New developments in surgery of CNS tumors

A personalized connectome-based approach

About > 1000 awake surgeries

Hugues Duffau, M.D., Ph.D.

Professor & Chairman
Department of Neurosurgery

Director

Team 4, INSERM U1051, Institute for Neurosciences
Gui de Chauliac Hospital, Montpellier University Medical Center, France
THE NEW PHILOSOPHY IN NEURO-ONCOLOGY

« Precocious » neurosurgery to improve BOTH

- Overall survival +++
- Quality of life +++

Diffuse low-grade glioma, oncological outcome and quality of life: a surgical perspective
Hugues Duffau, Curr Opin Oncol 2018, 30:383–389
HOW TO ACHIEVE THIS AMBITIOUS GOAL

- Early surgery
  - Even « preventive » surgery in incidental discovery of gliomas
  - Wait and see attitude should be abandoned

- Maximal resection
  -Extent of resection is correlated to survival
  -Supratotal resection when feasible

- Safe resection
  - With intraoperative mapping
  - Functional-based resection
PREOPERATIVE NEUROPSYCHOLOGICAL ASSESSMENT

NOT A LUXURY!

- Cognitive deficit despite a « normal life » in > 80% of cases
  - Working memory
  - Attention
  - Executive functions (increase reaction time)
  - Emotion
  - Social cognition
PREOPERATIVE COGNITIVE DEFICITS RELATED TO INFILTRATION OF SUBCORTICAL CONNECTIVITY

Negative correlation between semantic fluency scores and infiltration of IFOF

The left inferior fronto-occipital fasciculus subserves language semantics: a multilevel lesion study


Fabien Almairac · Guillaume Herbet · Sylvie Möritz-Gasser · Nicolas Menjot de Champfleur · Hugues Duffau

Mandonnet et al, J Neurooncol 2007
Growing Tumor (4 mm / year): NOT STABLE!!!!!
- invading the cortico-subcortical functional structures
- revealed by seizures (90%)
- young patients with no/slight deficit

« pre-malignant » tumor
- NOT benign!!!!!

Anaplastic transformation
- Around 50% within 5 years following the first symptoms

Deficit

Death (median survival: 6-7 years)

Mandonnet, Ann Neurol 2003
Duffau, Springer 2017
SURVIVAL IN RELATION TO EARLY RESECTION VERSUS BIOPSY: 2 NEAR-RANDOMIZED STUDIES

MS = 5.8 years with biopsy
MS = 14.4 years with resection - not related to molecular markers!!!

Jakola et al., Ann Oncol 2017

MS = 6.7 years with biopsy
MS not reached with resection (p = 0.003)

Results. Gross total resection was significantly associated with decreased mortality and likelihood of progression at all time points compared to subtotal resection. Early radiation was not associated with decreased mortality;
RESULTS : SURVIVAL IN RELATION TO THE EXTENT OF RESECTION

PROSPECTIVE STUDY +++

MS > 15 years with early resection (p < 0.0001)

Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases

Clinical article

LAURENT CAPELLE, M.D.,1 DENYS FONTAINE, M.D., Ph.D.,2 EMMANUEL MANDONNET, M.D., Ph.D.,3 LUC TAILLANDIER, M.D., Ph.D.,4 JEAN LOUIS GOLMARD, M.D.,5 LUC BAUCHET, M.D., Ph.D.,5 JOHAN PALLUD, M.D.,5 PHILIPPE PERUZZI, M.D., Ph.D.,5 MARIE HELENE BARON, M.D.,5 MICHELE KUJAS, M.D., Ph.D.,10 JACQUES GUYOTAT, M.D., Ph.D.,11 REMI GUILLEVIN, M.D., Ph.D.,12 MARC FRENAY, M.D.,13 SOPHIE TAILLIBERT, M.D.,14 PHILIPPE COLIN, M.D.,15 VALERIE RIGAU, M.D., Ph.D.,16 FANNY VANDENBOS, M.D., Ph.D.,17 CATHERINE PINELLI, M.D.,18 AND HUGUES DUFAU, M.D., Ph.D.,6 FOR THE FRENCH RESEAU D’ETUDE DES GLIOMES (REG)

SURVIVAL WITH EARLY SURGICAL RESECTION

A personal prospective series with 772 low-grade gliomas

25% of LGG patients still alive with > 20 years of follow-up

Duffau, in preparation
MOLECULAR PROFILE IS ONLY PART OF THE STORY
THE EXAMPLE OF IDH1 WILD-TYPE ASTROCYTOMAS

Molecular status is not enough to define individualized therapeutic approach.
IMPACT OF RE-OPERATION(S) ON WHO GRADE II GLIOMA, INCLUDING WITHIN ELOQUENT AREAS

Prognostic factors (multivariate analysis)

- postop volume
- location
- age < 54 years
- reoperation +++

French Glioma Network
J Neurosurg 2013 and Brain 2014
FROM LOCALISATIONISM TO A CONNECTOMAL ACCOUNT OF BRAIN PROCESSING

Broca, 1887; Wernicke, 1874

Duffau, Cortex 2014; Vigneau et al, Neuroimage 2006; Sarubbo et al., HBM 2016
Advantages

- Detection of ESSENTIAL areas: « epicenters »
- Cortical AND subcortical mapping
- Accurate (5 mm)
- Reliable
- On-line
- Safe


H Duffau, M Lopes, F Arthuis, A Bitar, J-P Sichez, R Van Effenterre, L Capelle

*J Neurol Neurosurg Psychiatry* 2005;76:845–851

Do not duplicate or distribute without permission from author and ESO
SELECTION OF INTRAOPERATIVE TASKS

- **Patient**
  - Job, hobby, habits, social activity (e.g. multilingualism…)

- **Preoperative clinical and neuropsychological assessment**
  - Neurological or cognitive deficit?
  - Handedness

- **Glioma location**
  - In relation to the « classical » anatomical landmarks
  - On the lights of functional neuroimaging
    - Hemispheric lateralization (language)?
    - Functional network?
THE « NEW TRADITION » FOR NEUROSURGEONS

LEFT TUMOR: AWAKE SURGERY FOR LANGUAGE

RIGHT TUMOR: GENERAL ANESTHESIA

SIMPLISTIC VIEW!!!

WHAT ABOUT THE NON-VERBAL FUNCTIONS

WHAT DOES MEAN «NON-DOMINANT» HEMISPHERE?
WHAT ABOUT OTHER FUNCTIONS?

Quality of Life

Verbal Language Processing

Sufficient?

Movement?
Spatial cognition?
Social cognition?
Non-verbal semantics?
Executive/working memory?
Conscious information processing?
Personality?

Damage to the left uncinate fasciculus is associated with heightened schizotypal traits: A multimodal lesion-mapping study
Anne-Laure Lemaitre¹,², Gilles Lafargue⁴, Hugues Dufau⁴,⁵, Guillaume Herbet⁴,⁵,⁶
Schizophrenia Research (2018)
Dual-tasking for executive processes

Assessing at the same time:
- Language
- Motor movements
- Executive functions
- Working memory

Semantic association task

Example of functional mapping during surgery (patient 3)

Cortical mapping
- RO: speech apraxia
- pmC: speech arrest

Subcortical mapping
- post SMG: anoma
- pG: articulatory disorder

Effect of IFOF DES (n = 8 patients)

Awake Craniotomy and Bedside Cognitive Mapping in Neurosurgery

Guillaume Herbet\textsuperscript{1,2,3} and Hugues Duffau\textsuperscript{1,2,3}
INTRAOPERATIVE MAPPING OF MENTALIZING

Interfering with the neural activity of mirror-related frontal areas impairs mentalistic inferences
Guillaume Herbet · Gilles Lafargue · Sylvie Moritz-Gasser · François Bonnetblanc · Hugues Dufau

A TAILORED PROTOCOL ACCORDING TO RELATIONSHIPS BETWEEN GLIOMA AND PATHWAYS

Projection fibers

Association fibers

Selection of intraoperative tasks for awake mapping based on relationships between tumor location and functional networks


ALEJANDRO FERNÁNDEZ COELLO, M.D., SYLVIE MORITZ-GASSER, PH.D.,
JUAN MARTINO, M.D., PH.D., MATTEO MARTINONI, M.D.,
ROYOSKE MATSUDA, M.D., PH.D.,
AND HUGUES DUFFAU, M.D., PH.D.
LIMITS OF RESECTION: CORTICAL AND SUBCORTICAL FUNCTIONAL STRUCTURES, WITH NO MARGIN

FUNCTIONAL-MAPPED GUIDED RESECTION

NOT IMAGE-GUIDED RESECTION !!!!!!!!

- No Neuronavigation
- No DTI
- No fMRI
- No intraoperative MRI
- No microscope
- No ECoG
REPEAT SURGERIES ARE POSSIBLE THANKS TO NEUROPLASTICITY, WITH AN INCREASE OF EOR

Postoperative functional rehabilitation +++

Iterative Surgical Resections of Diffuse Glioma With Awake Mapping: How to Deal With Cortical Plasticity and Connectomal Constraints?
The huge plastic potential of adult brain and the role of connectomics: New insights provided by serial mappings in glioma surgery

Hugues Duffau \(^{a,b,*}\)

---

*Do not duplicate or distribute without permission from author and ESO.*
RESULTS ABOUT 772 DIFFUSE LOW-GRADE GLIOMAS

1000 AWAKE SURGERIES IN « INOPERABLE » AREAS

Broca’s area; Wernicke’s area; Rolandic area; Paralimbic system; Corpus callosum

FUNCTIONAL REORGANIZATION

Duffau  Lancet Neurol 2005; Cortex 2014; Brain Plast 2016; Cortex 2017
With mapping:

- Mortality 0%
- 0.5% of severe permanent deficits
- 30% of improvements +++
- 80% of positive impact on epilepsy (p < 0.0001)
INDEPENDENT PREDICTORS OF UNCONTROLLED SEIZURES BEFORE ONCOLOGICAL TREATMENT

- Tumor location
  - Close to functional areas
  - Central region
  - Insular location

LGG-related epilepsy is triggered by interaction between glioma and cortex: seizures arise from the peritumoral cortex and not from the tumor core

This also supports supratotal resection!!!!!

Pallud et al., Epilepsia 2013 and Brain 2014
OUTCOME IN LOW-GRADE / HIGH-GRADE GLIOMAS SURGERY AND BRAIN MAPPING META-ANALYSIS WITH 8091 CASES

- 2x reduction of late severe deficits with stimulation mapping (3.4 vs 8.3%)
- With an improvement of the extent of resection (75 vs 58% of GTR)
- While involving eloquent locations more frequently
- Intraoperative mapping is standard of care for glioma resections ++++

Impact of Intraoperative Stimulation Brain Mapping on Glioma Surgery Outcome: A Meta-Analysis

Philip C. De Witt Hamer, Santiago Gil Robles, Aeliko H. Zwinderman, Hugues Duflga, and Michel S. Berger

JOURNAL OF CLINICAL ONCOLOGY © 2012 by American Society of Clinical Oncology
Tumor cells are present beyond the area of MRI signal abnormalities, up to 20 mm, even when gliomas are well defined on T2/FLAIR.

Pallud et al., Neurology 2010
THE CONCEPT OF « SUPRATOTAL RESECTION »

Why to stop according to the MRI signal abnormalities?

Duffau, Acta Neurochir 2016
SUPRA-COMPLETE RESECTION IN LOW-GRADE GLIOMA

AWAKE MAPPING IN « NON-ELOQUENT » AREAS

PREVENTING MALIGNANT TRANSFORMATION +++

Total resection
Relapse in 41% of patients (FU 36 months)
7/29 malignant transformations
CT or RT in 10 cases

Supratotal resection
Relapse in 26% of patients (FU 38 months)
NO malignant transformation (p=0.037)
CT in one case

Awake surgery for WHO Grade II gliomas within “noneloquent” areas in the left dominant hemisphere: toward a “supratotal” resection
Yordanka N. Yordanova, M.D., Sylvie Moritz-Gasser, S.T., and Hugues Duffau, M.D., Ph.D.


Do not duplicate or distribute without permission from author and ESO.
SUPRA-COMPLETE RESECTION IN LOW-GRADE GLIOMA

LONG-TERM OUTCOMES WITH 11-YEAR FOLLOW-UP

PREVENTING MALIGNANT TRANSFORMATION +++

Consecutive patients
Mean FU: 11 years (8 – 16.5)
NO postop adjuvant treatment
NO permanent deficit
NO death
NO malignant transformation
Recurrence in 50% of cases (average time to relapse: 6 years)

Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up
Hugues Duffau 1,2
EARLY RADIOTHERAPY IN DLGG HAS NO IMPACT ON MEDIAN SURVIVAL BUT INDUCES PROGRESSIVE COGNITIVE DECLINE

“Long-term survivors of LGG who did not have radiotherapy had stable radiological and cognitive status. By contrast, patients with LGG who received radiotherapy showed a progressive decline in attentional functioning, even those who received fraction doses that are regarded as safe ($\leq 2$ Gy)”

MS = 7.4 years

van den Bent et al, Lancet 2005

Douw et al., Lancet Oncol 2010
RADIATION-INDUCED BRAIN INJURY MAY OCCUR VERY QUICKLY AFTER RADIOTHERAPY

“Progressive late disruptions to the integrity of the related far-end white matter structure began to be significant after one year”

Identifying early diffusion imaging biomarkers of regional white matter injury as indicators of executive function decline following brain radiotherapy: A prospective clinical trial in primary brain tumor patients


Radiotherapy and Oncology 132 (2019) 27–33

Duffau, Submitted
OS IS LONGER WITH PCV+RT RATHER THAN WITH PCV

BUT

- No objective evaluation of EOR (only 9-11% of patients with total resection?!)  
  
- No arm with CT alone  
  
- No cognitive assessment (only MMSE) beyond 5 years +++

Buckner et al., NEJM 2016
CHEMOTHERAPY IS THE FIRST POSTSURGICAL OPTION

RADIOThERAPY SHOULD BE POSTPONED

“The results support the hypothesis that a high score predicts benefit from TMZ treatment for patients with IDHmt LGG, regardless of the 1p/19q status. This MGMT methylation score may identify patients who benefit from first-line treatment with TMZ, to defer RT for long-term preservation of cognitive function and quality of life.”
NEOADJUVANT CHEMOTHERAPY

Duffau et al., J Neurooncol 2006;
Blonski et al. J Neurooncol 2012

Temo
New concepts in the management of diffuse low-grade glioma: Proposal of a multistage and individualized therapeutic approach

An attempt to conceptualize the individual onco-functional balance: Why a standardized treatment is an illusion for diffuse low-grade glioma patients
DYNAMIC MULTIMODAL TREATMENT OF
DIFFUSE LOW GRADE GLIOMAS

Blonski et al., J Neurooncol 2013

After TMZ and surgeries
SURVIVAL

Median survival = 16 YEARS with early resection

Obara, Taillandier and Duffau, in prep
SUPRAMAXIMAL RESECTION OF LGG WITH FOCI OF MALIGNANT TRANSFORMATION

- Postponing the medical treatment in DLGG with foci of grade III or IV following (sub)total resection should be considered in selected patients, especially with:
  - younger age < 36.5 years
  - smaller preop FLAIR volume < 50 cc
  - slower tumor growth rate < 3.6 mm/year
  - oligodendroglioma
  - smaller postop FLAIR volume < 1.5 cc

5-years survival rate: 95.2%

Darlix, Rigau, Fraysse, Gozé, Fabbro and Duffau, Neurology, in press
MAXIMAL RESECTION IN LOW-GRADE GLIOMA
WITH NODULAR GRADE III FOCUS

Radical resection can radically change the natural history of gliomas

17 years of FU – Normal life – No seizures – no CT/RT

Radical resection can radically change the natural history of gliomas
MAXIMAL RESECTION IN LOW-GRADE GLIOMA WITH GRADE IV FOCUS

6 years of FU – Normal life – No seizures – NO CT/RT - Working full time

Supramarginal resection can radically change the natural history of gliomas
37 studies, 41,117 patients: decreased mortality for GTR compared with STR at 1 year and 2 years (p < 0.001)

Brown et al., JAMA Oncol 2016
5 years of FU – Normal life – No seizures – CT/RT - Working full time

Is Supratotal Resection of Glioblastoma in Noneloquent Areas Possible?

Duffau, World Neurosurg 2015
11 years of FU – Normal life – No seizures – CT/RT - Working full time

Duffau, Front Surg 2019
SUPRAMARGINAL RESECTION IN GLIOBLASTOMAS

BENEFIT ON SURVIVAL IN 643 PATIENTS

- Greater OS if > 53% of the FLAIR is resected

Li et al., J Neurosurg 2016
SUPRAMARGINAL RESECTION OF METASTASES

Fig. 2 Local and distant in-brain progression after supramarginal resection
HOW TO INCREASE THE RATE OF SUPRAMAXIMAL RESECTION?

« Preventive » neurosurgery

- Incidental LGG +++
- Screening +++

Higher-Order Surgical Questions for Diffuse Low-Grade Gliomas
Supramaximal Resection, Neuroplasticity, and Screening

Hugues Duffau, MD, PhD
Neurosurg Clin N Am 30 (2019) 119-128
TOWARD SURGERY IN ASYMPTOMATIC PATIENT
PREVENTIVE SURGICAL NEURO-ONCOLOGY ++++

100 patients; volume increase in all cases; 70 DLGGs in «eloquent areas»; smaller tumors; NO partial resection; 30% of supratotal resection +++; NO permanent deficits; NO EPILEPSY; 30% of malignant foci! Return to work in > 98% of cases

Awake surgery for incidental WHO grade II gliomas involving eloquent areas

Hugues Duffau

Is there a risk of seizures in “preventive” awake surgery for incidental diffuse low-grade gliomas?

Guilherme Lucas de Oliveira Lima, MD, PhD,1,2 and Hugues Duffau, MD, PhD1,4
SCREENING: A PILOT SURVEY IN 520 STUDENTS

Willingness to participate in a MRI program for glioma screening

MRI screening for glioma: a preliminary survey of healthy potential candidates

Emmanuel Mandonnet¹ ² ³ · Philip de Witt Hamer⁴ · Hugues Duffau⁵ ⁶
A PERSONALIZED CONNECTOME-BASED MAXIMAL SURGICAL APPROACH

Stimulation mapping of white matter tracts to study brain functional connectivity

Sarubbo et al., Hum Brain Mapp 2015
TAKE HOME MESSAGE IN GLIOMAS

- Surgery has a significant impact on natural history of diffuse gliomas +++
- Objective assessment of the extent of resection: postoperative FLAIR-weighted MRI +++
- (Supra)maximal functional-based surgical resection is the first treatment +++
- Surgery improves quality of life +++
- Reoperation(s) should be considered more systematically
- Be careful before to administer CT/RT too early in low-grade gliomas
- Objective neurocognitive examination is needed before and after each treatment +++
- QoL should be the first endpoint ++++++++
TAKE HOME MESSAGE IN LOW-GRADE GLIOMAS

- SUPRAMAXIMAL RESECTION HAS A SIGNIFICANT IMPACT ON THE COURSE OF LGG, BY AVOIDING MALIGNANT TRANSFORMATION +++
- IT LIMITS THE RISK OF SEIZURES, AND THEN IT IMPROVES QUALITY OF LIFE +++
- SUPRATOTAL RESECTION IS MORE FREQUENT IN INCIDENTAL LGGs, BECAUSE THEY ARE SMALLER
- SURGERY IS SAFER IN INCIDENTAL LGG, BECAUSE PLASTICITY DID NOT YET REACH ITS LIMITATION
- NEXT STEP: SCREENING
TAKE HOME MESSAGE

ADJUVANT TREATMENT IN LOW-GRADE GLIOMAS

- Postoperative therapeutic management depend on many factors
  - Age?
  - Postoperative tumoral volume (10-15 cc)
  - Growth rate of the residue (less than 8 mm/year)
  - Invasion of the subcortical connectivity (minimal common brain)
  - Possible spatial heterogeneity of histomolecular data

- CT induces shrinkage or at least stabilization in 90% of cases (RANO criteria NOT ADAPTED) with VERY FEW ADVERSE COGNITIVE EFFECTS

New concepts in the management of diffuse low-grade glioma: Proposal of a multistage and individualized therapeutic approach
Hugues Duffau and Luc Taillandier
Neuro-Oncology 17(3), 332–342, 2015

Do not duplicate or distribute without permission from author and ESO
TAKE HOME MESSAGE ABOUT RADIOTHERAPY IN LGG

- THE ACTUAL IMPACT OF EARLY RT PER SE on OS is NOT demonstrated

- Local RT, even with NEW methods of irradiation, may affect cognition due to damage of the SUBCORTICAL CONNECTIVITY, i.e., the LIMITATION OF NEUROPLASTICITY

- RADIOThERAPISTS, AS NEUROSURGEONS, MUST TAKE ACCOUNT OF THE FUNCTIONAL ANATOMY OF THE INDIVIDUAL BRAIN TO OPTIMIZE IRRADIATION PLAN (When? How?) SINCE RT MAY DECREASE THE POTENTIAL OF NEURAL REORGANIZATION

An attempt to conceptualize the individual onco-functional balance: Why a standardized treatment is an illusion for diffuse low-grade glioma patients

Emmanuel Mandonnet*, Hugues Duffau*
MEDECINE IS CURRENTLY AT A CROSSROADS

A MEDECINE PROTOCOLS-DRIVEN TREATING TUMORS…

- Dogmatic view of one single brain
- Abusive use of technology (neuronavigation, intraoperative MRI, robot,…) in a static view of cerebral processing
- Statistical results of trials applied to the individual level
- The apology of the survival with very few (no?) consideration concerning the quality of life defined by the patient himself
- A « molecular medicine » that ignores human beings
... OR A MEDICINE HUMAN BEING-CENTRED

- Treating a plastic brain able to (re)learn and to compensate lesion
- Understanding the individual dynamic functional organization by means of serial neuropsychological assessments and mapping
- Investigating the natural history of this disease in this given patient at this moment
- Defining the quality of life by the patient himself according to his work, hobby, lifestyle and psychological aspects
- Elaborating personalized management re-evaluated over time with the patient and his family
- Solving in real-time a big equation with many individual parameters (not only the molecular profile of the tumor!)
THE REVERSE PATH FROM MOLECULAR MEDICINE TO HIPPOCRATES: QoL AS THE FIRST ENDPOINT (NOT PFS!)

- Be careful about « evidence-based medicine » based upon artificial trials and not based upon objective observations of the truth in real-life
- The wishes of the patients are more important than the protocols
- We have to come back to good sense, empathy and wisdom, that is, to take into account the fact that each patient is UNIQUE
- Towards a medicine in agreement with Hippocratic Oath++++
- PREVENTION +++

Paradoxes of evidence-based medicine in lower-grade glioma
To treat the tumor or the patient?

Hugues Duffau, MD, PhD
Neurology® 2018;00:1-6. doi:10.1212/WNL.0000000000006288

Correspondence
Prof. Duffau
h-duffau@chu-montpellier.fr
SURVIVAL IN LOW-GRADE GLIOMAS

Median survival > **16 YEARS** by applying this philosophy

Obara, Taillandier and Duffau, in prep
THE FUTURE OF FUNCTIONAL NEURO-ONCOLOGY?

To know the glioma (location, volume, kinetics, genetics…)

Neurosurgeons, medical neurooncologists AND radiotherapists should ALSO know functional anatomy of the brain: to SPEAK THE SAME LANGUAGE

The dynamics of brain connectome should be taken into account in order to build an individualized therapeutic strategy, with (at least) 10 years of ANTICIPATION regarding BOTH oncological and functional issues
NEW CONCEPTS IN CNS TUMORS

PREVENTIVE AND INDIVIDUALIZED FUNCTIONAL NEURO-ONCOLOGY BASED ON A SUPRATOTAL MAPPING-GUIDED SURGICAL APPROACH

TREAT THE PATIENT, NOT THE TUMOR