Neuro-Oncology
21(7), 828–829, 2019 | doi:10.1093/neuonc/noz062 | Advance Access date 11 April 2019

New developments and new dilemmas in lower-grade gliomas

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See the article by Schiff et al. in this issue, pp. 837–853.

The optimal management of lower-grade gliomas (World Health Organization [WHO] grades II and III) is a matter of debate due to the rarity of these tumors and new developments in molecular pathology. The review by Schiff et al[1] has extensively covered the current understanding and future challenges.

Overall, the WHO classification of 2016,[2] by integrating molecular factors of prognostic significance with traditional histology, has formalized new subgroups (ie, isocitrate dehydrogenase [IDH]-mutated and 1p/19q-codeleted oligodendrogliomas, IDH-mutated and 1p/19q non-codeleted diffuse astrocytomas, and IDH wildtype diffuse astrocytomas) with a clear-cut correlation with outcome. This has led neuro-oncologists to redefine concepts of treatment, but is posing new dilemmas as well.

The distinction of patients with WHO grade II tumors after surgery into a low-risk group, needing observation with MRI only, and a high-risk group needing adjuvant treatments (radiation and/or chemotherapy) is evolving. IDH wildtype diffuse astrocytomas are now recognized as having a poor prognosis compared with IDH-mutated counterparts. In this regard, the International Consortium cIMPACT-NOW has recommended that IDH wildtype diffuse astrocytomas of grade II or III, when carrying epidermal growth factor receptor amplification or chromosome +7–10 or telomerase reverse transcriptase promoter mutations, should be redefined as tumors with molecular features of glioblastoma, grade IV.[3] Thus, such patients, even if non-enhancing on MRI and microscopically appearing to have grade II tumors, should be considered as high risk, requiring adjuvant treatments regardless of the extent of resection. Conversely, a minority of tumors diagnosed as IDH wildtype diffuse astrocytomas but with a different molecular profile (BRAF mutation, etc.) have an indolent course,[4] and aggressive treatments, especially after gross total resection, are questionable. For the future, DNA methylation profiling seems a more reliable method for a better segregation of tumor types of uncertain diagnosis,[5] but still needs validation, and is not largely available across laboratories.

Older age (>40 y) and incomplete surgical resection are traditionally considered as factors identifying a high-risk patient among grade II gliomas. However, it is unclear whether the prognostic value of age and extent of resection varies across molecular subtypes, and whether one factor alone is sufficient to decide the risk group attribution. Historically, the age cutoff of 40 years was based on the evidence that astrocytomas in older age were at higher risk of malignant transformation, but it is unknown whether this holds true for IDH-mutated astrocytomas. Conversely, for IDH-mutated and 1p/19q-codeleted oligodendrogliomas, which are commonly older and with less risk of an aggressive evolution, a higher age cutoff (at least 50 y) seems more reasonable.

There are studies suggesting that a small amount of residual tumor after surgery would not significantly impact overall survival (OS) in IDH-mutated and 1p/19q-codeleted oligodendrogliomas (probably due to the more indolent course), while being important in diffuse astrocytomas, either IDH-mutated or wildtype.[6,7] If this is the case, a patient with an incompletely resected IDH-mutated, 1p/19q-codeleted oligodendroglioma regardless of WHO grade could become a low-risk patient, while a patient with grade II IDH-mutated diffuse astrocytoma with a small residual tumor after surgery could be considered to have a high risk.

Regarding surgery, 3 points seem well accepted, even if there is lack of randomized studies. First, when total/subtotal resections are not feasible due to tumor extension and/or location, open biopsies are more reliable than stereotactic biopsies in order to reduce the risk of sampling errors and allow extensive molecular evaluations, in particular O^6-methylguanine-DNA methyltransferase (MGMT) methylation, which is unrevealing in small samples. Second, an early resection is more effective than a late resection across all molecular subgroups.[8] Third, all recent studies, employing a volumetric evaluation of the extent of resection on T2 fluid attenuated inversion recovery images, have shown that 80–90% of resections are associated with longer progression-free survival (PFS) and OS. What is unclear is the long-term preservation of cognitive functions—especially when using the tools of modern neurosurgery—that have allowed an increase of

the extent of resection of tumors close to eloquent areas. Also, the concept of a supratotal resection in lower-grade tumors within non-eloquent areas of the brain should be evaluated across the different molecular subtypes, and the value could differ between oligodendrogliomas and diffuse astrocytomas. Lastly, an increasing number of patients with lower-grade gliomas undergo reoperation at recurrence, and the same dilemmas around first surgery apply to reoperation.

What have we learned from major trials on radiation and chemotherapy in high-risk patients? The European Organisation for Research and Treatment of Cancer 22033–26033 trial has shown that patients with IDH mutant and 1p/19q intact astrocytomas, who received initial temozolomide, had shorter PFS compared with those who received initial radiotherapy, while there was no difference between chemotherapy and radiotherapy as initial treatment in IDH-mutated and 1p/19q-codeleted oligodendrogliomas. The Radiation Therapy Oncology Group 9802 trial has shown that PFS and OS were longer for patients receiving radiotherapy and procarbazine/lomustine/vincristine (PCV) compared with those receiving radiotherapy alone, and this was particularly evident for oligodendrogliomas. The single-arm phase II study from the University of California San Francisco has shown that 53% of patients with low-grade gliomas after incomplete resection could delay radiotherapy for a median of 5.8 years by employing temozolomide upfront. Overall, the values of PFS and OS after combined treatment appear clearly superior to any single modality. However, an open issue is the balance between length of survival and preservation of cognitive functions following early radiotherapy plus PCV or initial temozolomide with reoperation and/or radiotherapy plus PCV at recurrence. An MGMT methylation score could identify among patients with IDH-mutated grade II gliomas those at higher probability to benefit from first-line temozolomide.[9] Another issue is the feasibility and risk of morbidity of reoperation following chemotherapy or radiotherapy. Last, 60% to 90% of patients with lower-grade gliomas suffer from seizures as a unique symptom at diagnosis, and total/subtotal resection leads to seizure freedom in up to 70% of patients until tumor progression.[10] Persistent and pharmacoresistant seizures are associated with partial resections, and these patients require an early adjuvant treatment. The evaluation over time of seizure activity by diaries or electronic devices now represents a better clinical monitoring than the evaluation of Karnofsky or Eastern Cooperative Oncology Group scores.

In conclusion, all the aforementioned issues need to be clarified in prospective studies (randomized or not, depending on the questions to be answered and the sample size needed) designed with molecular inclusion criteria.

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