Neurosurg Rev (2016) 39:377–384
DOI 10.1007/s10143-015-0675-6

REVIEW

Incidental diffuse low-grade gliomas: from early detection to preventive neuro-oncological surgery

Guilherme Lucas de Oliveira Lima[1,2,3] · **Marc Zanello**[2,3] · **Emmanuel Mandonnet**[4,5] · **Luc Taillandier**[4,6] · **Johan Pallud**[2,3,4,7,10] · **Hugues Duffau**[4,8,9]

Received: 28 September 2014 / Revised: 5 March 2015 / Accepted: 9 August 2015 / Published online: 27 November 2015

Abstract Although a large amount of data supports early surgical resection for symptomatic diffuse low-grade glioma, the therapeutic strategy is still a matter of debate regarding incidentally discovered diffuse low-grade glioma. Indeed, early and "preventive" surgery has recently been proposed in asymptomatic patients with silent diffuse low-grade glioma with better outcomes. The present review discusses the importance of an early diagnosis and of a preventive surgical treatment to improve the outcomes of incidental diffuse low-grade glioma and suggests the possible relevance of a tailored screening policy.

Keywords Diffuse low-grade glioma · Incidental discovery · Preventive surgery · Outcomes

Introduction

World Health Organization grade II glioma (diffuse low-grade glioma, LGG) is a heterogeneous group of brain tumors characterized by a slow and continuous growth, by a preferential migration along white matter pathways and by an evolution toward a higher grade of malignancy [1–3]. Their natural history is a matter of debate and questions the possibility of an early detection in the attempt to apply preventive neuro-oncological treatments [4, 5]. Indeed, LGG are usually revealed by inaugural seizures in young adults with no or only mild neurological and neuropsychological deficits [1, 3, 6]. At the time of clinical revelation, a long "silent" period has passed and, even with maximal neuro-oncological treatment,

Previous presentation This study was not considered in any previous presentation.

Johan Pallud and Hugues Duffau contributed equally to this work.

✉ Johan Pallud
johanpallud@hotmail.com

[1] Department of Neurosurgery, Onofre Lopes University Hospital, Rio Grande do Norte Federal University, Natal, RN, Brazil

[2] Department of Neurosurgery, Sainte-Anne Hospital, Paris, France

[3] University Paris Descartes, Paris, France

[4] Réseau d'Etude des Gliomes (REG), Groland, France

[5] Department of Neurosurgery, Lariboisiere Hospital, Paris, France

[6] Department of Neuro-Oncology, Nancy Neurological Hospital, Nancy, France

[7] Histopathology and Animal Models, Institut Pasteur, Paris, France

[8] Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, 80 Avenue Augustin Fliche, 34295 Montpellier, France

[9] Institute for Neuroscience of Montpellier, INSERM U1051, Team "Plasticity of Central Nervous System, Human Stem Cells and Glial Tumors," Saint Eloi Hospital, Montpellier University Medical Center, 80 Avenue Augustin Fliche, 34091 Montpellier, France

[10] Department of Neurosurgery, Hôpital Sainte-Anne, 1 Rue Cabanis, Cedex 14, 75674 Paris, France

including maximal surgical resection under functional mapping, chemotherapy, and/or radiotherapy, it is already too late for a possible cure, as demonstrated by the outcomes [4, 5, 7]. The question of the management of incidentally discovered supratentorial LGG in adults is a recent topic since only few articles reported case series or individual case reports, the first series being published in 2010 by our group [8–13]. The present review discusses the natural history and evolution of silent diffuse low-grade glioma, discusses the possible usefulness of a screening policy for early diagnosis, and discusses the role of a "preventive" and early neurosurgical treatment in the attempt to improve the outcomes.

Natural history

Based on epidemiological and mathematical models describing the diffusion-proliferation processes, estimates for gliomagenesis support the evidence that LGG arises more likely "ex nihilo" rather than from a preexisting congenital lesion [14–16]. Based on the imaging observations that LGG are continuously slow-growing lesions, a four-period development can be proposed to summarize their natural history (Fig. 1): (1) the biological birth where glioma-initiating cells neoplastically transform, does not give rise to any symptoms and even remains below the detection limit of routine MRI; this is the occult stage; (2) at some point, the glioma becomes visible on MRI, yet the patient is still asymptomatic; this is the clinically silent stage; (3) the glioma elicits clinical symptoms, usually epileptic seizures; this is symptomatic stage; (4) at some point in time, the glioma switches its rather indolent behavior toward an aggressive one, in keeping with the onset of neoangiogenesis and malignancy, until the patient dies from tumor spread and growth; this is the malignant transformation [5, 7].

As the occult stage cannot be detected by MR images, we know virtually nothing until the glioma becomes visible on MRI. However, during the silent period, gliomas can be incidentally discovered on brain MRI. As incidental LGG represent earlier stages in the development of LGG, it appears valuable to investigate the genetic and molecular abnormalities that sequentially occur at the initial stage of the tumor's natural history. According to a model for chronological order of mutations, IDH mutations may be the first one to occur, followed by mutations in TERT promoter and 1p19q co-deletion. The chronological order for TERT promoter mutations and 1p19q co-deletion remains undetermined [17]. There are few data regarding molecular markers in incidental LGG. The two largest series only report histopathological subtypes, than are known to be correlated with molecular markers, and show no significant difference in subtype distribution by incidental or symptomatic discovery [8, 9]. A recent series analyzed the IDH1 mutation status, TERT promoter mutation status, and the 1p19q co-deletion status in 23 incidental LGG [18]. They

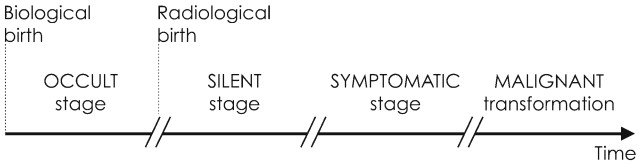

Fig. 1 Schematic illustration of the four-step natural course of a diffuse low-grade glioma from biological «birth» to transformation toward a higher grade of malignancy

also described that oligodendroglial component, IDH1 mutation, TERT mutation, and 1p19q co-deletion were present in 61, 96, 44, and 70 %, respectively. The distribution of molecular subgroups in this cohort suggested that incidental LGG was not a unique entity largely discrepant from other LGG. In addition, the high incidence of IDH mutations in incidental LGG supports the possibility that IDH mutations occurred early in the natural course of glioma development. The published case series highlights that incidental LGG are progressive tumors leading to clinical transformation and that they represent an earlier step in the natural history of a glioma than the symptomatic LGG [8]. Indeed, as compared to symptomatic LGG, incidentally discovered LGG have a lower age at radiological discovery and a smaller tumor volume at the time of diagnosis [8, 9, 18]. Previous studies showed that incidental LGG were progressive tumors with (1) a constant imaging growth with a velocity of diametric expansion of approximately 3.5 mm/year, i.e., very close to the growth rate of symptomatic LGG, (2) a clinical revelation toward symptomatic LGG at a median interval of 48 months after radiologic discovery, (3) histopathological and molecular findings similar to those of symptomatic LGG, (4) a risk of malignant transformation at about 30 % at a median interval of 5.7 years of follow-up (Fig. 2) [8, 9, 18–20]. Recently, the asymptomatic "silent" period has been estimated at about 14 years in a subset of 148 LGG [7]. This very long period of silent evolution, without clinical revelation and without dedicated oncological treatment, could explain the current failure to cure these tumors. In accordance, it has been shown that malignant microfoci with endothelial proliferation were already individualized in the tumor core in up to 27 % of incidental LGG operated on before clinical revelation, showing that the malignant transformation may occur before any clinical symptoms and imaging changes [10, 21]. This observation may explain why, in some cases, a tumor can be discovered as a secondary anaplastic glioma or a secondary glioblastoma, after the malignant but silent transformation of the LGG [5]. This suggests a possible benefit of an early diagnosis of LGG.

A rationale for brain screening?

The treatment options and survival of cancers are related to stage, which is generally characterized by the anatomic extent of disease. On this basis, it is assumed that the early detection

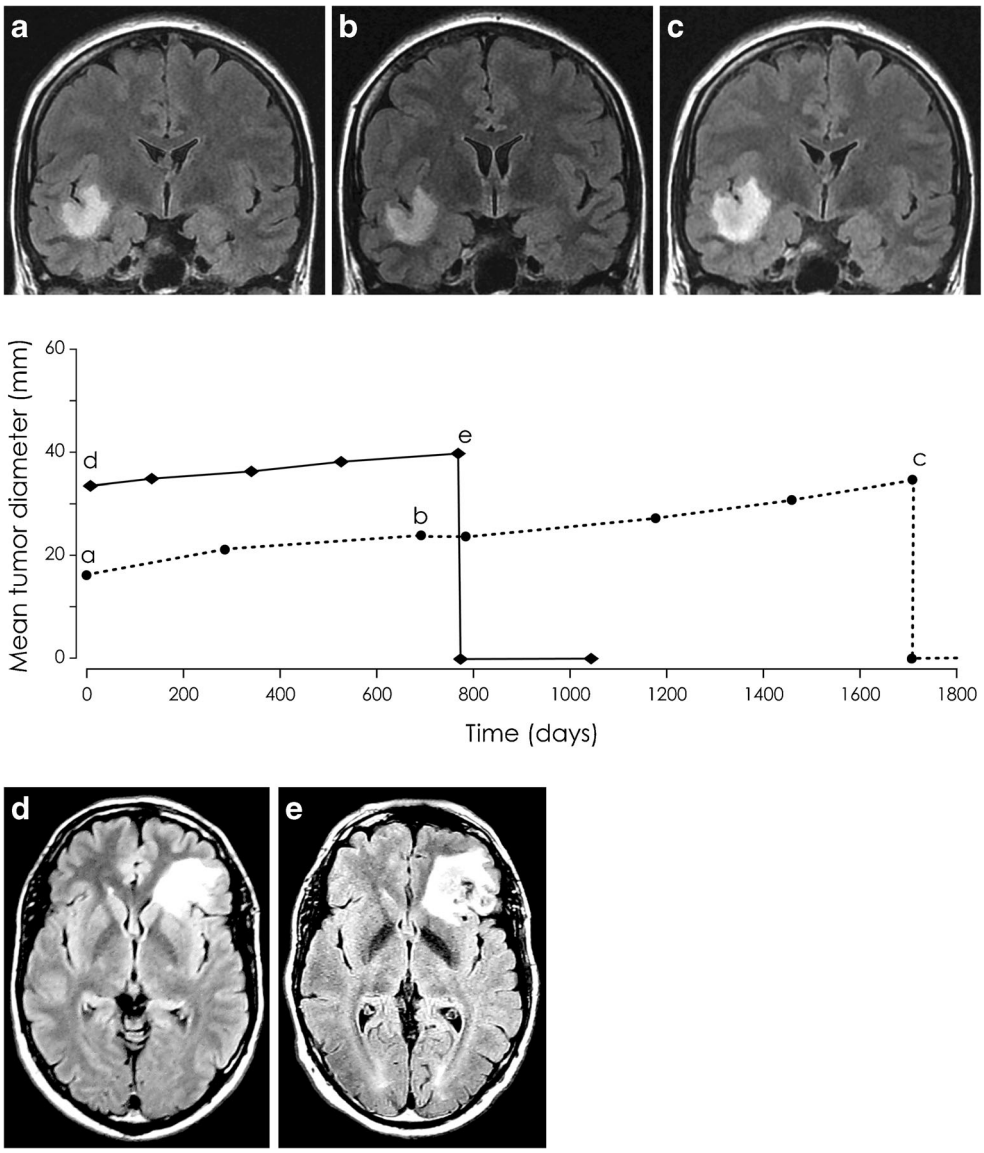

Fig. 2 Spontaneous velocity of diametric expansion of two incidentally discovered diffuse low-grade gliomas through the evolution of their mean tumor diameter over time. Each point represents an MR examination. Before any clinical revelation, the tumors grew spontaneously and continuously with a spontaneous velocity of diametric expansion at 2.4 mm/year in case of a right temporo-insular tumor (*dotted line*, **a** to **c**) and at 3.4 mm/year in the case of a left frontal LGG (*full line*, **d**, **e**)

of any cancer at an earlier stage may yield better outcomes. As advocated for nearly all cancers by the cancer screening program of the National Cancer Institute, the cancer screening programs in colon cancer, cervical cancer, melanoma, and breast cancer have been established since decades with doubtless results and with reasonable cost-effectiveness, even including incorporation of new immunogenetic tests and techniques [22–25]. Regarding gliomas, there is no consensus about the indication for brain screening. In the healthy population, the prevalence of silent LGG is estimated between 0.02 and 0.09 % and the rate of incidentally diagnosed gliomas was reported from 3 % in a series of 4309 gliomas from the French Brain Tumor Databank, 3.8 % in a French Glioma Study Group database of 1249 LGG, and up to 10.4 % in a recent Chinese series of 229 gliomas [4, 8, 17, 18, 26–30]. A "brain check-up" campaign made in Japan with 4000 asymptomatic subjects between 1996 and 2000 detected 11 (0.3 %) silent tumors; among all, one glioma , not surprisingly, became symptomatic after 2 years of follow-up without dedicated oncological treatment [31]. Even though, many authors question the usefulness of a brain screening program and advocate: (1) how can we be sure that there are more risks to decrease from the silent glioma detected by screening rather than from another cause with a glioma possibly remaining silent during the whole life of the patient? (2) We cannot currently prove that patients could be definitively cured from their silent LGG even by an early and supratotal resection? (3) Cost issues as the number needed to scan is of approximately 2000 subjects for one glioma diagnosis; (4) the difficult management of other central nervous system neoplasms or other pathological conditions that can be incidentally discovered under screening, such as meningiomas, schwannomas, pituitary adenomas, vascular malformations, or unspecific brain signal abnormalities; and (5) the anxiety

that can be induced by such a brain tumor screening program. Most of these concerns can be addressed without definite answers. First, when a silent glioma is incidentally diagnosed, there are more chances of dying from the evolution of the silent glioma toward a symptomatic glioma than dying from another cause with the glioma (which would have remained silent), unless patient survival is expected to be less than 4 years [5]. Second, a recent study demonstrated that a supratotal resection using awake surgery with intraoperative functional for LGGs involving non-eloquent areas significantly reduced the recurrence rates and the risk of malignant transformation and death [32]. Third, the question of cost effectiveness is a particularly difficult issue in this specific population as the long lead-time biases comparisons between symptomatic and incidental LGG survival times. A recent commentary discussed this fundamental point: if one assumes that the cost of a screening «basic» MRI is approximately $150 in US dollars, then the screening of 10,000 individuals will cost $1,500,000; and, among those screened, four will have a LGG incidentally detected [5]. Economists estimate that the value of one person/year is $120,000. This means that the cost effectiveness ratio of a screening policy for LGG will be positive if at least 3 years of life can be saved by applying an early oncological treatment in incidentally discovered LGG. As a practical example, a pilot project supported by the Brain Tumor Foundation in the United States of America offered head MRI scans to volunteers and demonstrated the practical feasibility of such approach [4]. The brain screening MRI strategy should incorporate low cost, rapid feasibility, and high sensibility. Thus, morphological sequences (Flair) that could be performed in less than 10 min should be preferred. With this approach, the cost of the brain screening MRI was reduced at approximately $70 [4]. In addition, the screening strategy can be refined at the light of previous clinical observations. The timing should be tailored on the fact that LGG appear to become visible on MRI without clinical revelation (i.e., entering the silent period) at a mean age of 25 to 30 years [16]. The screening might be focused on the 18- to 40-year-old population and on specific conditions, such as pregnancy. Indeed, it has been reported that pregnancy increased the tumor growth of LGG and a MRI might be proposed before conception or after delivery [33]. Moreover, we can reasonably anticipate that epidemiologic advances (including biomathematical models to determine the optimal class age to be targeted) and the availability of new biomarkers of glioma risk will enable the screening to focus on specific subpopulations, hence greatly reducing the cost. In this context, a French team recently proposed a blood test for identification of the R132H IDH1 gene mutation [34]. Although, the accuracy of this test was better in high-grade gliomas and in enhancing tumors with a volume greater than 3.5 mL, it appears as a feasible and promising concept for future screening.

Practical aspects of LGG screening using brain MRI

After the initial MRI discovery of a silent LGG, conventional and advanced MRI should be performed, including contrast-enhanced sequence, proton magnetic resonance spectroscopy, diffusion sequence, and dynamic susceptibility contrast sequences [3]. Indeed, the incorporation of advanced MR variables, including relative cerebral blood volume, relative apparent diffusion coefficients, N-acetyl-aspartate/creatine ratio at short echo time, and choline/creatine ratio at long echo time, improves glioma grading and the identification of restricted malignant areas within the tumor [35, 36]. If no malignancy is suspected, the patient and the possible tumor must be evaluated in the next 3 to 6 months, before any therapeutic management [14]. A complete language and neuropsychological evaluation is mandatory, as already proposed for symptomatic LGG [37, 38]. The second MRI should be performed, approximately 3 to 6 months after lesion discovery and should comprise the same sequences. It will allow the evaluation of imaging tumor growth, easily calculated by the evolution of the mean tumor diameter over time (the so-called velocity diameter expansion) [14]. The demonstration of a growing tumor on MRI, even in an asymptomatic patient, strongly suggests an incidental LGG (Fig. 2).

At the light of (1) a tumor growth demonstrated on follow-up MRI and/or (2) an impaired neurocognition in these patients, the neurosurgeon can propose a therapeutic management, which is, in our experience, a maximal surgical resection based on onco-functional balance [39]. Such an approach may help increase the outcomes of patients harboring a LGG with a compensatory balanced cost-effectiveness ratio if 3 years of active life can be saved by the yearly screening and treatment [5].

Toward a preventive therapeutic management?

Despite the lack of level I evidence, the recent literature strongly supports the significant impact of early and maximal resection in LGG patients [1, 6, 39–44]. For example, the Norway experience elegantly demonstrated that a proactive “early surgical” resulted in longer overall survival favoring operated patients, as compared with a conservative “biopsy-watchful waiting” approach [42]. Consequently, the first therapeutic option in European guidelines for LGG is surgical resection [3].

The management concerning incidental LGG is not well established [8, 13, 45–48]. Beyond ethical implications, the risk of inducing neurological deficits, seizures, or changes in quality of life must be discussed with the patient before final decision-making. Incidental LGG likely represent an earlier step in the natural history of glioma and have particular findings that may help their surgical management: (1) they have a smaller tumor volume in comparison with symptomatic LGG, (2) they are preferentially located in non-eloquent brain areas, (3) their surgical management allows the achievement of a

greater rate of both total and supratotal resections [8, 9, 18]. For example, the neurosurgical team of UCSF reported a 60 % rate of gross total resection in incidental LGG against only 31.5 % in symptomatic LGG [9]. This remains true in eloquent brain areas, where supratotal and total resections can be performed in 27 and 36 %, respectively, of incidental LGG [10]. The concept of a supratotal resection, i.e., the removal of a "security" margin around the tumor visible on FLAIR and/or T2-weighted MRI sequences when feasible in non-eloquent brain areas, was proposed at the light of the observation that isolated glioma cells were present at a distance of 10–20 mm beyond MRI-defined abnormalities [32, 49]. Thus, a larger resection is a possible way to change the natural history of LGG, especially by delaying their malignant transformation. This is an important issue and such a supratotal resection has been demonstrated to delay malignant transformation in a subset of LGG [32]. Recent reports confirm that patients operated on for an incidental LGG have significantly improved overall survival in comparison with a control group of symptomatic LGG [8, 9, 18]. However, the ideal margin of resection beyond MRI-defined abnormalities on MR imaging is unknown as isolated glioma cells were identified "as far as searched," up to 26 mm in a correlative study of MRI-based serial stereotactic biopsies in well-delineated LGG [49]. In this instance, a functional-based maximal resection under intraoperative functional mapping should be preferred to ensure the best onco-functional ratio by removing as much as possible infiltrated glioma beyond MRI-defined abnormalities without inducing definitive cognitive impairments [6].

At the light of these observations, the concept of "preventive surgery" has recently been proposed for incidental LGG [10, 46]. The surgical management of incidental LGG must be associated with an extremely low rate of morbidity and with a preserved quality of life. Previous reports have confirmed the low surgical morbidity after resection of incidental LGG explained by a smaller tumor volume, usually in non-eloquent brain areas [8, 9, 18]. About the risk of developing postoperative seizures or experiencing a worsening of the quality of life, the prospective follow-up of 21 patients operated on for an incidental LGG demonstrated only one (4.7 %) case experienced one postoperative partial seizure related to the abrupt disruption of the anti-epileptic drug [50]. This low rate is in agreement with the known risk of postoperative seizures after brain surgery [1, 51–54]. In addition, these 21 patients are still alive, all enjoying a normal familial, social, and professional life with preserved quality of life [10]. Of note, four patients were excluded from this analysis because they experienced seizures in the time interval between imaging discovery and surgery, confirming the risk of seizure occurrence in incidental LGG. This is in agreement with previous observations that demonstrated, in untreated incidental LGG, the clinical evolution toward symptomatic LGG at a median 48 months after imaging discovery [8].

Conclusions

The observation of the natural history of LGG confirms the continuum spectrum of this tumor since its biological birth then imaging discovery until progression toward symptomatic and then malignant glioma. The long silent period (of almost 15 years) before clinical revelation with no dedicated oncological treatment may explain the reason for not achieving better outcomes and possible cure. We discuss the rationale of a screening policy for LGG. In case of a possible LGG discovered incidentally, the patient should be oriented to perform multimodal and serial imaging investigations until confirmation of a progression on imaging follow-up. The proposition of preventive surgical resection should be made for delaying tumor progression, ensuring good quality of life, low risk of inducing seizures, and possibly better outcomes. Even if it is not possible to draw definitive evidence based on this review, these data support, from an oncological point of view, the concept of preventive and maximal resection for incidental LGG, before symptomatic revelation and before transformation toward a higher grade of malignancy. Such a proposal for screening and preventive surgery is conceivable only if the reliability of this treatment is optimal, with maximal resection and minimal morbidity, meaning that patients with incidental LGG should be referred to centers hyperspecialized in surgical neuro-oncology that are able to perform the required preoperative evaluations, pluridisciplinary discussions, maximal safe resections using intraoperative functional mapping, and postoperative evaluations of the benefit-to-risk ratio of the surgical resection [55, 56].

Author contributions All authors have participated in the writing of this manuscript, and all authors approve this final version. Conception and design was done by J. Pallud, H. Duffau. Acquisition of data was done by G. Lima. Analysis and interpretation of data were performed by G. Lima, J. Pallud, E. Mandonnet, L. Taillandier, and H. Duffau. Drafting the article was done by G. Lima and J. Pallud. Critically revising the article was made sure by G. Lima, M. Zanello, J. Pallud, E. Mandonnet, L. Taillandier, and H. Duffau.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Research support None

References

1. Pallud J, Audureau E, Blonski M et al (2014) Epileptic seizures in diffuse low-grade gliomas in adults. Brain 137:449–462. doi:10.1093/brain/awt345
2. Duffau H, Mandonnet E (2013) The "onco-functional balance" in surgery for diffuse low-grade glioma: integrating the extent of

resection with quality of life. Acta Neurochir (Wien). doi:10.1007/s00701-013-1653-9
3. Soffietti R, Baumert BG, Bello L et al (2010) Guidelines on management of low-grade gliomas: report of an EFNS-EANO* Task Force. Eur J Neurol 17:1124–1133. doi:10.1111/j.1468-1331.2010.03151.x
4. Kelly PJ (2010) Gliomas: survival, origin and early detection. Surg Neurol Int 1:96. doi:10.4103/2152-7806.74243
5. Mandonnet E, de Witt HP, Pallud J et al (2014) Silent diffuse low-grade glioma: toward screening and preventive treatment? Cancer 120:1758–1762. doi:10.1002/cncr.28610
6. Duffau H (2012) A new concept of diffuse (low-grade) glioma surgery. Adv Tech Stand Neurosurg 38:3–27. doi:10.1007/978-3-7091-0676-1_1
7. Pallud J, Capelle L, Taillandier L et al (2013) The silent phase of diffuse low-grade gliomas. Is it when we missed the action? Acta Neurochir (Wien) 155:2237–2242. doi:10.1007/s00701-013-1886-7
8. Pallud J, Fontaine D, Duffau H et al (2010) Natural history of incidental World Health Organization grade II gliomas. Ann Neurol 68:727–733. doi:10.1002/ana.22106
9. Potts MB, Smith JS, Molinaro AM, Berger MS (2012) Natural history and surgical management of incidentally discovered low-grade gliomas. J Neurosurg 116:365–372. doi:10.3171/2011.9.JNS111068
10. Duffau HH (2012) Awake surgery for incidental WHO grade II gliomas involving eloquent areas. Acta Neurochir (Wien) 154:575–584. doi:10.1007/s00701-011-1216-x
11. Rapp M, Heinzel A, Galldiks N et al (2013) Diagnostic performance of 18F-FET PET in newly diagnosed cerebral lesions suggestive of glioma. J Nucl Med 54:229–235. doi:10.2967/jnumed.112.109603
12. Floeth FW, Sabel M, Stoffels G et al (2008) Prognostic value of 18F-fluoroethyl-L-tyrosine PET and MRI in small nonspecific incidental brain lesions. J Nucl Med 49:730–737. doi:10.2967/jnumed.107.050005
13. Shah AH, Madhavan K, Heros D et al (2011) The management of incidental low-grade gliomas using magnetic resonance imaging: systematic review and optimal treatment paradigm. Neurosurg Focus 31, E12. doi:10.3171/2011.9.FOCUS11219
14. Pallud J, Taillandier L, Capelle L et al (2012) Quantitative morphological magnetic resonance imaging follow-up of low-grade glioma. Neurosurgery 71:729–740. doi:10.1227/NEU.0b013e31826213de
15. Duffau H, Pallud J, Mandonnet E (2011) Evidence for the genesis of WHO grade II glioma in an asymptomatic young adult using repeated MRIs. Acta Neurochir (Wien) 153:473–477. doi:10.1007/s00701-010-0917-x
16. Gerin C, Pallud J, Grammaticos B et al (2011) Improving the time-machine: estimating date of birth of grade II gliomas. Cell Prolif 45:76–90. doi:10.1111/j.1365-2184.2011.00790.x
17. Arita H, Narita Y, Fukushima S et al (2013) Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. Acta Neuropathol 126:267–276. doi:10.1007/s00401-013-1141-6
18. Zhang Z-Y, Chan AK-Y, Ng H-K et al (2014) Surgically treated incidentally discovered low-grade gliomas are mostly IDH mutated and 1p19q co-deleted with favorable prognosis. Int J Clin Exp Pathol 7:8627–8636
19. Jakola AS, Moen KG, Solheim O, Kvistad K-A (2013) "No growth" on serial MRI scans of a low grade glioma? Acta Neurochir (Wien) 155:2243–2244. doi:10.1007/s00701-013-1914-7
20. Pallud J, Mandonnet E (2013) Incidental low-grade gliomas. J Neurosurg 118:702–704. doi:10.3171/2012.2.JNS111956
21. Duffau H (2012) The rationale to perform early resection in incidental diffuse low-grade glioma: towards a "Preventive Surgical Neurooncology." WNEU 1–10. doi: 10.1016/j.wneu.2012.06.036
22. Bresalier RS, Kopetz S, Brenner DE (2015) Blood-based tests for colorectal cancer screening: do they threaten the survival of the FIT test? Dig Dis Sci. doi:10.1007/s10620-015-3575-2
23. Vassilakos P, Catarino R, Frey Tirri B, Petignat P (2015) Cervical cancer screening in Switzerland: time to rethink the guidelines. Swiss Med Wkly 145:w14112. doi:10.4414/smw.2015.14112
24. Sondak VK, Glass LF, Geller AC (2015) Risk-stratified screening for detection of melanoma. JAMA 313:616–617. doi:10.1001/jama.2014.13813
25. Ribeiro RA, Caleffi M, Polanczyk CA (2013) Cost-effectiveness of an organized breast cancer screening program in Southern Brazil. Cad Saude Publica 29(Suppl 1):S131–S145
26. Vernooij MW, Ikram MA, Tanghe HL et al (2007) Incidental findings on brain MRI in the general population. N Engl J Med 357:1821–1828. doi:10.1056/NEJMoa070972
27. Weber F, Knopf H (2006) Incidental findings in magnetic resonance imaging of the brains of healthy young men. J Neurol Sci 240:81–84. doi:10.1016/j.jns.2005.09.008
28. Bauchet L, Rigau V, Mathieu-Daudé H et al (2007) French brain tumor data bank: methodology and first results on 10,000 cases. J Neurooncol 84:189–199. doi:10.1007/s11060-007-9356-9
29. Katzman GL, Dagher AP, Patronas NJ (1999) Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. JAMA 282:36–39
30. Morris Z, Whiteley WN, Longstreth WT et al (2009) Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 339:b3016–b3016. doi:10.1136/bmj.b3016
31. Onizuka M, Suyama K, Shibayama A et al (2001) Asymptomatic brain tumor detected at brain check-up. Neurol Med Chir (Tokyo) 41:431–434, discussion 435
32. Yordanova YN, Moritz-Gasser S, Duffau H (2011) Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection. Clinical article. J Neurosurg 115:232–239. doi:10.3171/2011.3.JNS101333
33. Pallud J, Mandonnet E, Deroulers C et al (2010) Pregnancy increases the growth rates of World Health Organization grade II gliomas. Ann Neurol 67:398–404. doi:10.1002/ana.21888
34. Boisselier B, Gállego Pérez-Larraya J, Rossetto M et al (2012) Detection of IDH1 mutation in the plasma of patients with glioma. Neurology 79:1693–1698. doi:10.1212/WNL.0b013e31826e9b0a
35. Guzmán-De-Villoria JA, Mateos-Pérez JM, Fernández-García P et al (2014) Added value of advanced over conventional magnetic resonance imaging in grading gliomas and other primary brain tumors. Cancer Imaging 14:35. doi:10.1186/s40644-014-0035-8
36. Paulus W, Peiffer J (1989) Intratumoral histologic heterogeneity of gliomas. A quantitative study. Cancer 64:442–447
37. Klein M, Duffau H, Witt Hamer PC (2012) Cognition and resective surgery for diffuse infiltrative glioma: an overview. J Neurooncol 108:309–318. doi:10.1007/s11060-012-0811-x
38. Papagno C, Casarotti A, Comi A et al (2012) Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). J Neurooncol 108:269–275. doi:10.1007/s11060-012-0824-5
39. De Witt Hamer PC, Robles SG, Zwinderman AH et al (2012) Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 30:2559–2565. doi:10.1200/JCO.2011.38.4818
40. Rezvan A, Christine D, Christian H et al (2009) Long-term outcome and survival of surgically treated supratentorial low-grade glioma in adult patients. Acta Neurochir (Wien) 151:1359–1365. doi:10.1007/s00701-009-0435-x
41. Ius T, Isola M, Budai R et al (2012) Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients. J Neurosurg 1–14. doi: 10.3171/2012.8.JNS12393
42. Jakola AS (2012) Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade

gliomassurgical resection vs waiting in low-grade gliomas. JAMA 1. doi: 10.1001/jama.2012.12807
43. Mcgirt MJ, Chaichana KL, Attenello FJ et al (2008) Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. Neurosurgery 63:700–707. doi:10.1227/01.NEU.0000325729.41085.73, author reply 707–8
44. Schomas DA, Laack NNI, Rao RD et al (2009) Intracranial low-grade gliomas in adults: 30-year experience with long-term follow-up at Mayo Clinic. Neuro-Oncology 11:437–445. doi:10.1215/15228517-2008-102
45. Shah AH, Madhavan K, Sastry A, Komotar RJ (2012) Managing intracranial incidental findings suggestive of low-grade glioma: learning from experience. WNEU. doi:10.1016/j.wneu.2012.06.021
46. Yao Y, Zhou LF (2013) Perspectives. WNEU 80:e121–e122. doi: 10.1016/j.wneu.2012.10.022
47. Drazin D, Spitler K, Cekic M et al (2013) Incidental finding of tumor while investigating subarachnoid hemorrhage: ethical considerations and practical strategies. Sci Eng Ethics 19:1107–1120. doi:10.1007/s11948-012-9403-6
48. Roth J, Keating RF, Myseros JS et al (2012) Pediatric incidental brain tumors: a growing treatment dilemma. J Neurosurg Pediatr 10:168–174. doi:10.3171/2012.6.PEDS11451
49. Pallud J, Varlet P, Devaux B et al (2010) Diffuse low-grade oligodendrogliomas extend beyond MRI-defined abnormalities. Neurology 74:1724–1731. doi:10.1212/WNL.0b013e3181e04264
50. de Oliveira Lima GL, Duffau H (2015) Is there a risk of seizures in "preventive" awake surgery for incidental diffuse low-grade gliomas? J Neurosurg 1–9. doi: 10.3171/2014.9.JNS141396
51. Hwang S-L, Lin C-L, Lee K-S et al (2004) Factors influencing seizures in adult patients with supratentorial astrocytic tumors. Acta Neurochir (Wien) 146:589–594. doi:10.1007/s00701-004-0266-8, discussion 594
52. Ruda R, Bello L, Duffau H, Soffietti R (2012) Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. Neuro-Oncology 14:iv55–iv64. doi:10.1093/neuonc/nos199
53. Chang EF, Potts MB, Keles GE et al (2008) Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg 108:227–235. doi:10.3171/JNS/2008/108/2/0227
54. You G, Sha Z-Y, Yan W et al (2012) Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. Neuro-Oncology 14:230–241. doi:10.1093/neuonc/nor205
55. Mandonnet E, de Witt HP, Poisson I et al (2015) Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25 cases. Neurosurgery. doi:10.1227/NEU.0000000000000644
56. De Witt Hamer PC, Hendriks EJ, Mandonnet E et al (2013) Resection probability maps for quality assessment of glioma surgery without brain location bias. PLoS ONE 8, e73353. doi:10.1371/journal.pone.0073353

Comments

Michel Wager, Poitiers, France

This is a very nice article, addressing various aspects of low-grade glioma management. Three main themes emerge from this text:

The oncological rationale for early and aggressive surgical treatment of these tumors: this first aspect probably has become the most consensual today due to mounting evidence in literature during the last two decades. This paper brings an enriching view on what has now become the standard of care.

The second point, raising the question of a screening policy, might get a more mixed reaction from readers because it goes far beyond neurosurgical care per se and might even be somewhat polemical, all the more so that it calls upon partly intangible arguments. But in any event, this would be in my view a sound and healthy controversy.

Last but not least, the authors introduce the concept of centers «hyper-specialized in neuro-oncological care». This concept embodies the organizational aspects of the emerging concept of «functional neuro-oncology»[1].

Indeed, as any innovative therapeutic strategy, functional neuro-oncology requires a dedicated environment. Well-trained, dedicated surgeons—hyper-specialization is a well-illustrated cause of lower rates complications[2]—sustained and regular rate of procedures (awake brain surgeries on a minimum weekly basis would probably reach large agreement in the community); technical choices supporting the widest multidisciplinary management in the operating room[3]; committed, specialized anesthetists; mandatory presence, in the operating room, of speech therapists/neuropsychologist during awake procedures; detailed pre- and postoperative neuropsychological assessments; detailed neuro-oncological assessments—even standards of resection are now available for (not only) junior teams[4], allowing comparison with colleagues and monitoring of learning curves; expert neuroradiological diagnosis and follow-up; perfect timing of pre- and/or postoperative chemotherapy in collaboration with dedicated board-certified neuro-oncologists. Functional neuro-oncology is by essence multidisciplinary, and networks have long illustrated this, up to the European level as exemplified by the European Low Grade Glioma (ELLG) network[5].

In this context, the concept of «hyper-specialized centers in neuro-oncology» might constitute an encouragement for committed teams in presenting the healthcare provision of their institutions, on dedicated websites, for example. This would be of great help both for referring physicians and for patients, in making their choice of who will treat brain tumors in the future—on sound evidences.

This article, altogether expert and refreshing, should stimulate discussions and initiatives regarding these various aspects of that exciting growing field.

References

1. Duffau H. Introduction. Surgery of gliomas in eloquent areas: from brain hodotopy and plasticity to functional neurooncology. *Neurosurgical focus.* Feb 2010;28(2):Intro.
2. Trinh VT, Davies Jm Fau–Berger MS, Berger MS. Surgery for primary supratentorial brain tumors in the United States, 2000–2009: effect of provider and hospital caseload on complication rates. 20150202 DCOM-20150331 (1933–0693 (Electronic)).
3. Wager M, Rigoard P, Bataille B, et al. Designing an operating theater for awake procedures: a solution to improve multimodality information input. *British journal of neurosurgery.* Jun 17 2015:1–7.
4. De Witt Hamer PC, Hendriks EJ, Mandonnet E, Barkhof F, Zwinderman AH, Duffau H. Resection probability maps for quality assessment of glioma surgery without brain location bias. *PloS one.* 2013;8(9):e73353.
5. Beez T, Boge K, Wager M, et al. Tolerance of awake surgery for glioma: a prospective European Low Grade Glioma Network multicenter study. *Acta neurochirurgica.* Jul 2013;155(7):1301–1308.

Krasimir Minkin, Sofia, Bulgaria

Lima et al. try to defend the idea of preventive neuro-oncological surgery in cases of low-grade gliomas. The authors divide the clinical evolution of low-grade gliomas in occult, silent, symptomatic, and malignant transformation periods. Early surgery during the silent period (MRI visible but asymptomatic) was proposed based on the data of better tumor and symptom control in patients with possible gross total resection. This strategy could be also cost-effective after MRI protocols and target population adjustments. However, we have to keep in mind that cure of low-grade gliomas even treated in early stage remains an impossible

mission because of the extensive tumor spread probably during the occult, MRI invisible stage[1]. Real total and supratotal resections remain unachievable because of the high functional price, but quality of live and overall survival gains seem sufficient prerequisites for preventive neurooncological surgery[2,3,4].

References

1. Pallud J, Varlet P, Devaux B, Geha S, Badoual M, Deroulers C, Page P, Dezamis E, Daumas-Duport C, Roux FX. (2010) Diffuse low-grade oligodendrogliomas extend beyond MRI-defined abnormalities. Neurology 74:1724–1731

2. Chang EF, Clark A, Smith JS, Polley MY, Chang SM, Barbaro NM, Parsa AT, McDermott MW, Berger MS (2011) Functional mapping-guided resection of low-grade gliomas in eloquent areas of the brain: improvement of long-term survival. Clinical article. J Neurosurg 114:566–573

3. Yordanova YN, Moritz-Gasser S, Duffau H (2011) Awake surgery 468 for WHO Grade II gliomas within "noneloquent" areas in the left 469 dominant hemisphere: toward a "supratotal" resection. Clinical article. J Neurosurg 115:232–239

4. Klein M, Duffau H, De Witt Hamer PC (2012) Cognition and resective surgery for diffuse infiltrative glioma: an overview. J Neurooncol 108:309–318