Conflicts of Interest

M. Weller has received research grants from Abbvie, Adastra, Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Piqur and Roche, and honoraria for lectures or advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb (BMS), Celgene, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen.
Learning objectives

- Understand the current concepts of defining glioblastoma based on the 2016 WHO classification

- Understand the contributions of surgery, radiotherapy and pharmacotherapy to outcome in glioblastoma

- Understand the current controversies in the diagnosis and management of glioblastoma
Key messages

- Glioblastoma is now increasingly defined based on histomorphological and on molecular genetic features

- Combined modality treatment of surgery followed by chemoradiotherapy improves outcome, but is never curative

- Novel approaches of targeted therapy and immunotherapy may provide benefit in subgroups of patients

- Standardized multidisciplinary care and focus on symptomatic treatments, e.g., of epilepsy and vascular complications, are an important aspect of a comprehensive approach to glioblastoma
Our current standards of care are based on very few clinical trials and a lot of eminence-based medicine...
What is the “standard”? 

• What the guidelines say? If so, which? 
• What is approved? What is reimbursed? 
• What the boss says? 
• For which patients does the standard apply? 
• Who changes the standard?
What is glioblastoma in 2019?
What is glioblastoma in 2019?

Definition
A high-grade glioma with predominantly astrocytic differentiation; featuring nuclear atypia, cellular pleomorphism (in most cases), mitotic activity, and typically a diffuse growth pattern, as well as microvascular proliferation and/or necrosis, without mutations in the IDH genes.
What is glioblastoma in 2019?  

Figure 5 | Frequent genetic alterations in three critical signalling pathways. a–c, Primary sequence alterations and significant copy number changes for components of the RTK/RAS/PI(3)K (a), p53 (b) and RB (c) signalling pathways are shown. Red indicates activating genetic alterations, with frequently altered genes showing deeper shades of red. Conversely, blue indicates inactivating alterations, with darker shades corresponding to a higher percentage of alteration. For each altered component of a particular pathway, the nature of the alteration and the percentage of tumours affected are indicated. Boxes contain the final percentages of glioblastomas with alterations in at least one known component gene of the designated pathway.
Towards „molecular“ glioblastoma?

https://doi.org/10.1007/s00401-018-1913-0

**Correspondence**

cIMPACT-NOW update 3: recommended diagnostic criteria for “Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV”

Daniel J. Brat¹ · Kenneth Aldape² · Howard Colman³ · Eric C. Holland⁴ · David N. Louis⁵ · Robert B. Jenkins⁶ · B. K. Kleinschmidt-DeMasters⁷ · Arie Perry⁸ · Guido Reifenberger⁹,¹⁰ · Roger Stupp¹¹ · Andreas von Deimling¹²,¹³ · Michael Weller¹⁴

1. *EGFR* amplification

   OR

2. Combined whole chromosome 7 gain and whole chromosome 10 loss (+ 7/– 10)

   OR

3. *TERT* promoter mutation
European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas

Michael Weller, Martin van den Bent, Jörg C Tonn, Roger Stupp, Matthias Preusser, Elizabeth Cohen-Jonathan-Moyal, Roger Henriksson, Emilie Le Rhun, Carmen Balana, Olivier Chinot, Martin Bendszus, Jaap C Reijneveld, Frederick Dhermain, Pim French, Christine Marosi, Colin Watts, Ingela Oberg, Geoffrey Pilkington, Brigitta G Baumert, Martin J B Taphoorn, Monika Hegi, Manfred Westphal, Guido Reifenberger, Riccardo Soffietti, Wolfgang Wick, for the European Association for Neuro-Oncology (EANO) Task Force on Gliomas

The European Association for Neuro-Oncology guideline provides recommendations for the clinical care of adult patients with astrocytic and oligodendroglial gliomas, including glioblastomas. The guideline is based on the 2016 WHO classification of tumours of the central nervous system and on scientific developments since the 2014 guideline. The recommendations focus on pathological and radiological diagnostics, and the main treatment modalities of surgery, radiotherapy, and pharmacotherapy. In this guideline we have also integrated the results from contemporary clinical trials that have changed clinical practice. The guideline aims to provide guidance for diagnostic and management decisions, while limiting unnecessary treatments and costs. The recommendations are a resource for professionals involved in the management of patients with glioma, for patients and caregivers, and for health-care providers in Europe. The implementation of this guideline requires multidisciplinary structures of care, and defined processes of diagnosis and treatment.

Lancet Oncol 2017
Published Online
May 5, 2017
http://dx.doi.org/10.1016/ S1470-2045(17)30194-8
Clinical pathway Glioma according to EANO

**Favourable prognostic factors:**
- Age <40 years
- KPS ≥70

**Diffuse astrocytoma, IDH mutant, WHO grade II**

**Oligodendroglioma, IDH mutant and 1p/19q-co-deleted, WHO grade II**

**Anaplastic astrocytoma, IDH mutant, WHO grade III**

**Anaplastic oligodendroglioma, IDH mutant and 1p/19q-co-deleted, WHO grade III**

**Glioblastoma, IDH wild type, WHO grade IV**

(and IDH wild type, WHO grade III gliomas and IDH wild type, WHO grade II gliomas with unfavourable clinical or molecular profile)

**Unfavourable prognostic factors:**
- KPS <70
- Age >70 years
  - MGMT promoter non-methylated
  - MGMT promoter methylated

**Very unfavourable prognostic factors:**
- KPS <50 or inability to consent

**Favourable prognostic factors:**
- Age <55-60 years
- KPS ≥70

**Favourable prognostic factors:**
- Age <70 years
- KPS ≥70

**Favourable prognostic factors:**
- Age <72 h
- KPS ≥70

Wait and see or RT → PCV

RT → TMZ

RT → PCV

TMZ/RT → TMZ

Follow up in 4-6-monthly intervals: neurological examination and imaging

Early (<72 h) postoperative MRI or CT = baseline for monitoring and detection of progression

Follow up in 3-monthly intervals: neurological examination and imaging

Progression or recurrence

Options determined by KPS, neurological function, and prior treatment
- Second surgery
- Chemotherapy
- Bevacizumab
- Re-irradiation
- Experimental therapy

Palliative care

KPS, Karnofsky performance status.
Key recommendations according to EANO

<table>
<thead>
<tr>
<th>Glioblastoma, IDH-wild-type (WHO grade IV)</th>
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<th>A</th>
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<tbody>
<tr>
<td>Standard of care for glioblastoma, IDH-wild-type (age &lt;70 years, Karnofsky performance score ≥70) includes resection as feasible or biopsy followed by involved-field radiotherapy and 6 cycles of concomitant and maintenance temozolomide chemotherapy (EORTC 26981 NCIC CE.3 trial).</td>
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<tr>
<td>Temozolomide is particularly active in patients with MGMT promoter methylation whereas its activity in patients with MGMT promoter-unmethylated tumours is marginal.</td>
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<tr>
<td>Elderly patients not considered candidates for concomitant or maintenance temozolomide plus radiotherapy should be treated based on MGMT promoter methylation status (Nordic,\textsuperscript{19} NOA-08,\textsuperscript{20} and NCIC CE.6 EORTC 6062\textsuperscript{21} trials) with radiotherapy (eg, 15 × 2-6 Gy) or temozolomide (5 out of 28 days).</td>
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<tr>
<td>Standards of care are not well defined at recurrence. Nitrosourea regimens, temozolomide rechallenge and, with consideration of the country-specific label, bevacizumab are pharmacological options, but an effect on overall survival remains unproven. When available, recruitment into appropriate clinical trials should be considered.</td>
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Controversies in the management of glioblastoma

• MGMT testing for all patients, in the elderly or not at all?

• Maintenance temozolomide forever?

• Bevacizumab for recurrent glioblastoma?

• Are tumor-treating fields standard of care?
Controversies in the management of glioblastoma

• MGMT testing for all patients, in the elderly or not at all?

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Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma


O⁶-Methylguanin-methyltransferase (MGMT, AGAT), a DNA repair protein, counteracts the effect of alkylating agents:
**MGMT** promoter methylation in malignant gliomas: ready for personalized medicine?

Michael Weller, Roger Stupp, Guido Reifenberger, Alba A. Brandes, Martin J. van den Bent, Wolfgang Wick and Monika E. Hegi


**Unmethylated MGMT promoter**

MGMT promoter

**MGMT gene**

Transcription/translation

Chemo-resistance

**MGMT promoter methylation**

MGMT promoter

CH$_3$CH$_3$CH$_3$CH$_3$CH$_3$

**MGMT gene**

Inactive

Transcription/translation

Chemosenstivity
**MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma**

Monika E. Hegi, Ph.D., Anne-Claire Diesch, M.Sc., Thierry Goria, M.Sc.,
Marie-France Hamon, Nicolas de Tofolde, M.D., Michael Weber, M.D.,
Johan M. Kooi, M.D., Johannes A. Hanefelder, M.D., Warren Marion, M.D.,
Luigi Marian, M.D., Jacoline E.C. Bronberg, M.D., Peter Hau, M.D.,
Reinhard Mismanoff, M.D., J. Gregory Cameron, M.D., Robert C. Janzer, M.D.,
and Roger Stupp, M.D.


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**No. at Risk**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td>Unmethylated, radiotherapy</td>
<td>54</td>
</tr>
<tr>
<td>Unmethylated, radiotherapy plus temozolomide</td>
<td>60</td>
</tr>
<tr>
<td>Methylated, radiotherapy</td>
<td>46</td>
</tr>
<tr>
<td>Methylated, radiotherapy plus temozolomide</td>
<td>46</td>
</tr>
</tbody>
</table>

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**Graph:**

- Red line: Unmethylated, radiotherapy
- Blue line: Unmethylated, radiotherapy plus temozolomide
- Green line: Methylated, radiotherapy
- Orange line: Methylated, radiotherapy plus temozolomide

**Probability of Progression-free Survival (%)**

- P = 0.02
- P = 0.001
The rationale for MGMT testing in the elderly

Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

Wolfgang Wick, Michael Platten, Christoph Moritz, Jörg Feldberg, Chezah M Takhati, Matthias Simms, Guido Nitschke, Kerstin Papendorf, Joachim P Steinbach, Michael Selch, Stephan E Coombes, Jan Vorper, Christian Braun, Jürgen Meisenzahl, Raj Kalsotra, Regine Mayer-Stocker, Guido Reifenberger, Michael Walter, for the NOA-08 Study Group of the Neuro-oncology Working Group (NOA) of the German Cancer Society


Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

Annika Malmstrom, Björn Henrik Gränberg, Christine Marosi, Roger Stupp, Didier Frappaz, Henrik Schultz, Ejikul Aboagye, Björn Tavelin, Benoit Hermette, Monika E Hejls, Johan Rosel, Roger Henriksson, for the Nordic Clinical Brain Tumour Study Group (NCBTSC)

Lancet Oncol 2012; 13: 916-26

Figure 2. Kaplan–Meier analysis of overall and event-free survival in relation to MGMT promoter methylation status and treatment

(A) Overall survival. (B) Event-free survival. The p-values were calculated for any significant difference in at least two of the curves. See also table 2. RT-radiotherapy. TMZ=temozolomide.
The devil is in the detail....
Controversies in the management of glioblastoma

- MGMT testing for all patients, in the elderly or not at all?
- Maintenance temozolomide forever?
- Bevacizumab for recurrent glioblastoma?
- Are tumor-treating fields standard of care?
Maintenance temozolomide: 6 cycles is enough
Alkylating agent chemotherapy forever?

Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas

MICHAEL D. WALKER, M.D., EBER ALEXANDER, JR., M.D.,
WILLIAM E. HUNT, M.D., COLLIN S. MACCARTY, M.D.,
M. STEPHEN MAHaley, Jr., M.D., JOHN MEaley, Jr., M.D.,
HORACE A. NORRELL, M.D., GUY OWENS, M.D.,
JOSEPH RASSHOFF, M.D., CHARLES B. WILSON, M.D.,
EDMUND A. GEHAN, PH.D., AND THOMAS A. STRIKE, PH.D.
The Brain Tumor Study Group and the National Cancer Institute, National Institutes of Health, Bethesda, Maryland


Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D.,
Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D.,
Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D.,
Ulrich Bogdahn, M.D., Jürgen Curcancha, M.D., Robert C. Janzer, M.D.,
Samuel K. Ludwin, M.D., Thierry Golli, M.Sc., Anouk Albiges, Ph.D.,
Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D.,
and René O. Minimard, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group.


Fig. 1. Survival curves of patients who received A) best conventional care but no radiotherapy or chemotherapy, B) BCNU, C) radiotherapy, or D) BCNU and radiotherapy.
Alkylating agent chemotherapy forever?
Herrlinger et al. Lancet 2019;393:678-688

Figure 3: Kaplan-Meier plots of overall survival and progression-free survival
Kaplan-Meier plots of patients in both groups matched by respective centre and RPA class strata. Overall survival (A) in the modified intention-to-treat population (n=105; stratified log-rank test) and (B) in the intention-to-treat population (n=125; stratified log-rank test). Progression-free survival in the modified intention-to-treat population (C) and the intention-to-treat population (D). HR-hazard ratio. *Stratified log-rank test (primary analysis). †Multivariate Cox regression analysis.
Controversies in the management of glioblastoma

- MGMT testing for all patients, in the elderly or not at all?
- Maintenance temozolomide forever?
- Bevacizumab for recurrent glioblastoma?
- Are tumor-treating fields standard of care?
Responses to bevacizumab in recurrent glioblastoma
Lomustine and Bevacizumab in Progressive Glioblastoma

437 Patients underwent randomization

288 Were assigned to receive lomustine plus bevacizumab
  32 Were ineligible
  5 Did not start treatment

149 Were assigned to receive lomustine alone
  12 Were ineligible
  2 Did not start treatment

283 Received lomustine plus bevacizumab
  19 Were receiving ongoing intervention
  264 Discontinued intervention
    186 Had progressive disease
    53 Had adverse event
    10 Were withdrawn by investigator
    15 Had other reason or were lost to follow-up

147 Received lomustine alone
  3 Were receiving ongoing intervention
  144 Discontinued intervention
    120 Had progressive disease
    15 Had adverse event
    2 Were withdrawn by investigator
    7 Had other reason or were lost to follow-up

288 Were included in the intention-to-treat analysis
  253 Were included in the per-protocol analysis
  264 Had treatment data available
  283 Were included in the safety analysis
  274 Underwent central radiologic review
  241 Underwent molecular diagnostic testing

149 Were included in the intention-to-treat analysis
  136 Were included in the per-protocol analysis
  144 Had treatment data available
  147 Were included in the safety analysis
  144 Underwent central radiologic review
  126 Underwent molecular diagnostic testing

Figure 1. Randomization, Follow-up, and Analyses.
Controversies in the management of glioblastoma

- MGMT testing for all patients, in the elderly or not at all?
- Maintenance temozolomide forever?
- Bevacizumab for recurrent glioblastoma?
- Are tumor-treating fields standard of care?
Are tumor-treating fields standard of care?

NovoTTF-100A versus physician’s choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality


Fig. 2. Overall survival (A) and progression free survival (B) Kaplan–Meier curves.
Are tumor-treating fields standard of care?
Some facts on TTF


**TTF do not prolong survival in recurrent glioblastoma** Stupp et al. EJC 2012;48:2192-202

**TTF prolong survival in newly diagnosed glioblastoma patients who have not progressed after concomitant TMZ/RT** Stupp et al. JAMA 2015;314:2535-43, 2017;318:2306-16

**Extensive subgroup analyses have not resulted in a clinical, imaging or molecular profile associated with benefit (or lack thereof) from TTF in newly diagnosed glioblastoma**
**TTF: a SWOT view**

**Strengths** – positive phase III trial 1L, non-overlapping toxicity

**Weaknesses** – negative phase III trial 2L, no predictive biomarker, no specific imaging or pathology changes associated with response or failure, stigma, questionable commercialization strategy

**Opportunities** – combination, non-overlapping toxicity, expansion into other tumor entities

**Threats** – TTF might not work, might not be embraced by patients, relatives and HCP, might not be reimbursed, might be replaced by competing treatments
Soft standards of care in glioblastoma

- Always tell the truth, but do it in fractions…
- Check the need for steroids
- Check the need for anticonvulsants
- Watch out for treatment-related side effects
- Watch out for vascular complications: deep vein thrombosis, pulmonary embolism, haemorrhage, stroke
- Listen and watch for alternative treatment use
It is **not** standard of care:

- To use radiosurgery (including Gamma Knife and CyberKnife®) in the treatment of newly diagnosed or recurrent glioblastoma
- To put or maintain all patients with newly diagnosed glioblastoma on steroids during radiotherapy or even thereafter
- To put or maintain all patients with newly diagnosed glioblastoma on anti-epileptic drugs
- To withhold full-dose heparin or warfarin from glioblastoma patients with deep vein thrombosis or pulmonary embolism
References


