Neuro-Oncology Practice

4(4), 241–247, 2017 | doi:10.1093/nop/npw031 | Advance Access date 17 January 2017

Survey on current practice within the European Low-Grade Glioma Network: where do we stand and what is the next step?

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Abstract

Diffuse low-grade glioma form a rare entity affecting young people. Despite advances in surgery, chemotherapy, and radiation therapy, diffuse low-grade glioma are still incurable. According to current guidelines, maximum safe resection, when feasible, is the first line of treatment. Apart from surgery, all other treatment modalities (temozolomide, procarbazine-CCNU-vincristine regimen, and radiation therapy) are handled very differently among different teams, and this in spite of recent results of several phase 3 studies. Based on a European survey, this paper aimed to get a picture of this heterogeneity in diffuse low-grade glioma management, to identify clinically relevant questions raised by this heterogeneity of practice, and to propose new methodological frameworks to address these questions.

Key words

diffuse low-grade glioma | evidence-based medicine | GLIOCOM | surgery | survey

In June 2015, the 11th meeting of the European Low-Grade Glioma Network (ELGGN) took place in Paris. This network was initiated by Hugues Duffau in 2006, and gathers surgical and neuro-oncological centers with dedicated teams in charge of diffuse low-grade glioma patients. Although all participating centers are primarily involved in awake surgery, the network aimed to make the link between all subspecialties involved in the field: neurosurgeons, neuro-oncologists, radiation therapists, pathologists, oncomolecular biologists, neuroradiologists, anesthesiologists, speech therapists, neuropsychologists, and neuroscientists involved in brain function mapping. As a network, collaborative studies have been launched, some involving almost all centers,[1,2] some others involving only a subset of them.[3]

The ELGGN has a powerful potential to address major issues in the management of diffuse low-grade glioma, and as a first step towards the creation of a task force within the network, we set up, in preparation of the meeting, a survey about current practices in the different centers. The aim was to identify which aspects of the management were subject to a consensus, and which were more debated. This will allow us to highlight relevant questions for future studies.

Methods

The survey was built on Google forms and sent to 28 centers in May 2015. All recipients were members of the ELGGN, and only one answer per center could be registered. Indeed, it was specified that the questionnaire should be filled out during a multidisciplinary meeting. We did not ask participants to detail how any disagreements were adjudicated, precluding analysis of response heterogeneity at the center level. The survey contained 69 questions (see supplementary file S1), divided in 10 parts, following globally the chronological order of events in the management of a diffuse low-grade glioma patient (preoperative cognitive assessment [questions 1–7]; imaging pratice [questions 8–10]; initial management [questions 11–17]; intraoperative anesthetic management [questions 18–29]; intraoperative cognitive assessment [questions 30–31]; postoperative assessment [questions 32–36]; molecular biology [questions 37–41]; postoperative strategy [questions 42–44]; choice of chemotherapy [both unresectable and operated diffuse low-grade glioma] and follow-up under chemotherapy [questions 45–57]; radiation therapy [questions 58–69]).

Results

A total of 21 centers from 11 countries responded to the survey (see Figure 1). On average, 27 diffuse low-grade glioma patients per center are operated on each year (range, 3–165). About three-quarters of these patients are operated on in an awake state (range, 33%–100%), in keeping with the fact that many teams do not practice awake surgery for lesions on the right, nondominant side. The total numbers of patients followed within the ELGGN centers is 2048 (average = 97 per center; range, 21–400). Half of the centers do have a computerized database, with continuous updating in 50% of cases.

In the following sections, the most relevant results for each topics are listed. Detailed responses are provided as supplementary files (Fig. S1 to Fig. S69).

Preoperative Cognitive Assessment

The minimal core of testing was based on testing language (verbal fluency in 94% of centers and DO 80—which consists of naming 80 black and white images—in 59% of centers), working memory (forward and backward digital span and verbal span in 71% of centers), and executive functions (Stroop and trail making test in 65% of centers).

Two-thirds (71%) of the teams chose the tests according to tumor location. Among these individually chosen cognitive assessments, the Bell's test and the Read the Mind in the Eyes test were the most common, making up 66% and 33% of individually chosen tests, respectively.

Finally, quality of life was evaluated in only 31% of centers.

Imaging Practice

Spectrocospy (79%), perfusion (95%), and diffusion tensor imaging (84%) were of widespread use, whereas a minority of centers used PET (21%).

Initial Management

Treatment was triggered earlier for resectable glioma than for unresectable glioma (no watch-and-wait period in 52% of centers for resectable glioma versus 20% for unresectable glioma). As a direct consequence, it can be inferred that preoperative determination of diffuse low-grade glioma kinetics, which have been shown to be of great prognosis value,[7,8] was not widely integrated in daily clinical practice (see also Figure S53 for the proportion of centers determining the kinetics under chemotherapy).

Upfront radiation therapy in unresectable diffuse low-grade glioma was proposed by 25% of teams. Moreover, about 30% of teams did not envision temozolomide in a neoadjuvant setting (ie, with the aim to shrink a tumor to make it operable).[9–12]

Intraoperative Anesthetic Management

The results of the anesthetic part of the survey revealed a huge heterogeneity of practice in awake surgery. Since this topic is in some ways very specific, a dedicated paper will deal with the results of this part of the survey.

Intraoperative Cognitive Assessment

For language assessment, picture naming (DO 80) was by far the most popular test (95%). Other tests (repetition, lecture, semantic association test) were used in about half of centers.

For assessment of nonlanguage functions, line bisection and visual field evaluation were performed by two-thirds of centers, whereas the test Reading the Mind in the Eyes was proposed by a minority of centers (20%).

Fig. 1 European map of cities hosting centers participating in the survey. The map was adapted from http://d-maps.com/carte.php?num_car=13436&lang=fr.

Only 57% of centers used the double task, which adds a motor task (continuous repetitive movement of upper limb) in parallel to any other language task (like picture naming, for example).

Postoperative Assessment

Only 37% of centers were aware of the observed rate of work resumption after awake glioma surgery in their institution.

Molecular Biology

Despite the recognized value of molecular markers in the prognosis of diffuse low-grade glioma patients, 40% of the clinicians participating in the survey did not consider these biological markers for the therapeutic decision. 1p19q co-deletion (7/20) and IDH mutation (6/20) were the most frequently considered. One-third of the clinicians did not tell their patients the findings concerning biological markers, whatever the results were.

Postoperative Strategy

This part of the survey showed that centers widely agreed on a watch-and-wait approach in cases of complete resection on FLAIR imaging (80% of centers). In cases of subtotal resection, practices were more heterogeneous (see Figure S43), even if there was a trend towards watch and wait [57.9%]). During this follow-up period, a large majority of centers evaluate the growth of the residual tumor by quantitative measurements.

Choice of Chemotherapy and Follow-up Under Chemotherapy

Temozolomide was proposed for first-line chemotherapy for both unresectable and resectable diffuse low-grade glioma in 16 of 21 centers. Regarding monitoring, this part of the survey illustrated the existing gap between common practice and ideal conception. Indeed, while most centers were convinced that patients under chemotherapy should be monitored quantitatively, both on cognitive functions and on tumor volume, only 3 centers assessed cognitive functions and only half of the centers measured tumor volume quantitatively.

Radiation Therapy

If we try to compare the consistency between answers from all groups, then only 15% of teams recommend irradiating in the low-grade period as the first-line treatment, while 45% irradiate patients only after malignant transformation and 50% only in case of progressive disease after a first line of chemotherapy. More precisely, for upfront,

unresectable diffuse low-grade glioma, only 23.8% recommend radiation therapy as a first-line treatment.

Once the decision is made to irradiate, 3 major points are questioned: the target definition, the dose level, and the identification and preservation of organs at risk, particularly those involved in cognitive processes. The survey revealed a huge hetereogeneity regarding target definitions and technical implementation of irradiation in diffuse low-grade glioma patients. These fundamental issues deserve an in-depth analysis and a separate dedicated paper will be devoted to this topic.

Discussion

This survey showed mostly homogeneity in diffuse low-grade glioma management within the ELGGN. Nonetheless, we also found heterogeneities that deserve to be highlighted. Of note, questions were written as global scenarios and not as detailed individual cases and we acknowledge that this method might have biased responses (by artificially increasing or decreasing heterogeneities of responses).

First, it was observed that 28% of the teams do not select intraoperative testing according to tumor location. This strongly suggests that those teams restrict awake surgery to tumors involving cortical and axonal language areas. Hence, within the ELGGN, awake brain tumor surgery is not the standard of care for lesions in the nondominant hemisphere.[16] In the same vein, picture naming is the sole task used by many teams to evaluate language. The importance of adding other specific language tests has been recently explored.[13] It was concluded that the pyramid-palm-tree test and reading are the most important tasks to add. Depending on the preoperative discussion with the patient about the onco-functional balance, other tests, including famous face naming, syntax, repetition, multilingualism, and dual tasks, could be added on an individual basis. In the present survey, only 57% of centers use the double task. It should be mentioned that several teams have recently reported multitask testing.[14,15] How such strategies compare to the dual-task paradigm in preserving executive functions remains to be determined.

The ecological consequences (in terms of socio-professional life) for the patient undergoing a resection in the nondominant hemisphere without functional mapping or without any other language task than the sole picture naming are not well known. It would be expected that work resumption rates are higher in centers that perform awake operations also in the nondominant hemisphere and that add further task(s) in addition to the simple picture naming on the left-dominant hemisphere ("functionalist centers") compared with centers tailoring the resection according to tumor extent in an asleep patient on the right side and relying only on picture naming on the left side ("oncologist centers"). The return to remunerative employment after awake glioma surgery depends on multiple variables, including cognitive and physical demands of the job, the patient's philosophy of life, the employer's demands and expectations, and the level of the patient's health insurance. Nevertheless, neurological and cognitive outcomes are likely to be the major factors of a successful return to work. As such, rates of work resumption appear to be an essential proxy of good neurological and cognitive outcomes. It is worth noting that only very few studies in the literature are focusing on that topic.[17,18] We thus propose that extent of resection and rate of work resumption should be compared between "functionalist" and "oncologist" centers.

A second important heterogeneity was noted regarding (neo-)adjuvant treatments. The growing interest over the last 2 decades for biological markers in diffuse low-grade glioma culminated in 2016 with the revision of the WHO classification,[19] which now integrates IDH and 1p19q status in the definition of 3 subgroups among diffuse low-grade glioma. The major prognosis value of these 3 molecular profiles was the rationale for this mini-revolution.[20,21] Not surprisingly, and in accordance with the recent results of phase 3 trials,[22,23] it can be anticipated that treatment guidelines will follow, with an algorithmic procedure (see Figure 2a) based on the new classification (ie, on molecular markers). In this approach, radiation therapy with adjuvant procarbazine-CCNU-vincristine (PCV) would be recommended for IDH-mutated 1p19q co-deleted tumors.[22] Radiation therapy with concomittant temozolomide would be recommended for IDH wild-type tumors, as it has been shown that these tumors share genomic alterations with glioblastoma[20,21,24] (although it should be kept in mind that some non-IDH mutated tumors rather share genomic characteristics with pilocytic astrocytoma, and that adjuvant treatment would be questionable for this subgroup). Radiation therapy would be the standard option for the IDH-mutated, 1p19q non-codeleted group, although there is currently only little evidence supporting this option. Interestingly, over the last decades, another school of thought emerged that envisioned treatment of diffuse low-grade glioma as a dynamic multistage approach.[25,26] In this approach (Figure 2b), the decision of a specific treatment all along the disease evolution is not solely based on a single biological marker, but rather relies on the integration of many other parameters, such as age, cognitive and epileptic status, tumor kinetics, extent of resection, comparison between expected survival and expected long-term adverse effects of each treatment, and so on. Moreover, the ultimate goal is not to improve survival (which was the primary endpoint of the aforementioned phase 3 studies), but to optimize the quality of life while improving the survival.[5] Hence, in this state of mind, temozolomide is currently proposed as the first line of adjuvant treatment, whatever the molecular status, for the following reasons:

- radiation therapy has been shown to have the same survival benefit whether applied at radiographic tumor progression or right after diagnosis.[27] On the contrary, adverse cognitive effects become significant only after a long period of time (about 7 to 10 years).[28] Consequently, it naturally follows to wait until a later stage of the disease before irradiation (although it remains unknown whether synergy between radiation therapy and chemotherapy in a chemo-naïve patient would be found after a first chemotherapy exposure, meaning that concomitant

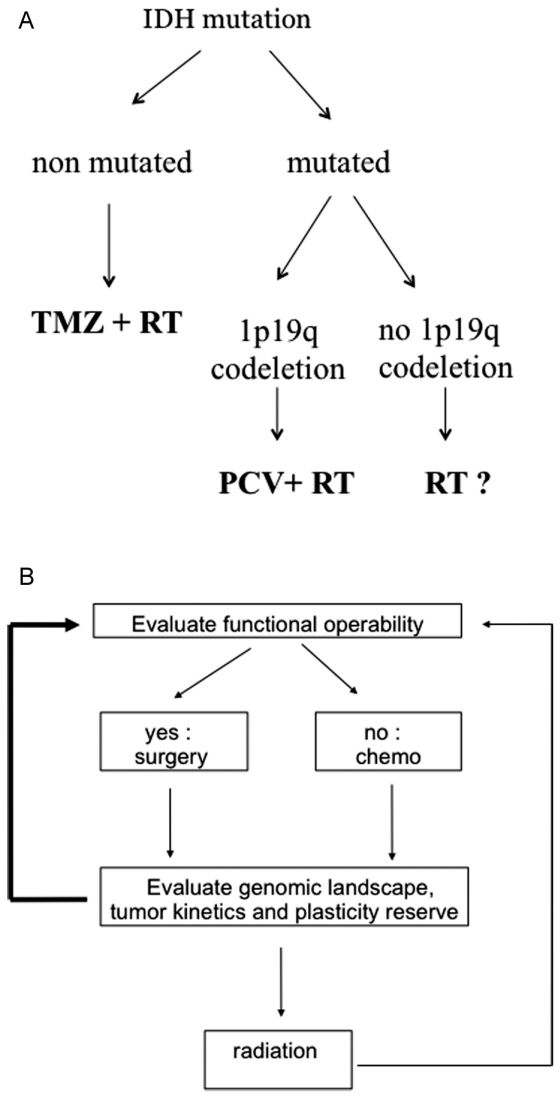

Fig. 2 **a.** Algorithmic approach based on molecular profile, in keeping with the new World Health Organization classification of diffuse low-grade glioma. **b.** Patient-specific multistage dynamic approach of diffuse low-grade glioma management. This figure is a simplified version of previously proposed strategies.[25,26]

treatment would improve both overall survival and area under the quality-of-life curve.)

- temozolomide could be prefered to PCV because it is much better tolerated, giving patients a better chance of enjoying a normal life under temozolomide treatment compared with PCV treatment.

Of note, recent results of the EORTC22033 might modulate this attitude. This trial suggests that patients with diffuse low-grade glioma (high risk, with need for treatment) that is IDH-mutated but 1p19q non-codeleted have shorter progression-free survival under temozolomide alone than under radiation therapy alone.[29] This strongly calls for an evaluation of PCV efficacy in this subset of patients, once again with the aim to delay radiation therapy as much as possible.

Finally, it was found that only 31% of centers evaluate the quality of life of their patients. This highlights that this major parameter in the management[4,5] is largely undermonitored, likely because of time constraints. Two solutions could overcome this problem: either a unique quick question or a self-administered computerized questionnaire.[6]

The results of the present survey show that supporters of the two schools can be found among the ELGGN, revealing a heterogeneity in practice that needs to be evaluated.

In summary, three clinical questions of major interest were identified:

1. How do exent of resection and rate of work resumption correlate?
2. What is the survival benefit of first-line PCV vs temozolomide?
3. What are the survival AND functional results in patients treated by upfront radiation therapy compared to patients treated by delayed radiation therapy (ie, at malignant transformation – either defined radiologically as an onset of contrast enhancement or histologically proven)?

The methodology to address question 1 is quite complex, although feasible. To evaluate extent of resection, each center can provide its resection probability map.[30] This tool allows comparison of extent of resection between centers.[3,17] One would expect that the rate of work resumption is lower in centers with higher extent of resections. In particular, differences should be detected between centers confining awake surgery to language dominant hemisphere and centers also performing awake surgery in the language nondominant hemisphere.

There is very little hope that randomized studies could give any helpful knowledge on the last 2 questions. We rather believe that dedicated diffuse low-grade glioma databases are required, which could be filled both retrospectively and prospectively. The choice of the database structure is a key point. Up to now, only centralized systems with an e-CRF have proven their efficiency. We formulate the hypothesis that a network architecture (where each database is locally managed), while far more complex to implement, would provide more powerful databases (thanks to a larger plasticity). The first step towards such sharing of patient data would be to create a common digital format, which we call GLIOCOM, to structure clinical data from glioma patients (see enclosed proposal in the supplementary file S2). To collect data in compliance with this format, software to view, analyze, and share the data needs to be developed, exactly in the same manner that DICOM images are viewed and analyzed by different software. Radiological data are quite easy to share, owing to the international DICOM format. Since the number of patients would be as high as 2000, the 2 challenging questions could be addressed.

Conclusion

This survey confirms that, even within a network comprising centers with a special interest in DLGG, management is far from being homogeneous. It is worth emphasizing that, even when class I evidence has been reached, consensus

does not necessarily follow, as previously reported.[31–34] We conclude that evidence-based practice in the field of diffuse low-grade glioma cannot be derived from the standard methodology of randomized clinical trials. This is not surprising, considering the very long survival of patients with this disease and the numerous parameters (age, clinical, epileptic and cognitive status, patient's way of life, histology, molecular biology, radiological kinetics, extent of resection, response to each chemotherapy line and radiation sequence) that have to be integrated to update decision making all along the course of the management. Nonetheless, rigorous evaluation of care is needed, for example to prove that the above-mentionned dynamic multistage strategy (Figure 2b) results in an optimal onco-functional benefit compared to the so-called gold standard treatment (Figure 2a). This can be done only by diversifying methodological frameworks, spanning different scales, from small prospective comparative studies focused on very specific questions, to extra-wide retrospective and consecutive studies with very long follow-up but a minimal set of patient parameters. We think that the compliance to an international GLIOCOM format for sharing patients' data would greatly facilitate such studies, allowing us to finally address clinically relevant questions, and ultimately leading to more evidence-based medicine in patients with diffuse low-grade glioma.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

Funding

The authors have no funding that supported the research.

Acknowledgements

Authors thank their collaborators: Åsa Alberius Munkhammar, Kerry Anderson-Kaye, Malin Andersson, Corrado D'Arrigo, Luc Bauchet, Vanessa Baudiffier, Foucaud du Boisgueheneuc, Coline Bouyer, Gill Boyer, Olivera Casar-Borota, Almudena Garcia-Castaño, Antoine Carpentier, Marie Charissoux, Paul Chumas, Seonaid Ewan, Michel Fabbro, Dimitris Giakoumettis, Catherine Gozé, Rémy Guillevin, Guillaume Herbet, Konstantinos Karakoulas, Carmel Loughrey, Melissa Maguire, Christine Kerr, João Leote,Sylwia Libard, Sylvie Moritz-Gasser, Daniel O'Hara, Antonio Pérez-Hick, Adria Rofes, Vasiliki Siatra, Ana Silvestre, Suzanne Spink, Staffan Stenson, Walter Tagnese, Georgia Tsaoussi, Abraham Tsitlakidis, Petra Witt Nyström, Elizabeth Wright.

Conflict of interest statement. The authors declare that they have no personal conflicts of interest and no institutional financial interest in any drugs, materials, or devices described in this manuscript.

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