low-grade gliomas (LGGs) are a heterogeneous group of tumors. The current evidence indicates that, after resection of the tumor, high-risk patients benefit from immediate adjuvant radiotherapy and chemotherapy, whereas initial observation (*watchful waiting* or *surveillance*) is a reasonable option for low-risk patients. However, how to identify high-risk patients remains controversial: molecular tumor markers play an important role, whereas clinical and radiologic characteristics have additional value.

Diffuse World Health Organization (WHO) grade II gliomas are a heterogeneous entity. They vary not only histologically and genetically but also in response to treatment and prognosis. In the revised WHO 2016 classification, gliomas are classified based on the presence of an isocitrate dehydrogenase (*IDH*) mutation and of a whole-arm co-deletion of chromosomal arms 1p and 19q (1p/19q co-deletion).[1] The diagnosis of an oligodendroglioma now requires the presence of a 1p/19q co-deletion combined with an *IDH* mutation. Oligodendrogliomas typically are associated with a prolonged survival (>14 years) and an excellent response to chemotherapy.[2] Astrocytomas are classified according to their *IDH* status as *IDH* mutated (mt) or *IDH* wildtype (wt) and lack the 1p/19q co-deletion. *IDHmt* astrocytomas generally have better survival rates than *IDHwt* astrocytomas (5-year survival rate, 93% vs 51%, respectively),[3] but the latter remains a very heterogeneous group of tumors with corresponding heterogeneous prognoses.[4] Other molecular parameters to stratify *IDHwt* low-grade glioma subgroups further are expected to receive an "official status" in the very near future. (see Addendum) The new WHO classification requires clinicians to reframe their approach to the treatment of these tumors based on a re-interpretation of the existing data.

The Management of High-Risk LGG

The postoperative treatment of low-grade glioma consists of radiation therapy and chemotherapy. Radiation therapy repeatedly has been proven effective, with no difference in outcomes with doses between 45.0 and 64.8 grays.[5,6] The Radiation Therapy Oncology Group (RTOG) 9802 study has demonstrated a clear benefit of the addition of combined procarbazine, lomustine, and vincristine chemotherapy to radiation therapy in patients with high-risk, low-grade glioma, with an increase in median progression-free survival from 4.0 to 10.4 years.[2] In that trial, high risk was defined as age >40 years or undergoing a less than total gross resection.

The choice for immediate postsurgical treatment would be no matter of controversy if treatment came without side effects, but that unfortunately is not the case. The direct side effects of radiotherapy to the brain followed by chemotherapy include fatigue, blood and bone marrow disorders, and nausea. It is noteworthy that temozolomide chemotherapy is less toxic than combined procarbazine, lomustine, and vincristine, and results from the CATNON trial (Concurrent and Adjuvant Temozolomide Chemotherapy in Non-1p/19q–Deleted Anaplastic Glioma) suggest that the use of temozolomide seems reasonable for both grade II and grade III tumors without co-deleted 1p/19q.[7] In the longer term, cognitive decline is an important side effect of radiotherapy. In a Dutch prospective cohort study, patients with low-grade glioma who received radiotherapy had progressive cognitive decline after a mean follow-up of 12 years, whereas those who did not receive radiotherapy did not have cognitive decline.[8] Cognitive

complications are relevant primarily for patients who actually achieve long-term survivorship.

Patients who have low-risk, low-grade glioma probably can defer treatment and thus postpone the significant high-risk adverse effects of postsurgical therapies for many years without compromising expectations for their survival; whereas, in high-risk patients, postponing postsurgical treatment poses a risk. This requires the definition of high-risk and low-risk patients

Low-Grade Glioma: Distinguishing Low-Risk and High-Risk

Because of the criteria used in the RTOG 9802 study, many clinicians now use age 40 years and a less than total gross resection as criteria to identify "high-risk: patients who require postoperative management without further delay.[2] However, the inclusion criteria for RTOG 9802 were designed to enroll patients who reasonably could receive postoperative treatment, and not to identify patients who require postoperative treatment. There is no clinical justification for a strict age cutoff, and other prognostic factors should be considered when deciding on adjuvant treatment. When facing the same challenge, the European Organization for Research and Treatment of Cancer Brain Tumor Group developed different criteria to identify patients who qualified for postoperative treatment.[9] With the arrival of a molecular classification, the clinical concept of high risk needs rethinking, because the presence of an *IDH* mutation is a more accurate prognostic marker than the classical criteria defined by Pignatti et al.[10] Still, even in this era of molecular diagnostics, tumor residue after surgery remains a convincing risk factor for poor outcomes, especially in patients with *IDHmt* astrocytoma.[11] Therefore, patients who have tumor residue should be considered as having a "higher risk," but the question here is whether 1 factor alone should guide the decision for treatment. Similarly, the historic age cutoff of 40 years to identify patients with *IDHmt* glioma who have a poor prognosis is at least questionable, and an older cutoff (eg, age 50 years) well may be justified.[12]

Delaying postoperative treatment is particularly attractive if prognostic factors indicate that a delay of progression for several years is likely. In everyday clinical practice, the question whether it is reasonable to delay treatment to postpone side effects in patients older than 40 years or in those with incompletely resected, *IDHmt*, low-grade glioma (who should be carefully monitored) remains largely unanswered. If they are well monitored, then treatment can be started when radiologic or clinical progression occurs in these patients—which raises the also unanswered question of how much progression is needed before progression is called. For that, the tumor size intuitively appears to be relevant. In patients with *IDHwt* tumors, it is important to identify other molecular features that indicate aggressive tumor behavior (eg, combined trisomy of chromosome 7 and loss of heterozygosity on chromosome 10 or *EGFR* amplification).[4,13] Patients with these tumors, which, on a molecular level, resemble glioblastoma, are likely to have a poor outcome and require immediate treatment regardless of age and extent of resection. In the absence of such findings, there is no evidence to support early treatment. Most likely, methylation profiles also can be used to identify glioblastoma-like molecular profiles.[14] In addition, patients with refractory epilepsy benefit from treatment with chemotherapy and radiotherapy, and this is a reason for not delaying postoperative treatment.[15]

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ADDENDUM

Following acceptance of this manuscript, Brat et al, *Acta Neuropathol* doi: 10.1007/s00401-018-1913-0 provided in the cIMPACT-NOW update 3 criteria for the diagnosis diffuse astrocytoma, *IDH* wildtype, with molecular features of glioblastoma, WHO grade IV.

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Author Bios

Marjolein Geurts, MD, PhD
Marjolein Geurts will complete her neurology residency in January 2019. She works at the University Medical Center Utrecht. During her residency, she strongly focused on neuro-oncology. She has performed a clinical specialization in the Brain Tumor Center at Erasmus Medical Center Cancer Institute (Rotterdam, The Netherlands; supervisor, Professor Martin J. van den Bent) and has worked as a research fellow in The James Comprehensive Cancer Center at The Ohio State University (Columbus, Ohio; supervisor, Dr. Arnab Chakravarti). In addition to her laboratory work, which focuses on microRNAs in glioblastoma, she is also interested in clinical research.

Martin J. van den Bent, MD, PhD
Martin J. van den Bent, neurologist, is a professor of neuro-oncology working at the Brain Tumor Center at Erasmus Medical Center Cancer Institute in Rotterdam. He has conducted many trials on grade II, III, and IV glioma and has published widely on these topics. He is an active member and past chair of the European Organization for Research and Treatment of Cancer Brain Tumor Group and the next president of the European Association of Neuro-Oncology; a member of the core group of the Response Assessment in Neuro-Oncology group; a recipient of the European Crohn's and Colitis Organization Clinical Research Award; and he twice received the Award for Excellence in Clinical Research from the Society for Neuro-Oncology.