Paradoxes of evidence-based medicine in lower-grade glioma

To treat the tumor or the patient?

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Abstract

Brain lower-grade gliomas (LGG) usually occur in young adults who enjoy an active life. This tumor has a high risk of malignant transformation resulting in neurologic deterioration and finally death. Early and multistage therapeutic management can increase survival over 10 years. Preservation of functional neural networks and quality of life is crucial. In the era of evidence-based medicine, the issues discussed are those associated with the design, analysis, and clinical application of randomized controlled trials (RCTs) for LGG. RCTs should take account of the following: considerable variability in the natural course of LGG; limited prognostic value of molecular biology at the individual level; large variability of brain organization across patients; technical and conceptual progress of therapies over years; combination or repetition of iterative treatments, taken as a whole and not only in isolation; and long-term consequences on oncologic and functional outcomes. As it is difficult to translate the results of an RCT into benefits for a unique patient with LGG, personalized decisions must be made by considering the tumor behavior, individual pattern of neuroplasticity, and patient needs, and not by administrating a standardized protocol exclusively based on an RCT.

Introduction

Gliomas represent a major public health issue. These tumors represent almost 50% of primary brain neoplasms and cause neurologic deterioration by invading the CNS, with an overall survival (OS) that is relatively short, particularly concerning glioblastomas (less than 1–1.5 years).[1] However, in lower-grade gliomas (LGG), which generally occur in young patients between 20 and 40 years of age, life expectancy is substantially longer in patients with active familial, social, and professional lives. As the natural course of diffuse LGG is to grow constantly and ultimately evolve into a higher grade of malignancy, the purpose of therapeutic management is to delay glioma degeneration as well as to preserve quality of life (QoL); that is, to transform this progressive neoplasm into a controlled chronic disease.[2,3] Nonetheless, elaborating an optimal treatment strategy at the individual level remains challenging due to considerable heterogeneity between LGG. Indeed, it is complex to predict when degeneration will occur, as well as the actual role of surgery, chemotherapy, and radiotherapy (in isolation or in combination) in the natural course of this neoplasm at that time.[3] In addition, the immediate and delayed consequences on QoL of a simple watch-and-wait attitude vs a therapeutic approach should be anticipated, to find the optimal balance between treating the tumor and treating the patient. In other words, tailoring a personalized treatment strategy must take into account not only the behavior of the glioma, but also its interaction with the dynamics of cerebral networks. In fact, these slow-growing tumors can induce functional reorganization of the brain or so-called neuroplasticity, explaining why LGG are usually diagnosed in epilepsy among patients who exhibit no (or only slight) neurologic deficits.[4] On the other hand, glioma cells migrate along white matter fibers, which represents the main limitation of cerebral

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Glossary

EANO = European Association of Neuro-Oncology; **EBM** = evidence-based medicine; **EOR** = extent of resection; **IDH** = isocitrate dehydrogenase; **iMRI** = intraoperative MRI; **LGG** = lower-grade gliomas; **MMSE** = Mini-Mental State Examination; **OS** = overall survival; **PCV** = procarbazine, lomustine, and vincristine; **PFS** = progression-free survival; **QoL** = quality of life; **RCT** = randomized controlled trial.

plasticity.[5] For this reason, tumor progression itself, as well as treatments, may damage neural circuits, resulting in neurocognitive or neurologic disorders and a reduction in QoL.

In this setting based upon complex relationships between glioma progression and brain reshaping, it seems difficult to tailor individualized, multistage management issued from evidence-based medicine (EBM). EBM was initially defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."[6] In this spirit, randomized controlled trials (RCTs) have been prioritized over population-based observational research because the power of randomization is supposed "to ensure that the only difference between treatment arms is exposure to the treatment of interest."[7] Although the principle of selecting treatments based upon a higher level of proven effectiveness makes sense, there has nonetheless been a progressive shift from the legitimate use of EBM for improving health care to an obligation to benefit from RCTs before proposing a therapy. Yet RCTs suffer from intrinsic limitations, especially the considerable differences in the management of patients enrolled in RCTs vs clinical practice, as well as the use of surrogate endpoints despite an absence of validation regarding their actual ability to predict improvement in OS or QoL; therefore, these endpoints can be problematic regarding their application to the treatment of patients in daily practice.[7] This is particularly true for patients with LGG because they currently have prolonged survival and there is a need to preserve their QoL for many years. Thus, it is almost impossible to design an RCT to test a standardized treatment for LGG that takes into account the huge variability in the natural history of these tumors, the limited prognostic value of molecular biology at the individual level, the large variability in the functional anatomy of the CNS across patients and in the same patients over time (due to possible neural remapping), the technical and conceptual progress of therapies over years (notably concerning cerebral surgery), the combination or repetition of iterative therapies (such as reoperation following adjuvant chemotherapy or radiotherapy) taken as a whole and not only in isolation, and the long-term consequences (at least within the next 10 years) for both oncologic and functional outcomes.[3]

Evidence-based medicine and surgery for LGG

Regarding the role of surgery, 2 near-randomized surveys compared the OS in parallel series of LGG from 2 departments with distinct surgical attitudes. In the German experience, a significant OS benefit was observed for patients with initial surgical removal vs biopsy, with 5-year OS 82% vs 54% and 10-year OS 67% vs 38%, respectively ($p = 0.003$).[8] In the Norwegian series, OS was 5.8 years in the department favoring watchful waiting vs 14.4 years in that favoring early resection ($p < 0.01$). Furthermore, the effect of resection was still found after adjustment for genetic markers ($p = 0.001$).[9] Indeed, although it could be argued that such data may be explained by the assumption that tumors amenable to surgical excision share a more favorable molecular profile, a cohort with 200 consecutive patients with LGG evidenced that improved resectability was independent of a favorable genetic pattern, supporting the benefit of surgical removal per se.[10] However, despite these strong results demonstrating that OS is nearly doubled with early surgery, which confirm the data from observational retrospective and prospective studies in which the extent of resection (EOR)—objectively calculated using postsurgical MRI—was significantly correlated to OS,[11–14] the role of surgery is not clearly recognized in recent guidelines under the argument that there are no RCTs.[15] It is nonetheless puzzling to note that in RCTs dedicated to medical treatments for LGG (see below), no objective evaluation of the EOR has been made, despite considerably increased OS owing to surgery, as mentioned above. In other words, applying the concept of EBM without any nuance results in the paradox that despite a major bias in the design of an RCT, its data have more value with respect to opinion within the medical community than a near-randomized study with adjustment for validated prognostic factors, including molecular biology, but with no actual randomization. This raises the following ethical problem: is it medically acceptable nowadays to enroll a patient in an RCT comparing initial biopsy vs surgery when OS is about 14–15 years with early resection[9,11] vs 6–7 years with biopsy,[8] just to claim that the benefit of surgery has finally been demonstrated with Level I evidence according to EBM? In addition, if such a trial were organized, another problem would be selection of the teams because oncologic and functional results of glioma resection are dependent on surgical expertise.[3] Another bias would be rapid advances in surgical techniques and concepts because such a randomized trial would last for at least 5–10 years. In the last decade, the benefits/risks ratio of surgical excision for glioma has dramatically improved owing to the use of intraoperative electrical mapping, as demonstrated by a meta-analysis on this topic.[16] It has been shown that functional mapping-based resection results in a significant reduction in the rate of severe, persistent deterioration (about 3.4%) while increasing the EOR, even in eloquent cerebral structures.

Yet the use of intraoperative MRI (iMRI) is increasingly advocated because one RCT found a significant improvement in the EOR for glioma in the iMRI arm—despite 13% new neurologic deficits—compared to the arm without iMRI.[17] In other words, although iMRI is expensive and available in only a few neurosurgery departments worldwide and despite the lack of demonstration that this technique can improve EOR while simultaneously decreasing postoperative morbidity (contrary to the inexpensive technique of intraoperative electrical mapping, as mentioned), more authors are supporting the use of iMRI under the pretext of EBM, that is, Level II evidence concerning this oncologic issue, despite the absence of consideration for patient QoL.[18,19] This is not a trivial issue because the concept of functional mapping-guided resection is completely different from the concept of image-guided resection, which in essence takes into account real-time neurocognitive monitoring of the patient intraoperatively.

Evidence-based medicine and medical treatment for LGG

Concerning radiotherapy in LGG, the sole RCT that compared early vs delayed radiotherapy found no significant difference in OS between both arms.[20] Of note, in this trial where many patients had a simple biopsy and in which the EOR was not objectively evaluated, the OS was 7.2 years in the control subgroup vs 7.4 years in the early radiotherapy subgroup, i.e., almost half compared with OS following early surgery.[9,11] It is interesting that the authors emphasized that progression-free survival (PFS) was significantly increased after early radiotherapy. In fact, this trial unintentionally supports that PFS is not a reliable surrogate endpoint in patients with LGG, because PFS was prolonged whereas OS was not. Of course, the goal for the patient is to live longer and not to benefit from increased PFS. Yet PFS continues to be used in RCTs in progress (see below). Moreover, from a functional perspective, one study showed that there is a risk of long-term cognitive deterioration associated with radiotherapy in patients with LGG. By examining long-term survivors of LGG (more than 6 years following diagnosis), patients with no radiotherapy had a stable cognitive assessment whereas patients who received irradiation experienced a gradual decline in attention and executive functions, even for fraction doses that are considered safe (≤2 Gy), although the percentage of patients with long-term mild cognitive defects following radiotherapy was low.[21]

Despite these important results provided by EBM, which show that early irradiation has no significant benefit on OS (about 7 years) and may induce delayed neurocognitive deficits, a recently published RCT compared irradiation alone with irradiation plus procarbazine, lomustine, and vincristine (PCV) chemotherapy in patients with LGG, with no arm without radiotherapy.[22] Therefore, although physicians say that they need more Level I evidence, they do not take into consideration such data once they have finally been obtained. Furthermore, in the recent RTOG 9802 trial by Buckner et al.,[22] there were no cognitive data beyond 5 years, whereas the risk of cognitive deterioration following irradiation was delayed. In that study, it is also puzzling to note that global cognitive functioning was evaluated in the first years using the Mini-Mental State Examination (MMSE), which is in fact designed for patients with dementia.[22] Finally, surgical EOR was not objectively calculated. Despite these serious limitations, which prevented any reliable conclusions to be drawn regarding long-term QoL because OS was significantly prolonged in the arm combining radiotherapy and PCV, those authors claimed that the new standard was to administer irradiation and PCV in all so-called high-risk patients with LGG over age 40 years or with incomplete surgical excision.[22] Surprisingly, these 2 criteria defining high risk are questionable: first, because the EOR was estimated based on the subjectivity of neurosurgeons with no quantification on postoperative imaging; and second, distinguishing patients older than 40 years is not in agreement with the literature. In fact, in the largest cohort reported on LGG surgery, an independent marker of worse prognosis was age over 55 years (not over 40 years).[11] In addition, Reuss et al.[23] investigated the age effect on OS in 3 independent series (a total of 1,360 adult isocitrate dehydrogenase [IDH]–mutated diffuse astrocytic gliomas) and found no difference. Of course, it might be argued that the RTOG 9802 trial opened in 1998, explaining its many biases. The problem is that based on this RCT of limited value, combined modality treatment of radiotherapy plus chemotherapy is now considered the standard of care.

To overcome the absence of a chemotherapy-only arm in the trial by Buckner et al.,[22] another RCT is in progress comparing radiotherapy alone vs temozolomide alone in high-risk LGG. The preliminary results show no significant PFS difference in patients with LGG treated with irradiation alone vs temozolomide alone.[24] It is of interest that despite the major limitation of PFS mentioned above, this surrogate endpoint was used nonetheless, thus preventing a clear conclusion from being reached. Again, the EOR was not objectively assessed using postoperative MRI. Finally, even though no significant difference was observed between both groups regarding the change in MMSE scores, the follow-up was only 36 months,[25] and postirradiation cognitive decline occurred beyond 6 years.[21] However, according to the strict application of EBM based upon current RCTs, there is no reason not to consider radiotherapy because of delayed cognitive risks, even though observational studies with longer follow-up have demonstrated the opposite. Thus, a paradox of EBM is that despite major design issues (especially no data at 10 years), the power of RCTs is regarded as superior to the real facts. For example, based on the National Cancer Data Base, 2 recent nonrandomized controlled trials demonstrated that no long-term OS difference was seen in 1,054 patients with LGG treated using chemotherapy alone vs chemotherapy and radiation,[26] and even that OS was longer in 2,253 patients with LGG who underwent surgery with chemotherapy alone (125.8 months) vs radiotherapy alone (98.9 months) ($p < 0.001$).[27] Therefore, on behalf of the European Organisation for Research and Treatment of Cancer, Bady et al.[28] recently proposed the use of a new

MGMT methylation score to identify patients with IDH-mutant LGG who may benefit from first-line treatment with temozolomide, "to defer radiotherapy for long-term preservation of cognitive function and quality of life." Of note, one could argue that the methodology of radiotherapy is currently superior to irradiation methods 10–20 years ago, but this argument would in fact support the limitations of RCTs for chronic diseases such as LGG. Indeed, as already mentioned for surgery, because at least a decade is needed to demonstrate the actual benefit of a specific treatment in a randomized trial, technical advances will likely occur in the meantime. Consequently, even if a trial can be modified to take into account these new developments, this will nonetheless introduce a bias. In addition, it is more than challenging to design an RCT within the framework of a multistage sequential strategy, which is increasingly proposed in patients with LGG due to their long survival.[2] In fact, the overall efficacy of each therapy cannot be evaluated only per se as it is highly dependent on its incorporation into the entire therapeutic sequence. Consequently, to select the optimal therapy at each step, clinicians must also take into account both the previous and the next stages.[29] For example, a (re)operation might be considered (or not considered) according to the response to chemotherapy, i.e., depending on the fact that chemotherapy has (or has not) induced tumor shrinkage in inoperable brain structures.[30] It might be argued that the purpose of randomization of a sufficient number of cases is to increase the likelihood that the confounding variables will be balanced across study arms; however, these statistics cannot be reliably applied at the individual level, to tailor a multistage treatment strategy for a given patient.

Evidence-based medicine and interindividual variability of brain organization in LGG

To preserve QoL (or to improve it, especially by controlling epilepsy), investigating the dynamics of the functional neural networks in each patient is essential before introducing any treatment. Progress in neurosciences has taught us that the functional anatomy of the CNS is variable across patients with LGG,[31] especially due to functional reshaping induced by slow progression of the neoplasm.[32] However, it is worth noting that this potential of neuroplasticity is high for the cortex whereas it is lower at the axonal level.[33] Because glioma cells migrate along the white matter fibers, this tumoral invasion may result in neurocognitive deterioration and may limit the surgical EOR if these subcortical pathways are involved.[34] Recent nonrandomized studies have revealed that radiotherapy of specific neural fascicles can cause cognitive disturbances, even when using new irradiation technologies.[35] This means that investigating glioma behavior is mandatory but not enough to tailor the optimal therapeutic management in patients with LGG. A better understanding of the adaptive brain processes in reaction to tumor growth is also critical at the individual level. To this end, neurocognitive evaluation must be conducted before and after each therapeutic step.[36] However, this considerable interindividual variability has never been integrated into RCTs studying oncologic issues (PFS and OS) but not the brain itself. Indeed, in RCTs dedicated to LGG, longitudinal evaluation of cognitive status and QoL have never been correlated with the neural networks involved in each therapy, as, for example, neurocognition/QoL and (1) the EOR following surgery performed up to the functional limits identified by means of intrasurgical electrostimulation mapping; (2) the volume of irradiation incorporating or preserving the main cerebral pathways; (3) shrinkage or progression of the glioma along the subcortical tracts under chemotherapy, and so forth. Of note, one RCT demonstrated the influence of cognitive rehabilitation on verbal memory, attentional processing, and mental fatigue in patients with glioma[37]; surprisingly, such cognitive rehabilitation programs are exceptionally proposed in clinical practice.

Evidence-based medicine and genetics in LGG: What does "personalized medicine" actually mean?

EBM has assisted in the development of "personalized medicine," or the ability to select therapies on the basis of genetic data that are quasi-unique to the patient's neoplasm.[38–40] Indeed, owing to recent advancements in the field of molecular biology, the 4th edition of the WHO classification has emphasized the role of genetics and established a new era in neuropathology, i.e., genotype is now incorporated into an integrated diagnosis.[41] This histomolecular classification is supposed to be helpful in determining subgroups with a better prognosis for a specific glioma histopathology and grade and helping to predict tumors that could be more sensitive to chemotherapy and radiation therapy.[42–44] Nonetheless, the prognostic value of molecular biology is not reliable at the individual level. For example, although IDH wild-type LGG have been described as displaying a glioblastoma-like genetic, transcriptomic, and epigenetic profile,[41,42,45] patients with these tumors may have survival that extends beyond 10 years.[46] Thus, a rigid view advocating that therapy should be selected mainly on the basis of the genetic profile is an oversimplification. This view reduces a complex multifactorial disease to a single criterion and may result in overtreatment, such as cerebral irradiation with negative effects on neurocognition, without taking account of the most important variable: the patient.

Currently, despite trials in progress, the possible benefit of therapy stratification based on genetic profiling has not yet been evidenced by RCTs. Predictive and prognostic values of markers used in routine practice, like IDH, TERT, and TP53, have been only studied in retrospective series or as an unplanned analysis of prospective investigations. As a consequence, according to the principle of EBM, it is difficult to understand why genomic classification should guide clinical decision-making. Yet, in the most recent guidelines of the

European Association of Neuro-Oncology (EANO), the main criterion used to define therapeutic strategy is represented by molecular biology, whereas clinical and radiologic characteristics do not seem to be critical.[15] Indeed, from a clinical point of view, almost nothing is mentioned about functional aspects such as QoL and cognitive issues, except the Karnofsky Performance Status score.[15] Of note, EANO published recommendations for palliative care in patients with glioma,[47] but even if this is an important issue, it is also crucial to preventively ensure the QoL of patients and their caregivers from the time that chronic disease is diagnosed—especially in LGG, owing to the long survival expectancy—and not solely at the end-of-life stage. In the same way, from a radiologic perspective, the volume and growth rate of the glioma are not taken into consideration, despite having been demonstrated as representing prognostic factors independent of molecular biology,[48] under the pretext that these criteria have not been evaluated in an RCT.[15] This is another paradox in EBM; indeed, do we really need an RCT to show clinical relevance, namely, that the prognosis is worse in tumors that grow faster,[49] knowing that substantial correlations between velocity diameter expansion and OS have already been demonstrated in observational studies?[50,51] Surprisingly, by strictly applying this same principle of EBM to the EANO guidelines for LGG, there are currently no RCTs that actually support the recent recommendations translating the WHO integrated histomolecular diagnosis into algorithm decision-making.[15] For example, although the 1p/19q codeletion is classically considered a predictive factor of chemosensitivity, a recent study supports that a high *MGMT* methylation score can predict a positive effect of temozolomide for IDH-mutant LGG, regardless of the 1p/19 profile.[28] In fact, genetics should only represent a part of the story because multistep management cannot be decided based only on routine molecular markers; it should be considered in conjunction with individual clinical and radiologic measures.[52] In other words, the concept involving various levels of EBM is questionable and must be called into question by anyone who believes in real "individualized medicine."

Discussion

Although the principle of EBM was laudable initially, in particular for comparing a new drug with existing treatments that were already validated, the current doctrine claiming that only RCTs can provide the absolute truth is abusive. In fact, issues regarding design, analysis, and reporting represent serious limitations for many RCTs and how they might be translated to clinical management, especially concerning a global multistage therapeutic strategy in patients with long survival. Despite the original definition of EBM by Sackett et al.,[6] aimed at "integrating individual clinical expertise with the best available evidence from systematic research," several decades later, a concept of comprehensive integrated individual therapy is given too little consideration. In practice, well-conducted clinical research with a high level of evidence could be helpful to investigate the actual benefit of a specific therapeutic tool, e.g., the role of intraoperative mapping in surgical outcome[16] or the optimal doses of radiation therapy.[53] These results from EBM might be used as isolated elements that are finally incorporated into a more integrated individual multistage therapeutic approach that is readapted in real time over years. Thus, RCTs should only be a part of the story. However, the new personalized medicine based almost exclusively on molecular biology of the tumor no longer considers the functional aspects. Yet, in neoplasms invading the brain, such as LGG, the patient and the patient's QoL cannot be reduced to the genetic profile of the glioma. In other words, this new philosophy could in time evolve into something contrary to real individualized-based medicine that cares for the needs of patients. In fact, given the rarity of LGG and the heterogeneity of tumors as well as patients, trials are more challenging in the era of molecular biology. The risk of EBM is that of treating the tumor but not the patient. Physicians should adhere to the Hippocratic Oath and accept that management must be tailored for each patient, and they should not exclusively apply guidelines based on RCTs and genetics. Medical doctors seem to forget that statistics do not have an absolute value at the individual level and that it is difficult to translate the results of RCTs into benefits for a unique patient. Furthermore, regarding ethical issues, clinicians have to bear the following paradox in mind: on one hand, claiming that the provision of care should be patient-centered, and on the other hand, proposing that patients be recruited into RCTs to provide evidence that will move the discipline forward. These days, can we promise the patient that there is no antagonism between their interests vs the interests of the discipline for the future? This is the reason why prospective data must be collected in a more systematic way, with the aim of implementing broad national and international databanks.[54]

EBM should never replace the unique relationship between the patient—particularly patients with a brain tumor, because of the considerable interindividual variations in cerebral (re) organization over years due to glioma progression and treatments—and the doctor, who must continue to make personalized decisions and not administrate a standardized protocol exclusively based on an RCT. Concretely, the recommendations from RCTs might serve as minimal guidelines of management in centers with no specific expertise in LGG, especially when they are geographically far from centers that are hyperspecialized in this rare disease. However, whenever possible, these patients should be referred to tertiary centers, so that they may benefit from a personalized therapeutic approach rather than a more generalized approach.

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