Online version at http://www.minervamedica.it

Journal of Neurosurgical Sciences 2020 August;64(4):313-34
DOI: 10.23736/S0390-5616.20.04982-6

GUIDELINES

Italian consensus and recommendations on diagnosis and treatment of low-grade gliomas

An intersociety (SINch/AINO/SIN) document

Roberta RUDÀ [1], Filippo F. ANGILERI [2] *, Tamara IUS [3], Antonio SILVANI [4], Silvio SARUBBO [5], Alessandra SOLARI [6], Antonella CASTELLANO [7], Andrea FALINI [7], Bianca POLLO [8], Marialaura DEL BASSO DE CARO [9], Costanza PAPAGNO [10, 11], Giuseppe MINNITI [12], Ugo DE PAULA [13], Pierina NAVARRIA [14], Antonio NICOLATO [15], Andrea SALMAGGI [16], Andrea PACE [17], Alessandra FABI [18], Maria CAFFO [2], Giuseppe LOMBARDI [19], Carmine M. CARAPELLA [17], Giannantonio SPENA [20], Maurizio IACOANGELI [21], Marco FONTANELLA [22], Antonino F. GERMANÒ [2], Alessandro OLIVI [23], Lorenzo BELLO [24], Vincenzo ESPOSITO [25, 26], Miran SKRAP [3], Riccardo SOFFIETTI [1]
on behalf of the SINch Neuro-Oncology Section, AINO and SIN Neuro-Oncology Section

[1]Department of Neuro-Oncology, Città della Salute e della Scienza, University of Turin, Turin, Italy; [2]Section of Neurosurgery, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy; [3]Neurosurgery Unit, Department of Neurosciences, Santa Maria della Misericordia University Hospital, Udine, Italy; [4]Department of Neuro-Oncology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [5]Department of Neurosurgery, Structural and Functional Connectivity Lab Project, "S. Chiara" Hospital, Trento, Italy; [6]Unit of Neuroepidemiology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [7]Neuroradiology Unit, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy; [8]Section of Oncologic Neuropathology, Division of Neurology V – Neuropathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [9]Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; [10]Center of Neurocognitive Rehabilitation (CeRiN), Interdepartmental Center of Mind/Brain, University of Trento, Trento, Italy; [11]Department of Psychology, University of Milan-Bicocca, Milan, Italy; [12]Radiation Oncology Unit, Department of Medicine, Surgery and Neurosciences, Policlinico Le Scotte, University of Siena, Siena, Italy; [13]Unit of Radiotherapy, San Giovanni-Addolorata Hospital, Rome, Italy; [14]Department of Radiotherapy and Radiosurgery, Humanitas Cancer Center and Research Hospital, Rozzano, Milan, Italy; [15]Unit of Stereotaxic Neurosurgery, Department of Neurosciences, Hospital Trust of Verona, Verona, Italy; [16]Neurology Unit, Department of Neurosciences, A. Manzoni Hospital, Lecco, Italy; [17]IRCCS Regina Elena National Cancer Institute, Rome, Italy; [18]Division of Medical Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy; [19]Unit of Oncology 1, Department of Oncology, Veneto Institute of Oncology-IRCCS, Padua, Italy; [20]Neurosurgery Unit, Department of Neurosciences, A. Manzoni Hospital, Lecco, Italy; [21]Department of Neurosurgery, Marche Polytechnic University, Umberto I General University Hospital, Ancona, Italy; [22]Division of Neurosurgery, Department of Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [23]Neurosurgery Unit, Department of Neurosciences, Università Cattolica del Sacro Cuore, Fondazione Policlinico "A. Gemelli", Rome, Italy; [24]Unit of Oncologic Neurosurgery, Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [25]Sapienza University, Rome, Italy; [26]Giampaolo Cantore Department of Neurosurgery, IRCCS Neuromed, Pozzilli, Isernia, Italy

*Corresponding author: Filippo F. Angileri, Section of Neurosurgery, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, G. Martino University Hospital, University of Messina, 98125 Messina, Italy. E-mail: fangileri@unime.it

ABSTRACT

In 2018, the SINch (Italian Society of Neurosurgery) Neuro-Oncology Section, AINO (Italian Association of Neuro-Oncology) and SIN (Italian Association of Neurology) Neuro-Oncology Section formed a collaborative Task Force to look at the diagnosis and treatment of low-grade gliomas (LGGs). The Task Force included neurologists, neurosurgeons, neuro-oncologists, pathologists, radiologists, radiation oncologists, medical oncologists, a neuropsychologist and a methodologist. For operational purposes, the Task Force was divided into five Working Groups: diagnosis, surgical treatment, adjuvant treatments, supportive therapies, and follow-up. The resulting guidance document is based on the avail-

able evidence and provides recommendations on diagnosis and treatment of LGG patients, considering all aspects of patient care along their disease trajectory.

(*Cite this article as:* Rudà R, Angileri FF, Ius T, Silvani A, Sarubbo S, Solari A, *et al*.; SINch Neuro-Oncology Section, AINO and SIN Neuro-Oncology Section. Italian consensus and recommendations on diagnosis and treatment of low-grade gliomas. An intersociety (SINch/AINO/SIN) document. J Neurosurg Sci 2020;64:313-34. DOI: 10.23736/S0390-5616.20.04982-6)

KEY WORDS: Glioma; Consensus; Health planning guidelines.

Introduction and method

In 2018, the SINch (Italian Society of Neurosurgery) Neuro-Oncology section, AINO (Italian Association of Neuro-Oncology) and SIN (Italian Association of Neurology) Neuro-Oncology section formed a collaborative Task Force to look at the diagnosis and treatment of low-grade gliomas (LGGs). The Task Force included neurologists, neurosurgeons, neuro-oncologists, pathologists, radiologists, radiation oncologists, medical oncologists, a neuropsychologist and a methodologist. For operational purposes, the Task Force was divided into 5 Working Groups: diagnosis, surgical treatment, adjuvant treatments, supportive therapies, and follow-up. The resulting guidance document is based on the available evidence and provides recommendations on diagnosis and treatment of LGG patients, considering all aspects of patient care along their disease trajectory.

The search included articles from the specialized English literature on brain tumors, as well as from other areas of patient care such as epilepsy and palliative care. Eight electronic databases were searched from inception to October 2019: Medline (PubMed), Embase, Cinahl, PsychInfo, Cochrane Library, Web of Science, Academic Search Premier and ScienceDirect. The search was expanded by looking at the references in the studies that were selected to be reviewed, and at clinical trials registries, guidelines (www.guidelines.gov), and health technology assessment websites (www.inahta.org).

Two Task Force members independently reviewed the titles and abstracts and discarded those that did not meet the inclusion criteria or were not suitable for a full evaluation. Full-text review of the selected studies was then performed by the two reviewers. Any disagreement regarding inclusion of individual studies was resolved by consensus. As for the methodological framework, the Task Force used the guidance document of the European Federation of Neurological Societies (EFNS).[1]

Each Working Group produced a section of the consensus document, supported by the list of studies that provided the evidence for all recommendations. The evidence of studies was graded Class I to IV and recommendations were graded Level A (established as effective), Level B (probably effective) and Level C (possibly effective).

The evaluation of the evidence and strength of recommendations for LGGs are summarized in Table I.

Epidemiology and natural history

Epidemiological studies on LGG patients providing useful data for incidence, prevalence and long-term outcome are few: the main data source is CBTRUS, a US population-based registry providing incidence data on the population between 2011 to 2015 and survival data for 26% of the population.[2] Other registries include the histologically-based French Brain Tumor Database describing newly diagnosed gliomas in the period 2004-2009 in a large number of French Neurosurgery Units, and the Danish Neuro-Oncology Registry providing data on 1930 adult glioma patients enrolled from 2009 to 2014 and histologically verified from the whole country.[3, 4]

Age-adjusted incidence rates for LGG as a whole range from 0.9/100,000/yr (1.3 including WHO grade I gliomas) in CBTRUS to 0.93/100,000/yr (1.1 including WHO grade I) in the Danish Neuro-Oncology Registry.[3]

All Registries have considered patients according to the WHO 2007 classification. Overall, LGGs account for approximately 15% of all gliomas and the average age at diagnosis is in the thirties. Concerning survival data, in the CBTRUS[2] the proportion of patients alive at 3, 5 and 10 years respectively, were 95.4%, 94.1% and 92.2% in pilocytic astrocytoma, 57.6%, 50.1% and 39.3% in diffuse astrocytoma, from 87.1%, 81.3% and 65.7% in oligodendroglioma and from 73.1%, 63.7% and 49% in oligoastrocytic tumors.

Survival rates at 5 years provided in the Danish Registry are 82% in grade I and 54% in grade II adult glioma patients.[3] In Italy, data concerning incidence and prevalence of LGG are not available on a national basis, with Italian Association of Cancer Registries (AIRTUM)[5] providing incidence and survival data for the whole group of primary malignant brain tumors.

TABLE I.—*Summary of class of evidence and strength of recommendation.*

Statement	Class of evidence	Level of recommendation
Imaging		
The standard protocol includes anatomical, two-dimensional T2-weighted and FLAIR sequences (slice thickness ≤4 mm) and three-dimensional T1-weighted images acquired pre- and post-contrast administration	II	B
DWI with maximum *b*-value of 1000 s/mm^2 is included in the EORTC-NBTS consensus recommendations	II	B
PWI is recommended for baseline assessment of suspected lower-grade gliomas that have not undergone histological evaluation or prior to biopsy	II	B
Other PWI techniques such as dynamic contrast-enhanced MRI or arterial spin labeling could be performed optionally	III	C
^{1}H-MRS is recommended as an optional modality in glioma imaging to be considered on an individual case basis for differential diagnosis and grading, especially in combination with other advanced techniques such as PWI	III	C
Amino-acid PET can be performed optionally to detect aggressive disease foci in anatomical MRI findings suggesting WHO grade II glioma, hence possibly guiding biopsy and tumor resection, as well as radiation dose boosting	III	C
An early postoperative MRI is strongly suggested and should be performed within 48 to 72 hours, including DWI	II	B
The use of PWI for serial follow-up assessment of lower-grade gliomas is recommended to identify malignant transformation and to distinguish therapy effects (pseudoprogression or radiation necrosis) from tumor progression, being DSC-derived rCBV the most validated parameter	II	B
^{1}H-MRS should be considered on an individual case basis especially in combination with other physiological techniques such as PWI for identification of true progression	III	C
Amino-acid PET cannot be recommended for routine monitoring in lower-grade glioma	III	C
Surgery		
The extent of surgical resection (EOR) is a strongest independent risk factor for both overall survival (OS), progression-free survival (PFS) and malignant transformation (MPFS)	II	B
Intraoperative neurophysiological monitoring is associated with lower risk of permanent postoperative deficits and a higher EOR of tumors in eloquent areas	III	C
Cortico-subcortical mapping is the most sensitive and specific technique for the identification of critical cortical hubs and white matter bundles	III	C
Awake surgery is an important option, mainly in young patients with lesions in the dominant hemisphere involving language, motor and somato-sensory areas	III	C
Awake surgery can be a valid strategy also for lesions harboring critical networks (*i.e.* visuo-spatial, social cognition, motor planning, semantic association, etc.) in the hemisphere not specialized in language elaboration (commonly the right in right-handers)	III	C
Intraoperative neurocognitive mapping		
Intraoperative neuropsychological monitoring is now considered a valid option for real-time optimization of extent of resection and clinical outcome ratio in LGGs surgery; however, a standardized and internationally approved battery for cognitive intraoperative monitoring has not yet been defined	III	C
Estimation of extent of tumor resection (EOR)		
The objective estimation of the extent of tumor resection is fundamental in planning postoperative adjuvant treatments and monitoring the growth curve of residual tumor volume over time	II	B
The volumetric analysis can be carried out by manual segmentation of the areas of interest or by using the so-called ellipsoid volume technique or software with automatic or manual segmentation	III	C
The role of the supratotal resection has not been clearly determined so far	III	C
Supratotal resection has been associated to a better outcome and reduction of epileptic seizures	III	C
Incidental low-grade gliomas (iLGGs)		
In iLGGs surgery may be considered after completion of accurate standard and advance MRI screening	III	C
Risk groups and adjuvant treatments after surgery		
Low-risk patients (younger than 40 years and/or after total resection) should be observed with MRI without any adjuvant treatment	II	B
In high risk patients, combined radiotherapy and adjuvant chemotherapy with PCV is associated with longer PFS and OS than radiotherapy alone	I	A
In high-risk patients initial radiotherapy or temozolomide may provide comparable benefits in terms of PFS	I	A
Oligodendrogliomas IDH-mutant and 1p/19q-codeleted and diffuse astrocytomas IDH-mutant and 1p/19q-non-codeleted derive a higher benefit in terms of survival from radiation followed by chemotherapy as compared to either radiotherapy or temozolomide alone	II	B
Oligodendrogliomas IDH-mutant and 1p/19q-codeleted have a definitive longer survival and higher chemosensitivity in comparison to diffuse astrocytomas IDH-mutant and 1p/19q-non-codeleted, thus initial chemotherapy alone with other salvage treatments at recurrence may be an option to better preserve overtime the cognitive functions	III	C
Diffuse astrocytomas IDH mutant should not receive as initial treatment chemotherapy alone as PFS is shorter as compared to radiotherapy alone	III	C
Diffuse astrocytomas IDH wild-type should receive a combination of radiotherapy and chemotherapy due to their aggressive behavior, especially when EGFR amplification or TERT mutation are present	III	C
Radiotherapy and chemotherapy can yield seizure control in case of partial resection or biopsy	III	C
Cognitive functions monitoring		
Neuropsychological tests should be integrated with patient reported outcome (PRO) tools and brain cancer-specific HRQL outcomes	III	C
Improvement in neurocognitive functioning may be obtained after large brain tumor resection	III	C
Cognitive rehabilitation may be an effective intervention for treating cognitive dysfunctions in brain tumor patients	III	C
Some psychostimulants like methylphenidate and modafinil may be of modest usefulness	III	C

(To be continued)

TABLE I.—*Summary of class of evidence and strength of recommendation (continues).*

Statement	Class of evidence	Level of recommendation
Antiepileptic drugs (AEDs)		
Glioma patients who never suffered seizures should not be treated with primary prophylaxis with antiepileptic drugs (AEDs)	I	A
Long-term treatment with AEDs is indicated for patients with persisting seizures after surgery	III	C
In terms of long-term tolerability, the second-generation AEDs offer advantages compared to the first generation	III	C
Efficacy, tolerability, lack of drug interactions, and intravenous availability make levetiracetam the first choice in brain tumor patients	III	C
Add-on lacosamide is effective in patients with persisting seizures after levetiracetam or standard AEDs	III	C
Whether and when patients who are seizure-free after tumor treatment may ultimately withdraw AEDs is uncertain	III	C
Prophylaxis of venous thromboembolism (VTE)		
Indication for VTE prophylaxis specific for LGG patients are not available		
Treatment of acute VTE in patient with brain tumors should follow the same protocols proposed for non-brain-tumor-associated VTEs	III	C
Treatment options at progression		
The role of second surgery at recurrence is not definitively defined and should be evaluated in individual patients	III	C
Positive prognostic factors in case of re-irradiation at recurrence are KPS, PTV volume and re-resection	III	C
Negative prognostic factors in case of re-irradiation at recurrence are time to first RT <12 months and older age	III	C
In case of re-irradiation, conventionally fractionated and hypofractionated schedules are preferable due to better tolerance	III	C
Alkylating chemotherapy (PCV, TMZ) is an option for all patients	III	C
In case of aggressive contrast-enhanced lesions bevacizumab may be active in reducing the need for steroids and improve QoL	IV	C

The natural history of LGGs typically includes a presymptomatic phase with a variable duration during which tumors may be detected incidentally,[6] followed by a symptomatic phase: in this phase patients develop various neurological signs/symptoms isolated or in combination, suggesting both focal and diffuse brain damage related to tumor growth and infiltration.

The duration of the symptomatic phase preceding malignant transformation is highly variable, depending on a number of clinical and molecular factors (age, tumor size and midline crossing, presence/absence of IDH1-2 mutations/ 1p-19q co-deletion, p53 status, neurological and global performance status, extent of resection, post-surgical treatments and rate of tumor growth) with an average of 7 years.

The third phase is characterized by malignant transformation (*i.e.* progression to grade III or IV glioma), with deterioration of pre-existing deficits/symptoms and appearance of new ones, and life expectancy similar to that of a newly diagnosed grade III or IV gliomas.

Clinical presentation

Clinical presentation of LGGs is dependent both on tumor site and growth pattern. A high proportion (from 70% to 90%) of patients with LGG present with seizures, more often of partial or complex partial type, or secondarily generalized. Oligodendrogliomas tend to be more epileptogenic due to their cortical infiltrative pattern.[7, 8] The widespread growth of LGG makes common cognitive symptoms also, with involvement of both executive functions and of more cortically-related higher functions (*i.e.* memory and language impairment).[9]

Changes in mood and behavior are reported in a proportion of patients at disease onset. Less frequently, slowly evolving motor and/or sensory deficits may characterize LGG presentation.

Up to 10% of LGGs are diagnosed during neuroradiological work up performed for unrelated reasons (*i.e.* after head trauma or in the context of long-standing headache with clinical features suggestive for primary headache).[6, 10]

The clinical-radiological diagnosis of LGG may be quite straightforward in most cases, but is sometimes challenging. The alternative diagnoses may include non-glial tumors, tumor-like demyelinating disease, CNS vasculitis and other rarer diseases.

In these cases, before proceeding to biopsy, MR spectroscopy, MR-perfusion and amino acid PET may help in suggesting the right diagnosis.[11] Brain CT scan is also useful and should be obtained in all cases, while CSF analysis is performed in selected cases when an inflammatory disease has to be ruled out.

Imaging

Diagnosis

Magnetic resonance imaging (MRI) is routinely employed in the diagnosis and clinical management of lower grade gliomas. Computed tomography (CT) may provide additional information by detecting calcifications or hemorrhages, but cannot distinguish subtle contrast between

tissues in the brain. Imaging protocol should refer to the EORTC-NBTS consensus recommendations,[12] that have been recently endorsed by the European Society of Neuroradiology (ESNR) for glioma imaging.[13] The standardized protocol includes anatomical, two-dimensional T2-weighted and FLAIR sequences (slice thickness ≤4 mm) and three-dimensional T1-weighted images acquired, pre- and post-contrast administration (Class II, Level B). The recommended minimum requirements for 1.5-T and 3.0-T MR image acquisition are outlined.[12] Three-dimensional FLAIR techniques (3D-FLAIR) are strongly endorsed for lower grade gliomas, especially for supporting the transition into volumetric tumor measurements (see below the 'Follow-up' section). 3D-FLAIR sequences are routinely used on newer MR systems, but may not be available on all MR scanners. Susceptibility-weighted imaging (SWI) may contribute in detecting intratumoral hemorrhage, calcifications, or tumoral neovascularity, but further evidence is needed to clarify the added value in lower grade glioma diagnosis.

Besides anatomical sequences, physiological imaging techniques, such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), add relevant structural and hemodynamic information for tumor diagnosis and classification, as well as for stratification of tumor response.[14, 15]

DWI with a maximum *b*-value of 1000 s/mm^2 is included in the EORTC-NBTS consensus recommendations[12] (Class II, Level B). The DWI-derived apparent diffusion coefficient (ADC) contributes to estimate non-invasively tumor cellularity and grade in brain gliomas.[16, 17] Moreover, quantitative apparent diffusion coefficient (ADC) measurements have been recently reported to support the molecular subtyping of non-enhancing lower grade gliomas in the clinical setting.[18]

PWI has shown to be a relevant technique for glioma imaging due to its ability to measure changes associated with neoangiogenesis, which correlate with tumor malignancy.[14] The dynamic susceptibility contrast (DSC) PWI technique is the primarily used perfusion method across Europe,[13] with DSC-derived rCBV being the most validated parameter to predict grading and outcome of patients with brain gliomas.[19] PWI is recommended for baseline assessment of suspected lower grade gliomas that have not undergone histological evaluation, or prior to biopsy[13] (Class II, Level B). Furthermore, raised rCBV in treatment-naïve lower grade gliomas has recently been highlighted as a powerful predicting feature of IDH wild-type tumors, being associated with a distinct hypoxia/angiogenesis transcriptome signature.[20]

Other PWI techniques such as dynamic contrast-enhanced MRI or arterial spin labeling could be performed optionally, as larger evidence is currently warranted to define their impact in glioma imaging[13] (Class III, Level C).

Quantification methods for PWI parameters, such as rCBV, is highly advocated to avoid pitfalls of subjectivity, being aware that threshold values are not simply transferable between institutions, as they very much depend on scan parameters and post-processing.[18] Standardization of PWI methods within and across sites is strongly advocated to ensure their reproducibility and reliability in clinical practice.[21]

MR spectroscopy (MRS) provides metabolic biomarkers that complement MRI anatomical and physiological information in gliomas. Proton MR spectroscopy (^{1}H-MRS) has been extensively used to detect and quantify a number of endogenous cellular metabolites.[22] Despite modern MR systems support MRS acquisition, routine use is largely restricted to specialized centers. Technical challenges toward obtaining reliable good-quality results have impeded the widespread adoption of this technique.[23] Hence, ^{1}H-MRS is recommended as an optional modality in glioma imaging, to be considered on an individual case basis for differential diagnosis and grading, especially in combination with other advanced techniques such as PWI[13, 15] (Class III, Level C)

In the last years, one of the most relevant advances of ^{1}H-MRS has been the possibility to non-invasively detect the intratumoral accumulation of 2-hydroxyglutarate (2HG) in gliomas, whose production and accumulation in tumor tissue results from the arginine 132 (R132) mutations in the IDH1 gene. 2HG has been recently used as a biomarker to detect the presence and spatial distribution of IDH-mutated cells in lower grade gliomas, with excellent specificity (Class II, Level B).[24] However, the application of this methodology in a clinical setting cannot be recommended as still technically challenging. Further studies are warranted to ensure a wide implementation for clinical glioma imaging.

Advanced neuroimaging techniques such as functional MRI (fMRI) and diffusion MR tractography have become an essential part of the presurgical and intraoperative workup of gliomas. These techniques can give relevant information on the anatomo-functional organization of eloquent cortical areas and subcortical connections close or inside a tumor, in order to support in the achievement of a maximal safe resection.[25, 26]

Preoperative task-based fMRI represents the best validated and most robust and widely used clinical applica-

tion of BOLD (blood oxygen level-dependent) imaging to localize non-invasively eloquent cortical areas. In patients with lower grade gliomas this technique is used to determine language lateralization, to localize the motor and visual cortex and to define the spatial relationship between the tumor and eloquent cortical areas. Despite an overall good accuracy in lower-grade gliomas,[25] task-based fMRI cannot replace intraoperative direct electrical stimulation (DES), which is considered the gold-standard technique for assessing true eloquent cortical and subcortical sites during surgery. Resting-state fMRI (rs-fMRI) enables to evaluate the spontaneous neural activity of regions which are functionally connected even if they are anatomically remote, with potential benefit to map multiple networks with a single acquisition.[25] However, a rigorous validation is still needed for a wide implementation of this technique in the clinical setting.

Diffusion imaging with MR tractography has been increasingly used to depict in vivo the white matter (WM) pathways in the brain, and one of main clinical application is mapping of eloquent tracts in cerebral tumors. MR Tractography is the only method allowing to detect noninvasively the course of the main WM bundles, and may provide information whether a tract is displaced, infiltrated/edematous, or interrupted by a tumor. For this reason, MR tractography is often an integral part of the presurgical and intraoperative workup of glioma patients, to delineate a map of the main eloquent tracts, like motor or language fascicles or subcortical connections involved in specific circuits close or inside a tumor.[27, 28] This map can be useful both in presurgical planning to choose the best approach for sparing eloquent tracts during surgery, for identifying the patients that may maximally benefit from surgery, and for guiding intraoperative mapping by giving an anatomical correlate of the functional data from intraoperative DES.[25] To date, the most common clinical technique is diffusion tensor imaging (DTI) tractography, which has proven to be a valid and highly sensitive tool for localizing eloquent subcortical areas in glioma patients. More recently, new tractography techniques have been developed, based on new diffusion models relying on high angular resolution diffusion-weighted imaging (HARDI), together with complementary probabilistic methods, and may improve the accuracy of MR tractography for glioma surgery.[25] Larger studies are warranted to define the impact of these new tractography models to optimize the identification of safe surgical resection margins, as well as to encourage their wide clinical implementation in the near future.

Functional molecular imaging, such as positron emission tomography (PET) uses tracers to detect and quantify biological processes, such as cell proliferation, membrane biosynthesis, glucose consumption, and uptake of amino acid analogs.[29] PET tracers used in clinical practice include ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG), [^{11}C-methyl]-methionine (^{11}C-MET), O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET), and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (^{18}F-FDOPA). Recommendations for PET imaging should refer to the RANO working group/EANO consensus guideline for the clinical use of PET imaging in gliomas.[30] Amino acid PET outperforms ^{18}F-FDG PET in differential diagnosis of neoplastic *versus* non-neoplastic tissue and can improve the sensitivity, specificity, and accuracy of diagnosis in cases of uncertainty. Furthermore, amino acid PET can be performed optionally to detect aggressive disease foci in anatomical MRI findings otherwise suggestive of WHO grade II glioma, hence the possibility to guide biopsy and tumor resection, as well as radiation dose boosting[30] (Class III, Level C). Current limitations depend on the scarce availability of amino acid PET and, only for ^{11}C-MET, the need for local access to a cyclotron. Studies are ongoing to obtain more comprehensive, prospective data in larger clinical cohorts.

Follow-up

The standardized brain tumor MR imaging protocol is recommended to follow-up lower grade gliomas.[12] An early postoperative MRI is strongly suggested and should be performed within 48 to 72 hours, including DWI[31] (Class II, Level B). Including PWI at this early timepoint is not recommended, as susceptibility effects from blood products in the surgical cavity may affect the estimation of DSC parameters such as rCBV, making this technique non-diagnostic. Nonetheless, due to the slow growth-rate of these tumors, postoperative MRI could be postponed up to 3-4 months after surgery and should include both DWI and PWI (when post-surgical blood degradation products have largely got reabsorbed). MRI is recommended before starting any adjuvant treatment (RT ± chemotherapy) as a baseline for comparison with the post-treatment scans.

Contrast-enhanced MRI represents the current backbone for monitoring treatment response in lower grade gliomas. First routine MRI follow up should be performed approximately 3 months after starting RT or CT. Intervals can be extended according to the individual case up to 6 months or even 12 months when longer observations have already been done (*e.g.* after 5 years of stable disease). Serial imaging is recommended to identify new areas of contrast enhancement or significant change in tumor size, which

can predict transformation to higher grade.[32, 33] Consistency in MR scanning hardware (especially field strength), contrast agent type and dose is strongly advocated to allow an accurate and reproducible follow-up assessment.[31]

Serial measurements of tumor size are highly recommended, either using two-dimensional FLAIR diameters or 3D-FLAIR volumetry, as this has been shown to increase diagnostic accuracy in the follow up. Volumetric tumor measurements are reliable and consistent over time and volumetric changes may reflect clinical response better than 2D size changes, as they more accurately assess the extension of irregularly shaped tumors and are less impacted by the presence of surgical cavity. Despite volumetry has been shown to be feasible in a clinical setting and easily to be implemented in routine clinical use with standard software, nowadays it is still not routinely performed in all neuroradiological centers throughout Italy.

The use of PWI for follow-up assessment of lower grade gliomas is recommended to identify malignant transformation and to distinguish therapy effects (pseudoprogression or radiation necrosis) from tumor progression with DSC-derived rCBV being the most validated parameter for the differential diagnosis[13] (Class II, Level B). Following radiotherapy, knowledge of irradiation fields and treatment dosimetry is crucial to correctly interpret PWI changes after treatment.

Among advanced MR imaging techniques, ^{1}H-MRS is recommended as an optional modality in lower grade glioma in the follow-up due to the difficulty in standardization in the clinical practice. ^{1}H-MRS should be considered on an individual case basis especially in combination with other physiological techniques, such as PWI for identification of true progression[13, 15] (Class III, Level C). Diffusion Tensor Imaging (DTI) has been proven to be helpful to identify changes in peripheral infiltration of lower grade gliomas after chemotherapy in a research setting,[14] but it is not routinely implemented in clinical software for follow-up evaluation.

Amino acid PET can be performed in cases in which conventional and physiological MR imaging is not conclusive, as it can be helpful for the metabolic detection of malignant transformation, for the evaluation of an early response to chemotherapy, and for the differentiation between treatment-related changes and true progression, with high sensitivity and specificity,[30] and early response to chemotherapy.[34] However, due to the aforementioned limitations and the use of ionizing radiations, amino acid PET cannot be recommended for routine use in lower grade gliomas (Class III, Level C).

Pathological and molecular classification

Brain tumors originating from glial cells are classified according to the last revision (2016) of the World Health Organization (WHO) classification of tumors of the Central Nervous System,[35] where histological parameters and molecular markers became integrated in the diagnosis and essential part of tumor assessment in modern neuro-oncology practice.

The histological diagnosis of LGGs is problematic and with high inter-observers variability. The application of advanced molecular biology technologies to brain tumors studies allowed the identification of genetic and molecular alterations specific for some histotypes, affecting tumor biological behavior.[36, 37] In particular, The Cancer Genome Atlas (TCGA) project, allowed to recognize genome abnormalities occurring in different tumor subtypes.[38] The use of molecular markers provides diagnostic, prognostic and predictive data on tumors with the same histological appearance.

In this regard, the clinical management of patients and therapeutic strategies have been changed and the implementation of some biomarkers into routine laboratory is recommended. This diagnostic approach provides information to classify these tumors into different classes of risk.

LGGs are a heterogeneous group of tumors with different morphologic characteristics. Mutational events in neoplastic cells at various stage of differentiation give rise to clones with different genotype and phenotype. These alterations change the morphology and biology of neoplastic cells that show increased proliferation activity and infiltration. This process is at the basis of the heterogeneity of glial tumors. For a correct diagnosis of LGGs it is recommended that the entire surgical specimen is analyzed by the pathologist with conventional morphological procedures (fixation and paraffin-embedding, routine hematoxylin and eosin staining, additional immunohistochemical and molecular analyses). Whenever possible, parts of the tissue should be frozen for future molecular marker studies.

Astrocytomas and oligodendrogliomas represent the two main entities of LGGs, further classified by molecular profile.[39]

The term "oligoastrocytoma," an entity previously described only by histologic characterization, in the 2016 WHO classification was restricted only to cases without genetic analysis or to rare cases with double components not further classifiable.

The most clinically relevant finding of the new classification is the isocitrate dehydrogenase 1 (IDH1) R132H mutation or, less commonly, IDH2 codon 172 missense muta-

tions which define diffuse and anaplastic astrocytomas and oligodendrogliomas as IDH-mutant tumors. IDH (isocitrate dehydrogenase) mutations are early lesions in gliomas and cluster in the active site of these enzymes at codon 132 of IDH1 and codon 172 of IDH2. The R132H mutation is the most frequent in gliomas and can be investigated by immunohistochemistry. Other mutations have been reported and they could be related to specific glioma subtypes.

In diffuse gliomas, absence of IDH1-R132H immunopositivity should be followed by DNA extraction and IDH1 and IDH2 sequencing to detect or exclude other, less common IDH mutations.

A subset of IDH-mutant tumors, as oligodendroglial tumors, also show co-deletion of chromosomes 1p and 19q, a feature that predicts improved survival. Strongly associated with oligodendroglial tumors, it is a good marker for sensitivity to chemotherapy and radiotherapy as well. Loss of chromosomal material on 1p/19q resulting from an unbalanced translocation, (loss of heterozygosity (LOH) 1p/19q) was first recognized as a good prognostic marker. The WHO classification does not suggest a specific technique for testing 1p/19q codeletion, but recommends a method useful to detect whole-arm chromosomal losses. However, many techniques are used, such as fluorescent in situ hybridization (FISH), chromogenic in situ hybridization, PCR-based microsatellite analysis, that requires autologous blood samples. More advanced molecular genetic testing, such as array comparative genomic hybridization (aCGH), multiplex ligation-dependent probe amplification (MLPA) or real-time PCR, that are independent from autologous DNA samples, are used for research purposes.

Mutations in the promoter of the telomerase reverse transcriptase gene (TERT) are frequently observed in pure oligodendrogliomas with deletion of 1p and 19q (1p/19q codeletion), but TERT promoter mutations are not restricted to IDH-mutant gliomas and could be also present in IDH-wild-type glioblastomas.[40]

IDH mutations are also associated with other molecular markers, including O6-methylguanine-DNA methyltransferase (MGMT), a marker that predicts responsiveness to alkylating chemotherapy. Detection of MGMT promoter methylation status by immunocytochemistry is not an adequate method on formalin fixed specimens and should be tested by the use of molecular genetic tests, such as methylation-specific PCR or pyrosequencing of bisulfite-modified tumor DNA.

IDH mutation is frequently associated with TP53 and alpha thalassemia/mental retardation syndrome X-linked (ATRX) mutations in astrocytic gliomas without 1p/19q codeletion. Immunohistochemical detection of nuclear staining for p53 and loss of nuclear ATRX expression (suggesting mutation) in IDH-mutant gliomas is characteristic of astrocytic differentiation and in such cases additional testing for 1p/19q codeletion could not be required, whereas widespread nuclear immunostaining of ATRX in an IDH-mutant glioma should be verified for 1p/19q codeletion to differentiate an IDH-mutant astrocytic glioma from an IDH-mutant and 1p/19q-codeleted oligodendroglioma.[31]

Astrocytoma, NOS (Not otherwise specified) and oligodendroglioma, NOS, are glioma categories introduced by WHO 2016 classification for those tumors, that cannot be tested for the relevant molecular markers, or when molecular testing is inconclusive.

Clinical and neuroimaging prognostic factors

Younger age is a well-established prognostic factor for survival: a relationship between younger age and better survival has been clearly demonstrated in large datasets from clinical trials.[41-43] A cut-off of 40 years has been the most commonly used in older series: however, it is unclear whether this holds true within the recent molecular subgroups of WHO 2016,[44] in particular for oligodendrogliomas.

The presence of seizures and the absence of neurological deficits at onset are associated with longer survival.[43]

Concerning the prognostic value of imaging features on conventional MRI, larger tumors and tumors crossing the midline are correlated with a worse prognosis both in terms of PFS and OS[43] (Class II, Level B). The role of contrast enhancement as a negative prognostic factor is still controversial. In the majority of series, the presence of contrast enhancement is associated with a worse prognosis;[45] however, some other Authors did not report a statistically significant correlation.[46] In a recent paper[47] contrast enhancement has been suggested to be of prognostic importance in grade II-III gliomas harboring IDH1/2 mutation but not in wild type tumors (Class III, Level C).

Preoperative and postoperative tumor volume has been suggested to be prognostic in LGG,[48, 49] but a validated cut-off has not been established yet (Class III, Level C).

Volumetric studies on MRI over time have demonstrated continuous tumor growth in the natural history of low-grade tumors and the growth rate seems to have a prognostic significance[33, 50] (Class III, Level C).

The measurement of cerebral blood volume (rCBV) can predict tumor behavior: a low rCBV correlates with longer PFS and OS[19, 51](Class III, Level C).

The prognostic and predictive value of MRS has been suggested by some small studies,[52] but still need validation.

Positron emission tomography (PET) has been increasingly used both for diagnosis and treatment monitoring of LGG. (^{18}F)-Fluorodeoxyglucose (FDG) is of limited value, since LGGs display a low and non-constant uptake of the FDG as compared to the normal cortex or basal ganglia. Amino acid tracers are considered more appropriate for the evaluation of LGGs.[53, 54] The superiority of amino acid tracers over FDG is based on the low background of MET in the normal brain, providing good contrast with tumor uptake. MET uptake at the disease onset has been identified as a prognostic factor in small low-grade tumors series[55, 56] (Class III, Level C). In a prospective study on LGGs, FET PET uptake, together with tumor growth pattern on MRI, has shown to be a strong prognostic factor.[57] Dynamic FET-PET has been shown to help stratifying prognosis, with 18F-PET positive gliomas with decreasing time activity curves in kinetic analysis showing shorter PFS and faster malignant transformation.[58]

Surgery

The role of surgery

Surgery represents the first step in clinical management of patients with low grade gliomas (LGGs) despite the lack of randomized Class I studies.[7, 59, 60] Several volumetric retrospective studies have shown that the extent of surgical resection (EOR) is the strongest independent prognostic factor both for overall survival (OS), progression-free survival (PFS) and malignant transformation (MPFS) (Class II, Level B).[48, 61-68]

Nevertheless, modern glioma surgery is focused on the cornerstone of the optimal balance between tumor removal and neuro-cognitive preservation:[48, 60, 63] to achieve this purpose, a detailed and customized anatomo-functional planning is crucial.[69] Nowadays, the neurosurgical oncologists have a variety of contemporary tools available, which include frameless navigational systems, intraoperative imaging, and functional mapping.[70] These tools can support in tailoring an optimal level of tumor resection with minimal and/or transient postoperative neurologic morbidity.[71]

In LGG surgery, intraoperative neurophysiological monitoring has been demonstrated to be associated with lower risk of permanent postoperative deficits and higher EOR of tumors in eloquent areas (Class III, Level C).[72]

Cortico-subcortical mapping is the most sensitive and specific technique for the identification of the critical cortical hubs and white matter bundles, and is recommended with Level III of evidence (Class III, Level C).

Direct electrical mapping (commonly known as direct electrical stimulation, DES) and neurophysiological monitoring (motor evoked potentials, PEMs, somatosensory evoked potentials, PESS) for executive motor functions are also possible under general anesthesia. The more complex motor and associative functions (*i.e.* language in its various sub-elaborations, vision, reading, calculation, attention) can be exclusively and safely monitored during awake surgery, where patients are asked to perform adequate and dedicated neuropsychological testing during cortico-subcortical DES.

Awake surgery is an important option, mainly in young patients, with lesions harboring the dominant hemisphere, especially when involving language, motor and somatosensory areas (Class III, Level C). Awake surgery can be a valid strategy also for lesions harboring critical networks (*i.e.* visuo-spatial, social cognition, motor planning, semantic association, etc.) in the hemisphere not specialized in language elaboration (commonly the right in right-handers) (Class III, Level C).[73, 74]

The fundamental principle in awake surgery lies in the combination of intraoperative cognitive monitoring and brain mapping through DES of the cortex and white matter, in order to obtain a real-time assessment of neural networks.[73-75] The cognitive sphere is the key component for enhanced health-related quality of life (HRQL) in LGG and represents an important outcome measure of the surgical performance. Patients need to perform an accurate and extensive neuropsychological testing (*i.e.* language, executive functions, visual and visuo-spatial cognition, attention, memory, praxis, etc.) before and after surgery.[76, 77]

Considering that gliomas are tumors usually infiltrating functional cortico-subcortical areas, a radical surgery is unfortunately limited to few and selected cases. Consequently, a customization of post-surgical treatments on the basis of EOR and tumor molecular profile, is strongly recommended. There is no general consensus in the literature regarding the cut-off value of EOR. Multicenter studies are needed to determine the cut-off value which could be of clinical use in the postoperative management of LGG.

Perioperative neuro-psychological assessment

The management of the patient with a presumptive diagnosis of a lower glioma must be aimed at defining the degree of functional reorganization achieved by the patient brain surrounding the tumor.[78-80] The management must there-

fore foresee a careful interview of the patient, associated with a detailed neuropsychological evaluation; data obtained from these analyses have to be integrated with those obtained from imaging. These data are used for making the eventual decision to treat, and for planning the resection. Patient interview is of particular importance and should detail the symptoms reported by the patient and the duration of the clinical history. A detailed epileptic history is mandatory because it provides information on both the progression and temporal and current extension of the neoplasm, as well as precious information on the degree of functional reorganization achieved by the surrounding brain due to the presence, growth and extension of the neoplasm itself. Additional data to be evaluated are the patient educational level, the job and future career development, current hobbies, future pregnancy in case of female patients.[81] These data, generally referred as patient needs, are crucial for the elaboration of a tailored surgical strategy, particularly in the context of the permanent effect that surgery may exert on the quality of life.[78, 82] Psychological evaluation consists of two components: neuropsychological and psycho-oncological evaluation. The neuropsychological evaluation evaluates the degree of functional reorganization achieved by the individual patient, and prepares the patient for the intraoperative testing, when this is needed. Extensive testing is used and usually explores all functional domains, comprehensive of memory, language, praxis, executive functions, and fluid intelligence.[83-85] The psycho-oncological evaluation is a complementary investigation and has the function of assessing the patient's needs, the presence of anxiety disorders, the understanding of the state of the disease and of the therapeutic process to which the patients will go through, along with the ability to perform part of the procedure in awake anesthesia if needed.[78, 79, 86]

Intraoperative neuro-cognitive mapping

Intraoperative neuropsychological monitoring is now considered a valid option for real-time optimization of extent of resection and clinical outcome ratio in LGGs surgery. It should be customized to each single case ("ad-hoc") and particularly with respect to patients' characteristics (age, education, job, cooperation degree, hemispherical dominance, preoperative cognitive assessment, daily activities) and tumor features (cortical and subcortical location, extension, radiological featuring, and lateralization). Thus far, a standardized and internationally approved battery for cognitive intraoperative monitoring has not yet been defined. Nevertheless, different papers are available, resuming newly proposed and consolidated tasks for intraoperative monitoring, and focusing on lesions' site and/or functional networks to be explored (Class III, Level C).[83, 87-89]

Language

Cognitive monitoring during surgery in the language-specialized hemisphere (basically, the left in right-handers and in 2/3 of left-handers) is commonly based on picture naming tests, *i.e.*, DO 80 in France, or the 48- picture naming task from the Semantic Battery[90] or the 60 -item naming task by Laiacona *et al.*[91] for Italians patients. Object naming easily allows the identification of semantic (*i.e.* semantic paraphasia), phonemic (*i.e.* phonemic paraphasia) or no response (*i.e.* anomia) errors.[83, 87, 92] If well-constructed, naming pictures of object also identifies possible semantic dissociations, *i.e.* between living and non-living categories.[93] Experts suggest also the execution of a semantic association test (namely, the palm-pyramid-tree test [PPTT])[94] when the non-dominant hemisphere is involved. Specific sites should be tested with more sensible tasks, such as the temporal pole, for which famous people naming is required,[95] or action naming in frontal tumors.[96] In this last case, the verb can be either produced in the infinitive form or the patient can be asked to produce the verb in the correct inflected form, allowing exploration of the grammatical abilities.

Counting test is a crucial step for the identification of speech arrest (anarthria), which is defined as a complete block of speech production with tongue movements preserved, or defective articulations.

Complementary intraoperative tasks for language (verbs generation, oral words comprehension, words and non-words repetition), reading and comprehension (words and non-words) monitoring are largely reported in the literature.[83, 96-99]

Considering the multimodal organization and the huge distribution of language networks at cortical and subcortical level, at least the use of a basic language monitoring is recommended in all the resections within the language dominant hemisphere. Reading tests are particularly indicated in the cortico-subcortical temporal, occipital, and temporo-parieto-occipital resections. Lastly, PPTT is recommended in the resections within the language non-dominant hemisphere (basically, the right) (Class III, Level C).

Executive functions

Stroop test (monitoring cognitive flexibility and control interferences) is the test most frequently used for executive func-

tions assessment during surgery.[100] This task is particularly indicated in the frontal resections (Class III, Level C).[100, 101]

Visual and visual fields

Visual functions and visual field scanning are commonly monitored with a naming task with stimuli reported on a four-quadrants screen (with a central cross to fix visual attention and dotted lines for spatial identification of eventual positive responses).[87, 102, 103] In fact, this task allows a double real-time monitoring of both language and visual functions, providing positive responses (*i.e.* phosphenes, color spots), particularly useful for tracking the subcortical anatomy-functional limits of resections aimed to an acceptable preservation of visual field (*i.e.* quadrantopsia), or negative responses (*i.e.* anomia, paraphasia, or more generally visual recognition troubles).

This task is particularly useful in temporal, occipital or parieto-temporal or parieto-occipital resections (Class III, Level C).

Visuo-spatial cognition

Unilateral spatial neglect is the most dramatic deficit related to the damage of spatial-cognition network. This function is easily and reliable monitored during surgery with a line bisection test (on digital or analogical support). This task is strongly recommended with resections in the right hemisphere, that is commonly specialized in visuo-spatial cognition, and particularly in the resection involving the parietal lobe (intra-parietal sulcus) and the fronto-parietal and temporo-parietal junctions and the white matter underneath (Class III, Level C).[101, 104, 105]

Social cognition

Recently it was proposed and tested a task for recognition of the emotions with the goal to improve the social cognition outcome of patients submitted to LGGs resection. This is a version of the "reading the mind in the eyes test" (or "*test degli occhi*" in the Italian version) adapted to the intraoperative setting.[105, 106] Additional results have been found by using the 60-item Ekman test, which requires recognition of emotion from the whole face (Class III, Level C).[107]

Additional tasks for intraoperative monitoring

There are additional testing possibilities during intraoperative mapping. For example, in left parietal resection it could be useful to test verbal short-term memory (by means of simple repetition of sequence of digits)[108] or to monitor the number and calculation system by reading numbers or performing simple calculations (in this case during surgery on both the left and right parietal lobe (Class III, Level C).[109-111]

There are several other cognitive functions that can be explored in relation to each patient's specific activities, such as multilingualism (picture naming of objects in different languages) or music (using stimuli from the Montreal Evaluation Battery for Amusia) (Class III, Level C).

Estimation of extent of tumor resection (EOR)

There are several qualitative descriptions of EOR that have been reported in literature, which include "gross total resection," "near total resection," "subtotal resection," "partial resection," and "extended biopsy" that are mainly based on a subjective evaluation and definition. The objective estimation of tumor resection extension is of utmost importance and fundamental in planning postoperative adjuvant treatments and monitoring the growth curve of the residual tumor volume over time (Class II, Level B).[31, 68]

The evaluation of EOR relies on different methods, such as the product of the maximal diameter, the sum of areas on consecutive sequences, and three-dimensional, software-based calculations, etc. None of these methods have been validated in prospective studies. Preoperative and postoperative T2-weighted or FLAIR sequences are generally used.

The volumetric analysis can be carried out by manual segmentation of the areas of interest (ROI, region of interest) on MR images with FLAIR or T2 sequences using the DICOM format. The following formula is used to estimate the EOR: "EOR=preoperative tumor volume- postoperative tumor volume/preoperative tumor volume". Alternatively, the so-called ellipsoid volume technique or software with automatic or manual segmentation can be used (Class III, Level C).

The supratotal resection refers to an EOR beyond the tumor margins highlighted in the FLAIR sequences. There are currently no studies in the literature that provide a definitive recommendation on the role of the supratotal resection (Class III, Level C).[74] The supratotal resection, according to the functional margins (supraflair resection) identified with the cortico-subcortical mapping in awake surgery, has been associated in some series, with a better outcome both in terms of survival and better quality of life thanks to the control of epileptic seizures (Class III, Level C).[112]

Role of biopsy

Biopsy instead of resection is a relatively rare option in low grade glioma and usually indicated in selected patients

(*i.e.* elderly patients, poor clinical condition, significant comorbidity, deep-seated/eloquent tumor locations, such as the basal ganglia or brain stem, etc.). The risk of an under-grading of the lesion is extremely high. This can be explained by the vast intra-tumoral heterogeneity of gliomas, which can present malignant transformation foci within the tumor.[113, 114] Cumulative morbidity and mortality of stereotactic biopsy are about 2%.[114]

The stereotactic biopsy with frameless or framelink techniques are characterized by the same diagnostic accuracy and morbidity. The associations of advanced imaging techniques (MRI and/or PET) are recommended in order to increase the accuracy of the biopsy target[115] (Class III, Level C).

Incidental low-grade gliomas

Patients with incidental LGG (iLGG) represent an extremely rare clinical subgroup of LGG, the incidence ranging between 0.04% and 0.2% in the general population.[116] iLGG are defined as gliomas found on imaging studies obtained for reasons unrelated to the underlying tumor, which include headache (during the diagnostic work up of suspected primary headache, mainly migraine-like), trauma, otolaryngology disorders, or MRI studies conducted in healthy volunteers for research purposes.

The natural history of iLGG prior to discovery is poorly understood,[6, 117] and the question of clinical management has become a topic of increasing interest in the recent literature.[6, 118-128]

Although recent studies support the indication for early surgical resection even for incidental iLGG, the therapeutic strategy is still a subject of debate.[121, 122, 124] Several studies recommend MRI screening to calculate the tumor growth and plan surgery based on changes in tumor volume.[118, 129, 130] Other studies suggest a direct surgical approach once the second level diagnostic imaging screening with spectroscopic MRI is completed (Class III, Level C).[128]

Adjuvant treatments after surgery: risk groups

The post-surgical management of LGGs is traditionally based on the distinction of low-risk and high-risk patients.[131] There is a general concern that low-risk patients, as defined by age less than 40 years and/or total resection, should be observed with MRI without any adjuvant treatment (Class II, Level B). This applies to oligodendrogliomas IDH mutant and 1p/19q codeleted and diffuse astrocytomas IDH mutant, while the poor prognosis of diffuse astrocytomas IDH wild-type[132] has led to an aggressive approach consisting of combination of radiotherapy and chemotherapy, especially when EGFR amplification or TERT promoter mutations are present (Class III, Level C). However, the recent recognition of a molecular and survival heterogeneity of this group[133, 134] is suggesting that a more personalized approach in terms of choice of post-surgical management will be increasingly adopted (Class IV, Level C).[133] The definition of high-risk patients is somewhat heterogeneous among the different trials and in the clinical practice, and variably includes patients with age >40 years and/or incomplete resection and/or radiological progression and/or intractable seizures and/or worsening neurological symptoms. Recent clinical trials on high risk patients have shed light on the role of the different adjuvant treatments, but still there are unsolved questions. The phase III EORTC 22033-26033 trial has compared in high-risk grade II gliomas standard radiation-therapy with dose dense temozolomide as initial treatments:[135] the median progression-free survival (PFS) did not differ significantly between treatment groups (46 months with radiotherapy *versus* 39 months with temozolomide) (Class I, Level A). However, a subgroup analysis showed that there were no differences between initial radiotherapy and temozolomide among patients IDH mutant and 1p/19q codeleted (61.6 months for radiotherapy *versus* 55.0 months for temozolomide), while patients IDH mutant and 1p/19q non-codeleted who received temozolomide, had a significantly shorter PFS as compared to those who received radiotherapy (36 months *versus* 55 months, P=0.013). At time of analysis (4 years of follow-up) data on overall survival (OS) of the EORTC trial were not mature. The phase III RTOG 9802 trial has compared in high-risk grade II gliomas radiation with radiation followed by chemotherapy with PCV.[136] Overall, with a median follow-up of 11.9 years, both median PFS and OS were significantly longer for patients receiving the combined treatment (Class I, level A). Median PFS was 4.0 years for radiation therapy alone *versus* 10.4 years for radiation therapy followed by PCV with a 10-year PFS of 21% and 51%, respectively. Median OS was 7.8 years for radiation therapy alone *versus* 13.3 years for radiation followed by PCV with a 10-year OS of 40% and 60%, respectively. The advantage of the combined treatment was more pronounced in patients with oligodendrogliomas and in those with IDH1 mutant tumors. A single arm phase II trial from US, has investigated the role of initial temozolomide for incompletely resected grade II gliomas.[49] With a median follow-up of 7.5 years, PFS was 4.2 years and OS 9.7 years (Class III, Level C). At tumor

progression, patients received second surgery in 59%, radiotherapy in 54% and further chemotherapy in 45%. Interestingly 53% of patients were not treated by salvage radiotherapy for a median follow-up of 5.8 years, and patients with 1p/19q codeletion did not progress under treatment. Similar results have been reported by a recent phase II AINO study.[137] In particular, patients with IDH mutation and 1p/19q codeletion had the maximum advantage in terms of response to chemotherapy and in more than 60% salvage radiotherapy was delayed for a median around 8 years (Class III, Level C).

How can we translate the results of these trials in treatment recommendations for daily clinical practice? Overall, the values of PFS and OS after combined treatment appear clearly superior to any single modality. Unfortunately, none of these trials investigated the cognitive functions over time. Looking at the different histo-molecular subgroups of WHO 2016, both diffuse astrocytomas IDH mutant and 1p/19q non codeleted, and oligodendrogliomas IDH mutant and 1p/19q codeleted derive a higher benefit in terms of survival from radiation followed by chemotherapy as compared to either radiotherapy or temozolomide alone (Class II, Level B). However, considering that these patients have a definitive longer survival in comparison to diffuse astrocytomas IDH mutant, a long-term risk of cognitive defects following an early radiotherapy is still unknown, and they have a better chemosensitivity, an approach consisting of initial chemotherapy alone with salvage reoperation and/or RT at recurrence may be an alternative to better preserve over time the cognitive functions[138] (Class III, Level C). Whether temozolomide, which is better tolerated, can replace PCV in the combined treatment or, conversely, whether PCV is more effective than temozolomide as initial therapy, is unknown, and trials are ongoing to investigate these issues. Thus far, there are no randomized trials that have compared chemotherapy alone with chemoradiation.

Persisting seizures are often associated with partial resection or biopsy: both radiotherapy and chemotherapy can yield a seizure control[139, 140] (Class III, Level C): the rate could be higher in case of chemotherapy, but more studies are needed. An open issue is whether an early alkylating chemotherapy can accelerate a malignant transformation,[141] but this does not seem to occur in the clinical setting.

Technical aspects of radiotherapy

In patients receiving radiotherapy, doses of 50.4-54 Gy are delivered in 30-33 daily fractions of 1.8 Gy. The use of postoperative MRI fused with the planning CT is required for accurate target identification and delineation. Ideally an MRI scan less than four weeks old should be used. The gross tumor volume (GTV) include the entire region of high signal intensity on T2-weighted or fluid attenuation inversion recovery (FLAIR) sequence MRI, plus the regions of enhancement and the tumor resection cavity. A margin of 1-1.5 cm (constrained at anatomical barriers, *e.g.* ventricles, falx, tentorium cerebelli) should be added to the GTV to generate the clinical target volume (CTV) to cover microscopic spread of disease; a further 0.3-0.5 cm margin is added to generate the planning tumor volume (PTV) which takes into account uncertainties in patient set-up and treatment delivery. For treatment planning, new radiation techniques, intensity modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT), are recommended over three dimensional conformal techniques because provide superior target coverage and organs at risk sparing in tumors that are in close proximity to sensitive structures, *e.g.* brainstem and optic chiasm, or which have irregular shapes. In addition, IMRT/VMAT techniques may allow for reduced doses to hippocampi without compromising target dose coverage.

Cognitive function monitoring

The rates of cognitive deficits in LGGs in the literature vary widely ranging between 19% and 90%, due to differences in inclusion criteria, treatment regimens and neuropsychological tests. However, cognitive deficits documented by formal neuropsychological evaluations are relevant, varying from 29% in the case of patients with LGG not receiving radiotherapy[142] to 53% observed in patients who underwent radiotherapy.[143, 144]

However, neurocognitive outcome has been assessed systematically (from baseline to long term follow-up) in a limited number of studies, with a relatively small number of patients and short follow-up. Objective neuropsychological functioning should be assessed with a battery of standardized neuropsychological tests assessing language, memory, logical-executive functions, attention, visuo-constructional abilities. Objective neuropsychological tests should be integrated with patient reported outcome (PRO) tools and brain-cancer-specific HRQL outcomes (Class III, Level C).[145]

Several factors may influence neurocognitive deficits in LGGs including tumor itself, tumor-related epilepsy, treatments (surgery, radiotherapy) and psychological distress.[146]

A study reporting a long-term follow-up at a mean of

12 years after diagnosis in patients with LGG showed that long-term survivors of LGG who did not have radiotherapy had stable radiological and cognitive status, while a limited number of patients who received radiotherapy showed a progressive decline particularly in attentional functioning.[147] The significant change in attentional performance in patients who had radiotherapy was independent of fraction dose, tumor lateralization, extent of resection, age, and antiepileptic drug use. However, the results of this study do not exclude that cognitive deficits in other domains might be related to antiepileptic drug use, the extent of resection, age, and lateralization of the tumor.

Several studies reported that neurocognitive adverse effects of AEDs can add to cognitive decline induced by tumor effect and previous surgery or RT. The older AEDs (phenobarbital, phenytoin, carbamazepine and valproic acid) are known to decrease neurocognitive functioning. Moreover, these drugs have pharmacological interactions with several chemotherapeutic agents[146] (Class III, Level C). New generation AEDs including gabapentin, lamotrigine, levetiracetam, lacosamide, perampanel, seem to have fewer adverse neurocognitive effects than old drugs.[148] Recent data reported an increased risk of neurocognitive impairment associated with topiramate.[149]

The impact of surgery on neurocognitive functions is still controversial. Recent studies reported intraoperative stimulation mapping in infiltrative glioma resections to be associated with fewer late severe neurologic deficits and more extensive resection, with a favorable impact on survival[150, 151] (Class III, Level C). Given the limited number of studies, including pre- and postoperative neurocognitive evaluations, thus far the incidence and extent of neurocognitive dysfunctions related to surgery is still unpredictable. However, improvement in neurocognitive functioning has been observed in several studies after brain tumor resection (Class III, Level C).[131]

Prospective, longitudinal studies are needed to improve the knowledge on the magnitude of neurocognitive deficits experienced by patients with LGGs.

Cognitive dysfunctions may have a large impact on functional independence and patients' quality of life. In a large study evaluating HRQL in 195 patients with LGG, the neurocognitive deficits and epilepsy were associated with negative HRQL outcomes.[152] Recently, neurocognitive function is increasingly incorporated as secondary outcome measure in clinical trials in patients with LGG.[153]

Unfortunately, treatment options for these cognitive deficits are scarce. Over the last years, a few intervention studies have been conducted in brain tumor patients, which demonstrated the positive effects of cognitive rehabilitation. A randomized controlled trial (RCT) in 140 glioma patients with stable disease reported positive effects of a 6-week face-to-face cognitive rehabilitation program, that consisted of psychoeducation, use of compensatory skills and retraining. This suggests that cognitive rehabilitation may be an effective intervention for treating cognitive dysfunction in brain tumor patients (Class II, Level B).[154]

Pharmacological strategies for neuroprotection or symptomatic treatment have been explored in the last years but the results are not conclusive. Some psychostimulants, like methylphenidate and modafinil, have shown modest activity but their role needs to be confirmed in larger studies (Class III, Level C).[155]

Supportive care

Antiepileptic drugs

LGGs are the most epileptogenic gliomas in adults.[156] Seizure represents the most frequent presenting symptom in LGG patients, occurring in up to 80% of cases. Most commonly, LGG patients present with localization-related seizures depending on tumor location: for this reason the largest amount of patients present with focal seizures.[118]

Glioma patients who never suffered symptomatic seizures should be not treated by primary prophylaxis with antiepileptic drugs (AEDs)[157]and in case of prophylactic use for surgery, AED can be withdrawal within the first weeks after surgery (Class I, Level A). AEDs are indicated for brain tumor patients who develop at least one seizure. Surgery, radiotherapy and chemotherapy could contribute to seizure control of LGG associated epilepsy[118] (Class III, Level C).

Any study has demonstrated a clear superiority of a single antiepileptic drug in the control of tumor epilepsy[158] (Class III, Level C). Moreover, all AEDs are associated with side effects: usually these toxicities are more frequent and relevant in brain tumor patients in comparison to non-neoplastic populations.

AEDs can be divided into two main groups: first-generation drugs (*e.g.* phenytoin, carbamazepine, valproic acid, ethosuximide, benzodiazepines and barbiturates) and second-generation drugs (*e.g.* levetiracetam, felbamate, gabapentin, lamotrigine, pregabalin, tiagabin, zonisamide, oxcarbazepine, vigabatrin, lacosamide and topiramate).

In terms of long-term tolerability, the second-generation AEDs offer several advantages as compared to the first generation AEDs[31] (Class III, Level C). Furthermore, phenobarbital, carbamazepine, oxcarbazepine and phenytoin,

can act as enzyme inducers, and increase the metabolism and clearance of many antineoplastic agents.

Valproate is a very active AED and in the past was suggested as an active antineoplastic agent but this was not confirmed in larger studies.[159] Due to enzyme-inhibitory properties, hematological toxicities could be increased when valproate is used together with chemotherapeutic agents.[158]

Currently, levetiracetam from 1000 mg/day up to 3000 mg/day is the most used AED in brain tumor patients, because of lack of drug interactions, efficacy, tolerability, fast dosing, and intravenous availability.[160, 161] (Class III, Level C).

Lamotrigine and topiramate are attractive alternatives but with a longer dosing. Lacosamide as add-on treatment has shown activity in glioma patients and can be used by intravenous administration (Class III, Level C).

As for perampanel, the mechanism of action could suggest some antineoplastic activity as well, but this must be confirmed in prospective studies. Benzodiazepines should be used only for small periods of time.

In brain tumor patients with epilepsy driving capabilities are subject to the same regulations of non-tumor patients. Although antiepileptic treatment in brain tumor patients is strongly recommended after a single seizure only low level of evidence is available concerning the question of whether patients seizure-free after tumor treatment (surgery and/or radiation therapy and/or chemotherapy) may safely withdraw AEDs. A recent prospective observational study[162] (Class III, Level C), has shown a 26% rate of seizure relapse (in some cases related to/or preceding tumor progression) after a follow-up of 2.2 years. Thus, the choice of drug withdrawal remains personalized and that should take into account, both tumor-related and patients-related issues: among the latter, fear of relapse and concerns about driving limitations are relevant.

End-of-life seizures may represent an important clinical challenge in glioma patients, as reported in the EANO guidelines.[163]

Venous thromboembolism

Venous thromboembolism is a frequent event in glioma patients occurring both in the perioperative period and during postoperative adjuvant treatments or follow-up. Events are more frequent in high grade glioma patients, and data in LGG patients indicate a value of 2% of 653 patients enrolled in the German Glioma Network:[164] this figure is most likely underestimated, since data in the GGN include patients prospectively enrolled from 2004 to 2010 with a relatively short follow-up.

Indications for VTE prophylaxis specific for LGG patients are not available. Current evidence derives from studies and meta-analyses in high grade glioma indicating that intermittent pneumatic compression in the perioperative period is to be preferred to other mechanic methods (Class II, Level B) with addition of LMWH (enoxaparin 4000 IU SC, to be started 24 hours after surgery and after exclusion of hemorrhage by CT), leading to a reduction of VTE but also to a slight increase in hemorrhages[165] (Class III, Level C).

Treatment of acute VTE should follow the same protocol as in non-brain tumors, although in high grade gliomas anticoagulant therapy seems to increase by 3-fold the risk of hemorrhage, but only with 1% of fatal hemorrhages[166] (Class III, Level C). Positioning of caval filters is not suggested, as it leads to complications in a substantial proportion of patients.

The recent availability of direct oral anticoagulants has prompted their use in alternative to warfarin and LMWH in the management of VTE also in brain tumors. Thus far we have not sufficient data from the large randomized trials to provide high-level evidence,[167, 168] but data from retrospective studies do suggest a very low occurrence of ICH in patients receiving either rivaroxaban or apixaban in comparison with LMWH. It must be stressed that the 67 patients analyzed were mostly high grade /unspecified glioma patients.[169]

Concerning direct oral anticoagulants' (DOACs) use in patients with LGG, recommendations by the European Heart Rhythm Association warn against the co-administration of Levetiracetam and possibly valproate in this context, even if this evidence stems from pre-clinical data (induction of Pgp by these AEDs might reduce the plasma concentrations of DOACs).[170]

Steroids

Steroids have been used for decades in the treatment of brain tumor edema. Unfortunately, they are linked with numerous and well-defined side-effects, such as gastrointestinal bleeding, myopathy, osteoporosis, immunosuppression and psychiatric disturbances. Concerning, the optimal dose and the duration of treatment to be used in brain tumor patients no results from clinical trials are available. Usually, rate and severity of side effects correlate both with the total daily dose and duration of steroid treatment. For this reason, the need to continue steroid administration and dosage should be reviewed at each single visit. The tapering of corticosteroids should be rapidly started after major resection of the tumor. Patients who have undergone

only biopsy might need a prolongation of steroids administration in particular when starting of radiotherapy.

Dexamethasone (4-8 mg in single daily dose) has become the drug of choice in neuro-oncology, due to long half-life, low mineralocorticoid activity, and lower tendency to induce psychosis. No randomized studies have been performed in glioma patients, and the available evidence derives from studies in metastatic brain tumor patients.[171]

Other approaches to replace steroids as anti-edema drugs are being explored.

Treatment options at tumor progression

Despite a modern, multidisciplinary approach in the management of LGG, a relapse will most often occur. In this scenario, surgery is usually the first option to be discussed with the patient. In a recent review, the role of surgery in recurrent LGG was investigated. Retrospective studies only have been selected in an extensive literature search. The authors concluded that, the main aims of surgery in recurrent LGG is to provide relief of symptoms and improve diagnosis (malignant transformation),[172] but there is still insufficient evidence to make any specific recommendations. More recently, it has been suggested that when feasible, surgical resection improves quality of life, by reducing mass effect, incidence of seizures, risk of malignant transformation and finally improving overall survival.[173, 174] Overall, even if surgery is continuously gaining space in the management of recurrent tumors, its role is not definitively defined and thus it should be decided on case-by-case evaluation (Class III, Level C).

The non-surgical management of recurrent LGGs is evolving; however, the standard of care has not yet clearly defined.[175]

For patients with progressive disease who had received chemotherapy alone, radiotherapy is given at doses of 50.4-54 Gy in 28-30 fractions (see below), or 59.4 Gy in 33 fractions for LGG undergoing anaplastic transformation. The recent advances in technology allow for safe re-irradiation in patients who had already received a first course of radiotherapy. A retrospective study, evaluating the impact of re-irradiation on recurrent gliomas of any grade at diagnosis, has found time to RT <12 months, older age and tumor grade[176] as negative prognostic factors (Class III, Level C). Another study has added high KPS, smaller PTV volume and re-resection[177] as positive prognostic factors (Class III, Level C).

A recent large retrospective series from the Radiation Oncology Italian Association,[178] has confirmed that re-irradiation is a safe and feasible treatment with limited risk of toxicities. For large tumor volumes in close proximity to brain sensitive structures, *e.g.* chiasm or brainstem, conventional fractionation and hypofractionation regimens are recommended, due to better tolerance (Class III, Level C).

Complete resection followed by adjuvant re-irradiation is of benefit in some subgroups of "fit" patients.[179] MRI/PET has been suggested as a tool to improve treatment planning.[180]

Alkylating chemotherapy (PCV, TMZ) is an option for all patients, with responses in uncontrolled studies ranging between 25% and 55%[172] (Class III, Level C). Carboplatin is not effective,[172] while in case of "aggressive" progression with contrast enhancement and edema bevacizumab could be of clinical usefulness[181] (Class IV, Level C) even if in Europe can be administered only as off-label drug.

Rehabilitation

Rehabilitation in patients with LGG may be proposed either in the context of post-surgical sequelae involving motor function and disturbances in speech and swallowing, or in the context of long-standing cognitive impairment. This latter area, more recently identified as highly relevant in young patients with diffuse tumors with a moderate to long life expectancy, is the subject of intense investigation. Overall, evidence is of low quality due to heterogeneity in patient groups and interventions. Early post-surgical rehabilitation has been shown to improve functional outcome in patients with brain tumors[182] and may lead to improvements similar to those obtained in non-tumor conditions.[183] A recent small randomized trial,[184] including 16 patients with grade I or II glioma and 9 with HGG, has suggested the efficacy of an approach of rehabilitation of executive functions by goal management training (Class III, level C). Earlier on[185] it was shown in a controlled Australian study that an integrated multidisciplinary rehabilitation is effective (primary outcome was the score at Functional Independence Measure [FIM]) (Class III, Level C). Cognitive rehabilitation has also been proven of some effectiveness at 6 months on verbal memory and attention.[154] The same group has more recently reported the feasibility of a home-based exercise with remote guidance in grade II and III gliomas with stable disease.[186]

Follow-up

Post-treatment follow-up with clinical and neuroimaging surveillance has not been extensively evaluated in adult LGG. LGGs represent a heterogeneous group of tumors with variable natural histories, and patients may survive in a stable state for several years after diagnosis. The 5-year

overall survival (OS) and progression-free survival (PFS) rates in randomized studies ranged from 58% to 72% and 37% to 55%, respectively.[131] These data were generated at the beginning of last decade (starting from 2010 on), and the most recent figures of survival in molecular basis studies are even better.[187, 188] However, the likelihood of recurrence is largely a function of tumor histological type, molecular and clinical prognostic factors and previous treatments.

Early detection of recurrence is likely to improve survival and may increase treatment options and prevent clinical symptoms. However, there is no definitive evidence that identifying recurrent disease earlier improve the outcome.

The frequency of clinical and neuroimaging follow-up after treatment may change according to different risk of recurrence in the different subgroup of patients.

In clinical practice, the schedule of surveillance after conclusion of first line treatments in patients with high risk LGGs (IDH1-2 wild type and no 1p/19q co-deletion) are not different from that adopted in malignant gliomas (grade III and IV) with clinical evaluation and brain MRI every 3-6 months.[189] In patients presenting good predictors of outcome (IDH1-2 mutation and 1p/19q codeletion), clinical evaluation, including cognitive and epilepsy assessment, combining with neuroimaging monitoring may allow early identification of recurrence/progression. In slow growing, "indolent", non-enhancing tumor, a clinical progression with cognitive decline and/or increase of epilepsy frequency, may anticipate radiological changes on MRI.[139, 190] Moreover, advanced MRI techniques, such as MR perfusion, diffusion tensor imaging and MR spectroscopy, may be clinically useful for an early identification of recurrence/progression.[191] PET with methionine, fluoro-dopa or flouro-ethyltyrosine may be useful for identification of tumor areas with high metabolic activity, for a pre-treatment evaluation and/or monitoring treatment response and progression[34, 192] (Class III, Level C). However, further evidence is required to better define strategies for surveillance of LGG patients after first line treatment.

References

1. Hughes RA, Barnes MP, Baron JC, Brainin M; European Federation of Neurological Societies. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces. Eur J Neurol 2001;8:549–50.

2. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. Neuro-oncol 2018;20(suppl_4):iv1–86.

3. Rigau V, Zouaoui S, Mathieu-Daudé H, Darlix A, Maran A, Trétarre B, *et al.*; Société Française de Neuropathologie (SFNP), Société Française de Neurochirurgie (SFNC); Club de Neuro-Oncologie of the Société Française de Neurochirurgie (CNO-SFNC); Association des Neuro-Oncologues d'Expression Française (ANOCEF). French brain tumor database: 5-year histological results on 25 756 cases. Brain Pathol 2011;21:633–44.

4. Rasmussen BK, Hansen S, Laursen RJ, Kosteljanetz M, Schultz H, Nørgård BM, *et al.* Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I-IV in the the Danish Neuro-Oncology Registry. J Neurooncol 2017;135:571–9.

5. Crocetti E, Buzzoni C; AIRTUM Working Group. [The contribution of the Italian association of cancer registries (AIRTUM)]. Epidemiol Prev 2016;40(Suppl 2):28–30. Italian.

6. Potts MB, Smith JS, Molinaro AM, Berger MS. Natural history and surgical management of incidentally discovered low-grade gliomas. J Neurosurg 2012;116:365–72.

7. Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, *et al.* Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg 2008;108:227–35.

8. Rudà R, Bello L, Duffau H, Soffietti R. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. Neuro-oncol 2012;14(Suppl 4):iv55–64.

9. van Kessel E, Baumfalk AE, van Zandvoort MJ, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. J Neurooncol 2017;134:9–18.

10. Smits A, Jakola AS. Clinical Presentation, Natural History, and Prognosis of Diffuse Low-Grade Gliomas. Neurosurg Clin N Am 2019;30:35–42.

11. He Q, Zhang L, Zhang B, Shi X, Yi C, Zhang X. Diagnostic accuracy of 13N-ammonia PET, 11C-methionine PET and 18F-fluorodeoxyglucose PET: a comparative study in patients with suspected cerebral glioma. BMC Cancer 2019;19:332.

12. Ellingson BM, Bendszus M, Boxerman J, Barboriak D, Erickson BJ, Smits M, *et al.*; Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro-oncol 2015;17:1188–98.

13. Thust SC, Heiland S, Falini A, Jäger HR, Waldman AD, Sundgren PC, *et al.* Glioma imaging in Europe: A survey of 220 centres and recommendations for best clinical practice. Eur Radiol 2018;28:3306–17.

14. Castellano A, Falini A. Progress in neuro-imaging of brain tumors. Curr Opin Oncol 2016;28:484–93.

15. Fouke SJ, Benzinger T, Gibson D, Ryken TC, Kalkanis SN, Olson JJ. The role of imaging in the management of adults with diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline. J Neurooncol 2015;125:457–79.

16. Maier SE, Sun Y, Mulkern RV. Diffusion imaging of brain tumors. NMR Biomed 2010;23:849–64.

17. Miloushev VZ, Chow DS, Filippi CG. Meta-analysis of diffusion metrics for the prediction of tumor grade in gliomas. AJNR Am J Neuroradiol 2015;36:302–8.

18. Thust SC, Hassanein S, Bisdas S, Rees JH, Hyare H, Maynard JA, *et al.* Apparent diffusion coefficient for molecular subtyping of non-gadolinium-enhancing WHO grade II/III glioma: volumetric segmentation versus two-dimensional region of interest analysis. Eur Radiol 2018;28:3779–88.

19. Law M, Young RJ, Babb JS, Peccerelli N, Chheang S, Gruber ML, *et al.* Gliomas: predicting time to progression or survival with cerebral blood volume measurements at dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Radiology 2008;247:490–8.

20. Kickingereder P, Sahm F, Radbruch A, Wick W, Heiland S, Deimling A, *et al.* IDH mutation status is associated with a distinct hypoxia/angiogenesis transcriptome signature which is non-invasively predictable with rCBV imaging in human glioma. Sci Rep 2015;5:16238.

21. Anzalone N, Castellano A, Cadioli M, Conte GM, Cuccarini V, Bizzi

A, *et al.* Brain Gliomas: Multicenter Standardized Assessment of Dynamic Contrast-enhanced and Dynamic Susceptibility Contrast MR Images. Radiology 2018;287:933–43.

22. Oz G, Alger JR, Barker PB, Bartha R, Bizzi A, Boesch C, *et al.*; MRS Consensus Group. Clinical proton MR spectroscopy in central nervous system disorders. Radiology 2014;270:658–79.

23. Wilson M, Andronesi O, Barker PB, Bartha R, Bizzi A, Bolan PJ, *et al.* Methodological consensus on clinical proton MRS of the brain: review and recommendations. Magn Reson Med 2019;82:527–50.

24. Suh CH, Kim HS, Jung SC, Choi CG, Kim SJ. 2-Hydroxyglutarate MR spectroscopy for prediction of isocitrate dehydrogenase mutant glioma: a systemic review and meta-analysis using individual patient data. Neuro-oncol 2018;20:1573–83.

25. Castellano A, Cirillo S, Bello L, Riva M, Falini A. Functional MRI for Surgery of Gliomas. Curr Treat Options Neurol 2017;19:34.

26. Raffa G, Conti A, Scibilia A, Sindorio C, Quattropani MC, Visocchi M, *et al.* Functional Reconstruction of Motor and Language Pathways Based on Navigated Transcranial Magnetic Stimulation and DTI Fiber Tracking for the Preoperative Planning of Low Grade Glioma Surgery: A New Tool for Preservation and Restoration of Eloquent Networks. Acta Neurochir Suppl (Wien) 2017;124:251–61.

27. Raffa G, Conti A, Scibilia A, Cardali SM, Esposito F, Angileri FF, *et al.* The Impact of Diffusion Tensor Imaging Fiber Tracking of the Corticospinal Tract Based on Navigated Transcranial Magnetic Stimulation on Surgery of Motor-Eloquent Brain Lesions. Neurosurgery 2018;83:768–82.

28. Raffa G, Quattropani MC, Scibilia A, Conti A, Angileri FF, Esposito F, *et al.* Surgery of language-eloquent tumors in patients not eligible for awake surgery: the impact of a protocol based on navigated transcranial magnetic stimulation on presurgical planning and language outcome, with evidence of tumor-induced intra-hemispheric plasticity. Clin Neurol Neurosurg 2018;168:127–39.

29. la Fougère C, Suchorska B, Bartenstein P, Kreth FW, Tonn JC. Molecular imaging of gliomas with PET: opportunities and limitations. Neuro-oncol 2011;13:806–19.

30. Albert NL, Weller M, Suchorska B, Galldiks N, Soffietti R, Kim MM, *et al.* Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. Neuro-oncol 2016;18:1199–208.

31. Weller M, van den Bent M, Tonn JC, Stupp R, Preusser M, Cohen-Jonathan-Moyal E, *et al.*; European Association for Neuro-Oncology (EANO) Task Force on Gliomas. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncol 2017;18:e315–29.

32. Brasil Caseiras G, Ciccarelli O, Altmann DR, Benton CE, Tozer DJ, Tofts PS, *et al.* Low-grade gliomas: six-month tumor growth predicts patient outcome better than admission tumor volume, relative cerebral blood volume, and apparent diffusion coefficient. Radiology 2009;253:505–12.

33. Rees J, Watt H, Jäger HR, Benton C, Tozer D, Tofts P, *et al.* Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation. Eur J Radiol 2009;72:54–64.

34. Roelcke U, Wyss MT, Nowosielski M, Rudà R, Roth P, Hofer S, *et al.* Amino acid positron emission tomography to monitor chemotherapy response and predict seizure control and progression-free survival in WHO grade II gliomas. Neuro-oncol 2016;18:744–51.

35. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al.* The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803–20.

36. Ceccarelli M, Barthel FP, Malta TM, Sabedot TS, Salama SR, Murray BA, *et al.*; TCGA Research Network. Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma. Cell 2016;164:550–63.

37. Caruso G, Merlo L, Caffo M. Nanotechnologies for brain tumor therapy. In: Mathur AB, editor. Nanotechnology in Cancer. Amsterdam: Elsevier; 2017. p. 171–90.

38. Brat DJ, Verhaak RG, Aldape KD, Yung WK, Salama SR, Cooper LA, *et al.*; Cancer Genome Atlas Research Network. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med 2015;372:2481–98.

39. van den Bent MJ, Smits M, Kros JM, Chang SM. Diffuse Infiltrating Oligodendroglioma and Astrocytoma. J Clin Oncol 2017;35:2394–401.

40. La Torre D, Conti A, Aguennouz MH, De Pasquale MG, Romeo S, Angileri FF, *et al.* Telomere length modulation in human astroglial brain tumors. PLoS One 2013;8:e64296.

41. Bauman G, Lote K, Larson D, Stalpers L, Leighton C, Fisher B, *et al.* Pretreatment factors predict overall survival for patients with low-grade glioma: a recursive partitioning analysis. Int J Radiat Oncol Biol Phys 1999;45:923–9.

42. Daniels TB, Brown PD, Felten SJ, Wu W, Buckner JC, Arusell RM, *et al.* Validation of EORTC prognostic factors for adults with low-grade glioma: a report using intergroup 86-72-51. Int J Radiat Oncol Biol Phys 2011;81:218–24.

43. Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, *et al.*; European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group; European Organization for Research and Treatment of Cancer Radiotherapy Cooperative Group. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 2002;20:2076–84.

44. Rudà R. New developments and new dilemmas in lower-grade gliomas. Neuro-oncol 2019;21:828–9.

45. Pallud J, Capelle L, Taillandier L, Fontaine D, Mandonnet E, Guillevin R, *et al.* Prognostic significance of imaging contrast enhancement for WHO grade II gliomas. Neuro-oncol 2009;11:176–82.

46. Chaichana KL, McGirt MJ, Niranjan A, Olivi A, Burger PC, Quinones-Hinojosa A. Prognostic significance of contrast-enhancing low-grade gliomas in adults and a review of the literature. Neurol Res 2009;31:931–9.

47. Suchorska B, Schüller U, Biczok A, Lenski M, Albert NL, Giese A, *et al.* Contrast enhancement is a prognostic factor in IDH1/2 mutant, but not in wild-type WHO grade II/III glioma as confirmed by machine learning. Eur J Cancer 2019;107:15–27.

48. Ius T, Isola M, Budai R, Pauletto G, Tomasino B, Fadiga L, *et al.* 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: clinical article. J Neurosurg 2012;117:1039–52.

49. Wahl M, Phillips JJ, Molinaro AM, Lin Y, Perry A, Haas-Kogan DA, *et al.* Chemotherapy for adult low-grade gliomas: clinical outcomes by molecular subtype in a phase II study of adjuvant temozolomide. Neuro-oncol 2017;19:242–51.

50. Pallud J, Mandonnet E, Duffau H, Kujas M, Guillevin R, Galanaud D, *et al.* Prognostic value of initial magnetic resonance imaging growth rates for World Health Organization grade II gliomas. Ann Neurol 2006;60:380–3.

51. Caseiras GB, Chheang S, Babb J, Rees JH, Pecerrelli N, Tozer DJ, *et al.* Relative cerebral blood volume measurements of low-grade gliomas predict patient outcome in a multi-institution setting. Eur J Radiol 2010;73:215–20.

52. Guillevin R, Menuel C, Taillibert S, Capelle L, Costalat R, Abud L, *et al.* Predicting the outcome of grade II glioma treated with temozolomide using proton magnetic resonance spectroscopy. Br J Cancer 2011;104:1854–61.

53. Law I, Albert NL, Arbizu J, Boellaard R, Drzezga A, Galldiks N, *et al.* Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [18F]FDG: version 1.0. Eur J Nucl Med Mol Imaging 2019;46:540–57.

54. Roelcke U, Leenders KL. PET in neuro-oncology. J Cancer Res Clin Oncol 2001;127:2–8.

55. De Witte O, Goldberg I, Wikler D, Rorive S, Damhaut P, Monclus M, *et al.* Positron emission tomography with injection of methionine as a prognostic factor in glioma. J Neurosurg 2001;95:746–50.

56. Ribom D, Eriksson A, Hartman M, Engler H, Nilsson A, Långström B, *et al.* Positron emission tomography (11)C-methionine and survival in patients with low-grade gliomas. Cancer 2001;92:1541–9.

57. Floeth FW, Pauleit D, Sabel M, Stoffels G, Reifenberger G, Riemenschneider MJ, *et al.* Prognostic value of O-(2-18F-fluoroethyl)-L-tyrosine PET and MRI in low-grade glioma. J Nucl Med 2007;48:519–27.

58. Jansen NL, Suchorska B, Wenter V, Eigenbrod S, Schmid-Tannwald C, Zwergal A, *et al.* Dynamic 18F-FET PET in newly diagnosed astrocytic low-grade glioma identifies high-risk patients. J Nucl Med 2014;55:198–203.

59. Ius T, Ciani Y, Ruaro ME, Isola M, Sorrentino M, Bulfoni M, *et al.* An NF-κB signature predicts low-grade glioma prognosis: a precision medicine approach based on patient-derived stem cells. Neuro-oncol 2018;20:776–87.

60. Wijnenga M, French P, Dubbink H, Dinjens W, Atmodimedjo P, Kros J, *et al.* SURG-05. The impact of surgery in molecularly defined low-grade glioma: an integrated clinical, radiological and molecular analysis. Neuro-oncol 2017;19(Suppl 6):vi236.

61. Claus EB, Horlacher A, Hsu L, Schwartz RB, Dello-Iacono D, Talos F, *et al.* Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. Cancer 2005;103:1227–33.

62. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, *et al.* Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008;26:1338–45.

63. Sanai N, Chang S, Berger MS. Low-grade gliomas in adults. J Neurosurg 2011;115:948–65.

64. Sanai N, Polley MY, Berger MS. Insular glioma resection: assessment of patient morbidity, survival, and tumor progression. J Neurosurg 2010;112:1–9.

65. Skrap M, Mondani M, Tomasino B, Weis L, Budai R, Pauletto G, *et al.* Surgery of insular nonenhancing gliomas: volumetric analysis of tumoral resection, clinical outcome, and survival in a consecutive series of 66 cases. Neurosurgery 2012;70:1081–93, discussion 1093–4.

66. Capelle L, Fontaine D, Mandonnet E, Taillandier L, Golmard JL, Bauchet L, *et al.*; French Réseau d'Étude des Gliomes. Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases: clinical article. J Neurosurg 2013;118:1157–68.

67. Nitta M, Muragaki Y, Maruyama T, Ikuta S, Komori T, Maebayashi K, *et al.* Proposed therapeutic strategy for adult low-grade glioma based on aggressive tumor resection. Neurosurg Focus 2015;38:E7.

68. Clark VE, Cahill DP. Extent of Resection Versus Molecular Classification: What Matters When? Neurosurg Clin N Am 2019;30:95–101.

69. Rizzo V, Terranova C, Conti A, Germanò A, Alafaci C, Raffa G, *et al.* Preoperative functional mapping for rolandic brain tumor surgery. Neurosci Lett 2014;583:136–41.

70. Raffa G, Quattropani MC, Germanò A. When imaging meets neurophysiology: the value of navigated transcranial magnetic stimulation for preoperative neurophysiological mapping prior to brain tumor surgery. Neurosurg Focus 2019;47:E10.

71. Sanai N. How to Build a Neurosurgical Oncology Practice Specializing in Gliomas. Neurosurg Clin N Am 2019;30:129–36.

72. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 2012;30:2559–65.

73. Duffau H. Awake mapping is not an additional surgical technique but an alternative philosophy in the management of low-grade glioma patients. Neurosurg Rev 2018;41:689–91.

74. Duffau H. Is non-awake surgery for supratentorial adult low-grade glioma treatment still feasible? Neurosurg Rev 2018;41:133–9.

75. Skrap M, Marin D, Ius T, Fabbro F, Tomasino B. Brain mapping: a novel intraoperative neuropsychological approach. J Neurosurg 2016;125:877–87.

76. Barzilai O, Ben Moshe S, Sitt R, Sela G, Shofty B, Ram Z. Improvement in cognitive function after surgery for low-grade glioma. J Neurosurg 2018;130:1–9.

77. Dallabona M, Sarubbo S, Merler S, Corsini F, Pulcrano G, Rozzanigo U, *et al.* Impact of mass effect, tumor location, age, and surgery on the cognitive outcome of patients with high-grade gliomas: a longitudinal study. Neurooncol Pract 2017;4:229–40.

78. Duffau H, Taillandier L. New concepts in the management of diffuse low-grade glioma: proposal of a multistage and individualized therapeutic approach. Neuro-oncol 2015;17:332–42.

79. Fountain DM, Allen D, Joannides AJ, Nandi D, Santarius T, Chari A. Reporting of patient-reported health-related quality of life in adults with diffuse low-grade glioma: a systematic review. Neuro-oncol 2016;18:1475–86.

80. Herbet G, Maheu M, Costi E, Lafargue G, Duffau H. Mapping neuroplastic potential in brain-damaged patients. Brain 2016;139:829–44.

81. van den Bent MJ, Wefel JS, Schiff D, Taphoorn MJ, Jaeckle K, Junck L, *et al.* Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol 2011;12:583–93.

82. Duffau H. Preserving quality of life is not incompatible with increasing overall survival in diffuse low-grade glioma patients. Acta Neurochir (Wien) 2015;157:165–7.

83. Mandonnet E, Sarubbo S, Duffau H. Proposal of an optimized strategy for intraoperative testing of speech and language during awake mapping. Neurosurg Rev 2017;40:29–35.

84. Rofes A, Mandonnet E, Godden J, Baron MH, Colle H, Darlix A, *et al.* Survey on current cognitive practices within the European Low-Grade Glioma Network: towards a European assessment protocol. Acta Neurochir (Wien) 2017;159:1167–78.

85. Rostomily RC, Keles GE, Berger MS. Radical surgery in the management of low-grade and high-grade gliomas. Baillieres Clin Neurol 1996;5:345–69.

86. Reijneveld JC, Sitskoorn MM, Klein M, Nuyen J, Taphoorn MJ. Cognitive status and quality of life in patients with suspected versus proven low-grade gliomas. Neurology 2001;56:618–23.

87. Fernández Coello A, Moritz-Gasser S, Martino J, Martinoni M, Matsuda R, Duffau H. Selection of intraoperative tasks for awake mapping based on relationships between tumor location and functional networks. J Neurosurg 2013;119:1380–94.

88. De Witte E, Satoer D, Colle H, Robert E, Visch-Brink E, Mariën P. Subcortical language and non-language mapping in awake brain surgery: the use of multimodal tests. Acta Neurochir (Wien) 2015;157:577–88.

89. De Witte E, Satoer D, Robert E, Colle H, Verheyen S, Visch-Brink E, *et al.* The Dutch Linguistic Intraoperative Protocol: a valid linguistic approach to awake brain surgery. Brain Lang 2015;140:35–48.

90. Catricalà E, Della Rosa PA, Ginex V, Mussetti Z, Plebani V, Cappa SF. An Italian battery for the assessment of semantic memory disorders. Neurol Sci 2013;34:985–93.

91. Laiacona M, Barbarotto R, Baratelli E, Capitani E. Revised and extended norms for a picture naming test sensitive to category dissociations. Neurol Sci 2016;37:1499–510.

92. Bello L, Gallucci M, Fava M, Carrabba G, Giussani C, Acerbi F, *et al.* Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. Neurosurgery 2007;60:67–80, discussion 80–2.

93. Papagno C, Gallucci M, Casarotti A, Castellano A, Falini A, Fava E, *et al.* Connectivity constraints on cortical reorganization of neural circuits involved in object naming. Neuroimage 2011;55:1306–13.

94. Duffau H. Stimulation mapping of white matter tracts to study brain functional connectivity. Nat Rev Neurol 2015;11:255–65.

95. Papagno C, Miracapillo C, Casarotti A, Romero Lauro LJ, Castellano A, Falini A, *et al.* What is the role of the uncinate fasciculus? Surgical removal and proper name retrieval. Brain 2011;134:405–14.

96. Rofes A, Miceli G. Language mapping with verbs and sentences in awake surgery: a review. Neuropsychol Rev 2014;24:185–99.

97. Moritz-Gasser S, Duffau H. The anatomo-functional connectivity of word repetition: insights provided by awake brain tumor surgery. Front Hum Neurosci 2013;7:405.

98. Sierpowska J, Gabarrós A, Fernandez-Coello A, Camins À, Castañer S, Juncadella M, *et al.* Words are not enough: nonword repetition as an indicator of arcuate fasciculus integrity during brain tumor resection. J Neurosurg 2017;126:435–45.

99. Rofes A, Spena G, Miozzo A, Fontanella MM, Miceli G. Advantages and disadvantages of intraoperative language tasks in awake surgery: a three-task approach for prefrontal tumors. J Neurosurg Sci 2015;59:337–49.

100. Wager M, Du Boisgueheneuc F, Pluchon C, Bouyer C, Stal V, Bataille B, *et al.* Intraoperative monitoring of an aspect of executive functions: administration of the Stroop test in 9 adult patients during awake surgery for resection of frontal glioma. Neurosurgery 2013;72(Suppl Operative):ons169–80, discussion ons180–1.

101. Duffau H. Awake surgery for nonlanguage mapping. Neurosurgery 2010;66:523–8, discussion 528–9.

102. Gras-Combe G, Moritz-Gasser S, Herbet G, Duffau H. Intraoperative subcortical electrical mapping of optic radiations in awake surgery for glioma involving visual pathways. J Neurosurg 2012;117:466–73.

103. Sarubbo S, De Benedictis A, Merler S, Mandonnet E, Balbi S, Granieri E, *et al.* Towards a functional atlas of human white matter. Hum Brain Mapp 2015;36:3117–36.

104. Vallar G, Bello L, Bricolo E, Castellano A, Casarotti A, Falini A, *et al.* Cerebral correlates of visuospatial neglect: a direct cerebral stimulation study. Hum Brain Mapp 2014;35:1334–50.

105. Vilasboas T, Herbet G, Duffau H. Challenging the Myth of Right Nondominant Hemisphere: Lessons from Corticosubcortical Stimulation Mapping in Awake Surgery and Surgical Implications. World Neurosurg 2017;103:449–56.

106. Herbet G, Lafargue G, Moritz-Gasser S, Bonnetblanc F, Duffau H. Interfering with the neural activity of mirror-related frontal areas impairs mentalistic inferences. Brain Struct Funct 2015;220:2159–69.

107. Papagno C, Pisoni A, Mattavelli G, Casarotti A, Comi A, Fumagalli F, *et al.* Specific disgust processing in the left insula: new evidence from direct electrical stimulation. Neuropsychologia 2016;84:29–35.

108. Papagno C, Comi A, Riva M, Bizzi A, Vernice M, Casarotti A, *et al.* Mapping the brain network of the phonological loop. Hum Brain Mapp 2017;38:3011–24.

109. Della Puppa A, De Pellegrin S, d'Avella E, Gioffrè G, Munari M, Saladini M, *et al.* Right parietal cortex and calculation processing: intraoperative functional mapping of multiplication and addition in patients affected by a brain tumor. J Neurosurg 2013;119:1107–11.

110. Della Puppa A, De Pellegrin S, Lazzarini A, Gioffrè G, Rustemi O, Cagnin A, *et al.* Subcortical mapping of calculation processing in the right parietal lobe. J Neurosurg 2015;122:1038–41.

111. Semenza C, Salillas E, De Pallegrin S, Della Puppa A. Balancing the 2 Hemispheres in Simple Calculation: Evidence From Direct Cortical Electrostimulation. Cereb Cortex 2017;27:4806–14.

112. Yordanova YN, Moritz-Gasser S, Duffau H. Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection. Clinical article. J Neurosurg 2011;115:232–9.

113. Muragaki Y, Chernov M, Maruyama T, Ochiai T, Taira T, Kubo O, *et al.* Low-grade glioma on stereotactic biopsy: how often is the diagnosis accurate? Minim Invasive Neurosurg 2008;51:275–9.

114. Pedeutour-Braccini Z, Burel-Vandenbos F, Gozé C, Roger C, Bazin A, Costes-Martineau V, *et al.* Microfoci of malignant progression in diffuse low-grade gliomas: towards the creation of an intermediate grade in glioma classification? Virchows Arch 2015;466:433–44.

115. Thon N, Kunz M, Lemke L, Jansen NL, Eigenbrod S, Kreth S, *et al.* Dynamic 18F-FET PET in suspected WHO grade II gliomas defines distinct biological subgroups with different clinical courses. Int J Cancer 2015;136:2132–45.

116. Eskandary H, Sabba M, Khajehpour F, Eskandari M. Incidental findings in brain computed tomography scans of 3000 head trauma patients. Surg Neurol 2005;63:550–3, discussion 553.

117. Jakola AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgård G, *et al.* Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. JAMA 2012;308:1881–8.

118. Pallud J, Fontaine D, Duffau H, Mandonnet E, Sanai N, Taillandier L, *et al.* Natural history of incidental World Health Organization grade II gliomas. Ann Neurol 2010;68:727–33.

119. Pallud J, Mandonnet E. Incidental low-grade gliomas. J Neurosurg 2013;118:702–4.

120. Zhang ZY, Chan AK, Ng HK, Ding XJ, Li YX, Shi ZF, *et al.* Surgically treated incidentally discovered low-grade gliomas are mostly IDH mutated and 1p19q co-deleted with favorable prognosis. Int J Clin Exp Pathol 2014;7:8627–36.

121. Lima GL, Duffau H. Is there a risk of seizures in "preventive" awake surgery for incidental diffuse low-grade gliomas? J Neurosurg 2015;122:1397–405.

122. Lima GL, Zanello M, Mandonnet E, Taillandier L, Pallud J, Duffau H. Incidental diffuse low-grade gliomas: from early detection to preventive neuro-oncological surgery. Neurosurg Rev 2016;39:377–84.

123. Lima GL, Dezamis E, Corns R, Rigaux-Viode O, Moritz-Gasser S, Roux A, *et al.* Surgical resection of incidental diffuse gliomas involving eloquent brain areas. Rationale, functional, epileptological and oncological outcomes. Neurochirurgie 2017;63:250–8.

124. Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. Acta Neurochir (Wien) 2016;158:51–8.

125. Cochereau J, Herbet G, Duffau H. Patients with incidental WHO grade II glioma frequently suffer from neuropsychological disturbances. Acta Neurochir (Wien) 2016;158:305–12.

126. Cochereau J, Herbet G, Rigau V, Duffau H. Acute progression of untreated incidental WHO Grade II glioma to glioblastoma in an asymptomatic patient. J Neurosurg 2016;124:141–5.

127. Opoku-Darko M, Lang ST, Artindale J, Cairncross JG, Sevick RJ, Kelly JJ. Surgical management of incidentally discovered diffusely infiltrating low-grade glioma. J Neurosurg 2018;129:19–26.

128. Ius T, Cesselli D, Isola M, Pauletto G, Tomasino B, D'Auria S, *et al.* Incidental Low-Grade Gliomas: Single-Institution Management Based on Clinical, Surgical, and Molecular Data. Neurosurgery 2020;86:391–9.

129. Mandonnet E, de Witt Hamer P, Pallud J, Bauchet L, Whittle I, Duffau H. Silent diffuse low-grade glioma: toward screening and preventive treatment? Cancer 2014;120:1758–62.

130. Shah AH, Madhavan K, Sastry A, Komotar RJ. Managing intracranial incidental findings suggestive of low-grade glioma: learning from experience. World Neurosurg 2013;80:e75–7.

131. Soffietti R, Baumert BG, Bello L, von Deimling A, Duffau H, Frénay M, *et al.*; European Federation of Neurological Societies. Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force. Eur J Neurol 2010;17:1124–33.

132. Aibaidula A, Chan AK, Shi Z, Li Y, Zhang R, Yang R, *et al.* Adult IDH wild-type lower-grade gliomas should be further stratified. Neuro-oncol 2017;19:1327–37.

133. Brat DJ, Aldape K, Colman H, Holland EC, Louis DN, Jenkins RB, *et al.* cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". Acta Neuropathol 2018;136:805–10.

134. Poulen G, Gozé C, Rigau V, Duffau H. Huge heterogeneity in survival in a subset of adult patients with resected, wild-type isocitrate dehydrogenase status, WHO grade II astrocytomas. J Neurosurg 2018;1–10.

135. Baumert BG, Hegi ME, van den Bent MJ, von Deimling A, Gorlia T, Hoang-Xuan K, *et al.* Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. Lancet Oncol 2016;17:1521–32.

136. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, *et al.* Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. N Engl J Med 2016;374:1344–55.

137. Rudà R, Pellerino A, Pace A, Carapella CM, Dealis C, Caroli M, *et al.* Efficacy of initial temozolomide for high-risk low grade gliomas in a phase II AINO (Italian Association for Neuro-Oncology) study: a post-hoc analysis within molecular subgroups of WHO 2016. J Neurooncol 2019;145:115–23.

138. Rudà R, Bruno F, Soffietti R. What Have We Learned from Recent Clinical Studies in Low-Grade Gliomas? Curr Treat Options Neurol 2018;20:33.

139. Koekkoek JA, Dirven L, Heimans JJ, Postma TJ, Vos MJ, Reijneveld JC, *et al.* Seizure reduction is a prognostic marker in low-grade glioma patients treated with temozolomide. J Neurooncol 2016;126:347–54.

140. Rudà R, Magliola U, Bertero L, Trevisan E, Bosa C, Mantovani C, *et al.* Seizure control following radiotherapy in patients with diffuse gliomas: a retrospective study. Neuro-oncol 2013;15:1739–49.

141. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, McLean CY, *et al.* Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science 2014;343:189–93.

142. Klein M, Heimans JJ, Aaronson NK, van der Ploeg HM, Grit J, Muller M, *et al.* Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. Lancet 2002;360:1361–8.

143. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. Neurosurgery 2000;47:324–33, discussion 333–4.

144. Zucchella C, Bartolo M, Di Lorenzo C, Villani V, Pace A. Cognitive impairment in primary brain tumors outpatients: a prospective cross-sectional survey. J Neurooncol 2013;112:455–60.

145. Gabel N, Altshuler DB, Brezzell A, Briceño EM, Boileau NR, Miklja Z, *et al.* Health Related Quality of Life in Adult Low and High-Grade Glioma Patients Using the National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS) and Neuro-QOL Assessments. Front Neurol 2019;10:212.

146. Klein M. Neurocognitive functioning in adult WHO grade II gliomas: impact of old and new treatment modalities. Neuro-oncol 2012;14(Suppl 4):iv17–24.

147. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, *et al.* Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol 2009;8:810–8.

148. Vecht C, Royer-Perron L, Houillier C, Huberfeld G. Seizures and Anticonvulsants in Brain Tumours: Frequency, Mechanisms and Anti-Epileptic Management. Curr Pharm Des 2017;23:6464–87.

149. Meador KJ. Cognitive and memory effects of the new antiepileptic drugs. Epilepsy Res 2006;68:63–7.

150. Duffau H. New concepts in surgery of WHO grade II gliomas: functional brain mapping, connectionism and plasticity—a review. J Neurooncol 2006;79:77–115.

151. Klein M, Duffau H, De Witt Hamer PC. Cognition and resective surgery for diffuse infiltrative glioma: an overview. J Neurooncol 2012;108:309–18.

152. Aaronson NK, Taphoorn MJ, Heimans JJ, Postma TJ, Gundy CM, Beute GN, *et al.* Compromised health-related quality of life in patients with low-grade glioma. J Clin Oncol 2011;29:4430–5.

153. Meyers CA, Rock EP, Fine HA. Refining endpoints in brain tumor clinical trials. J Neurooncol 2012;108:227–30.

154. Gehring K, Sitskoorn MM, Gundy CM, Sikkes SA, Klein M, Postma TJ, *et al.* Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. J Clin Oncol 2009;27:3712–22.

155. Rapp SR, Case LD, Peiffer A, Naughton MM, Chan MD, Stieber VW, *et al.* Donepezil for Irradiated Brain Tumor Survivors: A Phase III Randomized Placebo-Controlled Clinical Trial. J Clin Oncol 2015;33:1653–9.

156. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 2007;6:421–30.

157. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, *et al.* Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;54:1886–93.

158. Vecht CJ, Kerkhof M, Duran-Pena A. Seizure prognosis in brain tumors: new insights and evidence-based management. Oncologist 2014;19:751–9.

159. Happold C, Gorlia T, Chinot O, Gilbert MR, Nabors LB, Wick W, *et al.* Does Valproic Acid or Levetiracetam Improve Survival in Glioblastoma? A Pooled Analysis of Prospective Clinical Trials in Newly Diagnosed Glioblastoma. J Clin Oncol 2016;34:731–9.

160. Dinapoli L, Maschio M, Jandolo B, Fabi A, Pace A, Sperati F, *et al.* Quality of life and seizure control in patients with brain tumor-related epilepsy treated with levetiracetam monotherapy: preliminary data of an open-label study. Neurol Sci 2009;30:353–9.

161. Iuchi T, Kuwabara K, Matsumoto M, Kawasaki K, Hasegawa Y, Sakaida T. Levetiracetam versus phenytoin for seizure prophylaxis during and early after craniotomy for brain tumours: a phase II prospective, randomised study. J Neurol Neurosurg Psychiatry 2015;86:1158–62.

162. Kerkhof M, Koekkoek JA, Vos MJ, van den Bent MJ, Taal W, Postma TJ, *et al.* Withdrawal of antiepileptic drugs in patients with low grade and anaplastic glioma after long-term seizure freedom: a prospective observational study. J Neurooncol 2019;142:463–70.

163. Pace A, Dirven L, Koekkoek JA, Golla H, Fleming J, Rudà R, *et al.*; European Association of Neuro-Oncology palliative care task force. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. Lancet Oncol 2017;18:e330–40.

164. Seidel C, Hentschel B, Simon M, Schnell O, Heese O, Tatagiba M, *et al.* A comprehensive analysis of vascular complications in 3,889 glioma patients from the German Glioma Network. J Neurol 2013;260:847–55.

165. Salmaggi A, Simonetti G, Trevisan E, Beecher D, Carapella CM, DiMeco F, *et al.* Perioperative thromboprophylaxis in patients with craniotomy for brain tumours: a systematic review. J Neurooncol 2013;113:293–303.

166. Zwicker JI, Karp Leaf R, Carrier M. A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. J Thromb Haemost 2016;14:1736–40.

167. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, *et al.* Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol 2018;36:2017–23.

168. Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, *et al.*; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406–15.

169. Carney BJ, Uhlmann EJ, Puligandla M, Mantia C, Weber GM, Neuberg DS, *et al.* Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. J Thromb Haemost 2019;17:72–6.

170. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, *et al.* [The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary]. Kardiol Pol 2018;76:1283–98. Polish.

171. Vecht CJ, Hovestadt A, Verbiest HB, van Vliet JJ, van Putten WL. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology 1994;44:675–80.

172. Nahed BV, Redjal N, Brat DJ, Chi AS, Oh K, Batchelor TT, *et al.* Management of patients with recurrence of diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline. J Neurooncol 2015;125:609–30.

173. Picart T, Herbet G, Moritz-Gasser S, Duffau H. Iterative Surgical Resections of Diffuse Glioma With Awake Mapping: How to Deal With Cortical Plasticity and Connectomal Constraints? Neurosurgery 2019;85:105–16.

174. Ferracci FX, Michaud K, Duffau H. The landscape of postsurgical recurrence patterns in diffuse low-grade gliomas. Crit Rev Oncol Hematol 2019;138:148–55.

175. Post CC, Kramer MC, Smid EJ, van der Weide HL, Kleynen CE, Heesters MA, *et al.* Patterns of re-irradiation for recurrent gliomas and validation of a prognostic score. Radiother Oncol 2019;130:156–63.

176. Combs SE, Edler L, Rausch R, Welzel T, Wick W, Debus J. Generation and validation of a prognostic score to predict outcome after re-irradiation of recurrent glioma. Acta Oncol 2013;52:147–52.

177. Kessel KA, Hesse J, Straube C, Zimmer C, Schmidt-Graf F, Schlegel J, *et al.* Modification and optimization of an established prognostic score after re-irradiation of recurrent glioma. PLoS One 2017;12:e0180457.

178. Navarria P, Minniti G, Clerici E, Tomatis S, Pinzi V, Ciammella P, *et al.* Re-irradiation for recurrent glioma: outcome evaluation, toxicity and prognostic factors assessment. A multicenter study of the Radiation Oncology Italian Association (AIRO). J Neurooncol 2019;142:59–67.

179. Combs SE, Kessel KA, Hesse J, Straube C, Zimmer C, Schmidt-Graf F, *et al.* Moving Second Courses of Radiotherapy Forward: Early Re-Irradiation After Surgical Resection for Recurrent Gliomas Improves Efficacy With Excellent Tolerability. Neurosurgery 2018;83:1241–8.

180. Fleischmann DF, Unterrainer M, Corradini S, Rottler M, Förster S, la Fougère C, *et al.* Report of first recurrent glioma patients examined with PET-MRI prior to re-irradiation. PLoS One 2019;14:e0216111.

181. Soffietti R, Bertero L, Pinessi L, Rudà R. Pharmacologic therapies for malignant glioma: a guide for clinicians. CNS Drugs 2014;28:1127–37.

182. Bartolo M, Zucchella C, Pace A, Lanzetta G, Vecchione C, Bartolo M, *et al.* Early rehabilitation after surgery improves functional outcome in inpatients with brain tumours. J Neurooncol 2012;107:537–44.

183. Kim WJ, Novotna K, Amatya B, Khan F. Clinical practice guidelines for the management of brain tumours: A rehabilitation perspective. J Rehabil Med 2019;51:89–96.

184. Richard NM, Bernstein LJ, Mason WP, Laperriere N, Maurice C, Millar BA, *et al.* Cognitive rehabilitation for executive dysfunction in brain tumor patients: a pilot randomized controlled trial. J Neurooncol 2019;142:565–75.

185. Khan F, Amatya B, Drummond K, Galea M. Effectiveness of integrated multidisciplinary rehabilitation in primary brain cancer survivors in an Australian community cohort: a controlled clinical trial. J Rehabil Med 2014;46:754–60.

186. Gehring K, Kloek CJ, Aaronson NK, Janssen KW, Jones LW, Sitskoorn MM, *et al.* Feasibility of a home-based exercise intervention with remote guidance for patients with stable grade II and III gliomas: a pilot randomized controlled trial. Clin Rehabil 2018;32:352–66.

187. Sanson M, Marie Y, Paris S, Idbaih A, Laffaire J, Ducray F, *et al.* Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol 2009;27:4150–4.

188. Weller M, Berger H, Hartmann C, Schramm J, Westphal M, Simon M, *et al.*; German Glioma Network. Combined 1p/19q loss in oligodendroglial tumors: predictive or prognostic biomarker? Clin Cancer Res 2007;13:6933–7.

189. UK National Institute for Health and Care Excellence (NICE). Brain tumours (primary) and brain metastases in adults; 2018 [Internet]. Available from: https://www.nice.org.uk/guidance/ng99 [cited 2020, May 4].

190. Avila EK, Chamberlain M, Schiff D, Reijneveld JC, Armstrong TS, Ruda R, *et al.* Seizure control as a new metric in assessing efficacy of tumor treatment in low-grade glioma trials. Neuro-oncol 2017;19:12–21.

191. Jalbert LE, Neill E, Phillips JJ, Lupo JM, Olson MP, Molinaro AM, *et al.* Magnetic resonance analysis of malignant transformation in recurrent glioma. Neuro-oncol 2016;18:1169–79.

192. Villani V, Carapella CM, Chiaravalloti A, Terrenato I, Piludu F, Vidiri A, *et al.* The Role of PET [18F]FDOPA in Evaluating Low-grade Glioma. Anticancer Res 2015;35:5117–22.

Conflicts of interest.—Roberta Rudà has received personal fees from UCB, Mundipharma, Novocure as a member of the Advisory Board. Riccardo Soffietti has received personal fees from Merck, Eisai, and Astra Zeneca as a member of the Advisory Board. Alessandra Solari has received grants from FISM and EAN, and personal fees from Almirall, Excemed, Genzyme, Merck, and Teva. Alessandra Fabi has received personal fees from Roche, Novartis, Eisai, Pfizer, Italfarmaco, and Amgen as a member of the Advisory Board. All other authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

History.—Article first published online: April 29, 2020. - Manuscript accepted: April 27, 2020. - Manuscript received: April 16, 2020.