Neuro-Oncology

Neuro-Oncology 17(3), 323–326, 2015
doi:10.1093/neuonc/nou368

Much debated controversies of diffuse low-grade gliomas

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See the article by Duffau and Taillandier, on pages 332–342.

Duffau and colleagues present a comprehensive and provocative review of the concepts of surgical and medical management of adult diffuse low-grade gliomas (DLGG). The review takes a very strong position, which will likely generate debate and stimulate much discussion regarding the establishment of guidelines for care of patients with DLGG. Here we provide a counterpoint to summarize the perspectives on observation and delayed intervention in management of DLGG.

The management of DLGG remains controversial, as the level of evidence to support best practices is not conclusive, and as a result, there is variation in practice patterns for individual patients who present with DLGG. The principal controversies include: the necessary components of the diagnostic workup; the role of a "wait-and-see" strategy; following patients based on their clinical status and imaging alone; and the nature and goals of surgical intervention. Following initial treatment decisions, postoperative management issues include but are not limited to: role of imaging, role of repeat surgery, adjuvant treatment, and follow-up. Although we have a better understanding of the isocitrate dehydrogenase–mutant, glioma cytosine/phosphate/guanine island methylator phenotype–positive subclass of DLGG, there are further biological signatures that will likely distinguish DLGG into subgroups, which will impact the outcome, extent and timing of tumor progression, as well as impairment of neurological and neurocognitive function.

Mounting evidence, based primarily on retrospective studies, suggests that early upfront extensive microsurgical resection of DLGG is associated with a more favorable prognosis.[1–18] European guidelines recommend maximal resection as the first therapeutic option in DLGG.[19] American guidelines similarly recommend maximal safe surgical resection; however, observation is appropriate for selected patients.[20] Yet, the best management strategy remains controversial, and upfront wide resection is not universally agreed upon since,[21] as proponents of a more conservative approach would point out, large-scale studies are needed to prove definitively an improvement in overall survival and one that outweighs the risks of complication to the patient. An important distinction to make, and one that should temper review of the literature, is that the association with longer survival may not in fact be a direct consequence of extent of resection per se, but more a direct reflection of earlier detection, tumor location including relationship to eloquent structures, and ultimately biology of the tumor. Currently little to no data exist to guide how to correlate molecular subtypes of DLGG with extent of resection and outcome. This is an area where we need to heavily consider the biology of the tumor and integrate this into our decision making for patient management.

Functional plasticity is a much debated area. In this review, the authors perhaps take a more optimistic perspective relative to the paucity of objective evidence in the literature to support this concept in adults. It is true that changes in functional architecture have been observed after an initial surgery for DLGG, when at the time of a subsequent surgery the mapping indicates new locations for certain functions. However, the authors appear to extend this phenomenon to a situation where surgery has not occurred; that is, during the development and growth of the DLGG itself. One has to acknowledge that our understanding of the adult brain plasticity in the context of DLGG is in its very early stages and more long-term large multicenter studies incorporating longitudinal functional imaging and neuropsychological and language testing are needed to answer this postulate. Clearly, the role of cerebral plasticity in the evolution and treatment of neurological deficits in patients with DLGG is not fully understood and is a fruitful area for future work.

Historically the management of DLGG has favored a "wait-and-see" approach for some, but the past 2 decades have shown a trend to earlier surgical intervention thanks to safer surgery using awake craniotomy mapping, recognition of safety and efficacy for delayed radiotherapy, and a better understanding of the natural history. Elsewhere, Duffau and Taillandier describe a "personalized, functional, and preventative neuroncology" approach whereby a tailored treatment

Received 7 December 2014; accepted 12 December 2014

plan is implemented for the individual based upon a clinical, radiological, histo-molecular strategy. They very rightly advocate that all patients with DLGG should not be treated with a "one size fits all" approach as in other tumors (eg, Stupp protocol for glioblastoma) but rather with a treatment personalized to their disease whereby recurrent surgeries and pre- or postoperative chemotherapy are implemented when indicated. The strength in their approach lies in their meticulous collection of pre-, intra-, and postoperative data, specifically in analyzing tumor growth, timing of intervention, degree of resection, use of awake craniotomy and cortical-subcortical mapping, short- and long-term neurocognitive function, and survival. The reality we must recognize is that in large part a more thorough integration of tumor biology and molecular genetics will be the most critical evolution in our ability to treat DLGG, where we can have a comprehensive and true personalization and refinement of treatment based on the clinical situation and the biology of the tumor.

One has to consider the importance of surgical experience and expertise of the surgical team in successfully achieving the type of surgical resection Duffau et al propose. Professor Duffau undoubtedly has among the largest surgical experience and specific expertise, not readily reproducible at all institutions. This is an important factor to keep in mind when reviewing experience of an expert and attempting to apply this broadly to patient management. It would be interesting to know the current practice patterns among neurosurgeons. How many are still practicing a "wait-and-see" approach and what is their rationale? From the published literature, we are aware that this remains current practice at some institutions.[22] Is the approach suggested by the authors one that is more restricted to those with experience and expertise at high-volume centers? Achieving a "safe" resection while maximizing tumor resection usually requires mapping (with or without an awake craniotomy). Do all surgeons have the capability of performing this at their hospital or institution? Alternatively, should this be restricted or prioritized to "centers of excellence"[23] where access to advanced preoperative imaging and a neurocognitive battery of tests, experience with awake craniotomy, and intraoperative mapping are available? Awake craniotomy performed at high-volume academic centers may be associated with a high rate of postoperative deficits[24]; however, this may be confounded by a lack of subcortical white matter stimulation that is standard practice at other centers.[25] If high-volume centers of excellence are experiencing a high rate of postoperative deficits, it is not surprising that many experienced surgeons might be hesitant to implement a more "aggressive" surgical approach.

The value of using intraoperative adjuncts, in particular use of intraoperative electrostimulation monitoring (IEM), remains controversial. While IEM is valuable, some of the current limitations of this approach prevent it from becoming widely adopted at many institutions. IEM is a valuable tool for the modalities that can be effectively monitored during surgery, most often including expressive and receptive speech, motor, and simple sensory and visual functions. In the setting of surgery, even with the support of experienced neuroanesthesiologists, more subtle functions are difficult, if not impossible, to monitor and preserve. These functions include subdomains of memory and executive function, complex computational skills, and integration of diffuse inputs. Also, this supra-maximal approach applies primarily to DLGG located in classically non-eloquent cortex, or relatively small tumors, which would apply to only a subset of DLGG patients. Ultimately, the literature on this topic is predominantly based on retrospective data, without level 1 evidence, for both surgery and nonsurgical interventions, including neurorehabilitation.

Duffau and Taillandier's assertion that it is crucial to measure the tumor growth rate as well as volume deserves comment. The work of these authors and other French investigators suggests that the rate of change of mean tumor diameter (MTD) is an independent prognostic factor for overall survival in DLGG. MTD is derived by taking the cubed root of the product of 3 orthogonal maximum tumor diameters on T2/fluid attenuated inversion recovery (FLAIR) images. While a 400+ patient study[26] demonstrates this to be an independent prognostic factor, there are some caveats. These include the lack of independent validation (a single investigator measured all scans, and large studies of MTD outside of France have not been reported to our knowledge), potential difficulty differentiating tumor from postoperative gliosis and measuring irregular residual tumor surrounding a resection cavity, and incompleteness of molecular data in their multivariate model. Although the authors state that Response Assessment in Neuro-Oncology (RANO) DLGG criteria are inadequate, it remains to be proven that the use of 3 orthogonal FLAIR measurements is superior to the 2 orthogonal measurements and 25% bidimensional product threshold from RANO.

The authors stress the importance of a tumor volume threshold of 10 cc as an indicator of when to reoperate or intervene with chemotherapy, based on the observation that residual or recurrent tumor exceeding this volume has a greater risk of anaplastic or malignant transformation.[2] They define transformation as the development of new or increasing contrast enhancement or tissue confirmation of development of grade III or IV glioma.[27] While transformation so defined is unquestionably an unfavorable development, that 10 cc represents a biologically meaningful or critical threshold remains unproven. Without questioning the burgeoning data supporting the role of maximum safe resection in low-grade gliomas (LGGs), it seems premature to use the 10 cc volume as a cutoff for deciding that a patient with otherwise favorable prognostic factors should be considered high risk and receive additional therapy on that basis. The principles of Gompertzian growth curves, drug resistance (the Goldie–Coldman hypothesis), and first-order kinetic killing of tumor cells with chemotherapy indicate that a tumor should be easiest to eradicate completely if cytotoxic treatment is started when the tumor is at its smallest. While these principles do not necessarily supersede issues of toxicity and quality of life, and may require validation in vivo, firm data should underlie their disregard.

Concerns of delayed cognitive damage lead the authors to recommend deferring radiotherapy when possible. Duffau and Taillandier recommend using chemotherapy, specifically temozolomide, in an attempt to defer radiation for tumors that require treatment despite maximal surgical efforts. Newly available data heighten the possibility that this approach might compromise overall survival. Early results from a phase III trial randomizing LGG patients to temozolomide or radiation suggest that temozolomide is not a superior initial strategy to radiation for either progression-free or overall survival.[28]

Moreover, updated results of RTOG 9802, a phase III trial that randomized adults with LGG to fractionated radiotherapy plus or minus 6 cycles of postradiation procarbazine/lomustine/vincristine (PCV) chemotherapy, demonstrate a substantial improvement in overall survival in the PCV arm (13.3 vs 7.8 y).[29] While analyses of benefit by tumor histology and molecular profile are not yet available, this result strongly suggests that when radiation is given, chemotherapy should follow immediately. It is far from certain that immediate postradiation alkylator chemotherapy will have the same benefit in patients previously treated with single modality alkylating chemotherapy, since previously treated tumors may have acquired resistance.[30] Much remains to be elucidated about the incidence, severity, and timing of development of clinically relevant radiation-induced cognitive damage with current radiation technology. Patients armed with such data might make different choices regarding DLGG therapy sequencing based upon tradeoffs between overall survival and anticipated quality of survival reflecting individual priorities and values.

Duffau and Taillandier's several suggestions regarding chemotherapy warrant comment. They favor temozolomide over PCV because of its favorable side effect profile. While this is reasonable, it should be acknowledged that we lack data that temozolomide is as effective as PCV in DLGG, and the substantial survival advantage with PCV over no adjuvant chemotherapy seen in RTOG 9802 raises the bar for temozolomide. Preliminary results of a single arm phase II study of radiation/temozolomide (RTOG 0424) are encouraging, with a 3-year overall survival of 73% compared with 54% in a historical control group, but long-term outcome data are unavailable.[31] The authors also state, "Protracted low doses of TMZ could offer potential advantages over standard doses, especially in unmethylated tumours." Dose-dense temozolomide has been studied in LGGs with encouraging results,[32,33] but it must be acknowledged that these results are not obviously superior to standard temozolomide schedules. Moreover, dose-dense temozolomide to circumvent unmethylated MGMT has not been proven superior to standard temozolomide administration postradiation in glioblastoma[34] and in fact was inferior in one high-grade glioma trial.[35]

The authors additionally recommend giving a longer total course of temozolomide for larger residual tumors and tumors with a more rapid growth rate, a conjecture requiring confirmatory evidence. There are few examples of successful maintenance cytotoxic chemotherapy in medical oncology, where the usual evidence-based paradigm regardless of tumor size and growth rate is several cycles of dose-intense chemotherapy followed by observation. Similarly, the suggestion to study alternating several-month periods of temozolomide and observation carries the risk of selecting for resistant clones. This criticism does not detract from the potential value of studying the role of a second course of temozolomide in DLGG patients with tumor progression while on observation after a successful first course of the drug.

In closing, the authors should be commended and congratulated for their clear expertise and long-standing experience in surgical management of patients with DLGG, providing here, as with previous publications, a thorough description of their approach and review. However, the widespread applicability of their skills and techniques, together with experience in patient selection, is difficult to replicate in all institutions that manage DLGG. The wait-and-see approach is still widely practiced and will continue to be an area of controversy.[36,37] The reality is that the neuro-oncological community must continue to study this chronic brain disorder, with further work on controlled clinical trials and targeted therapeutics. Given the relatively small subpopulation of patients affected by DLGG, consideration should be given to focusing management of DLGG in comprehensive recognized centers of excellence, in parallel with clinically-relevant molecular profiling to correlate biology with clinical course. As we are understanding the molecular biology of all brain tumors better, the role of molecular signatures and evolution of tumors longitudinally will be a key determinant of therapeutic strategies.

Disclosures

None declared.

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