

Malignant glioma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

R. Stupp¹ & F. Roila²

On behalf of the ESMO Guidelines Working Group*

¹Multidisciplinary Oncology Center, University of Lausanne Hospital, Lausanne, Switzerland; ²Department of Medical Oncology, S. Maria della Misericordia Hospital, Perugia, Italy

incidence

The incidence of malignant glioma is 5–7/100 000. Malignant glioma may develop at all ages, the peak incidence being in the fifth and sixth decades of life.

diagnosis

Malignant glioma comprises glioblastoma [World Health Organization (WHO) grade IV], anaplastic astrocytoma (WHO grade III), mixed anaplastic oligoastrocytoma (WHO grade III) and anaplastic oligodendroglioma (WHO grade III). Diagnosis after biopsy or tumor resection is made according to the revised WHO classification.

staging and risk assessment

Staging includes imaging of the brain, ideally with magnetic resonance imaging (MRI). If repeat imaging is deemed necessary to determine residual disease, it should be carried out within 24–48 h after surgery. Lumbar puncture is generally not necessary, with the exception of adult patients with medulloblastoma (in whom it should be carried out 3 weeks after surgery) and staging of other organs is not needed.

Other than lower tumor grade, good performance status and an intact neurological function, tumor resection and age <50 years have been identified as more favorable prognostic factors.

Prognosis depends on tumor grade and histology. Glioblastoma carries the worst prognosis, while pure oligodendroglioma tends to have a better outcome and improved response to therapy. Prognosis of mixed anaplastic oligoastrocytoma and anaplastic astrocytoma is

intermediate between glioblastoma and pure anaplastic oligodendroglioma.

treatment plan

Patients should be evaluated by a specialized multidisciplinary team. Special consideration needs to be given to performance status and neurological function.

newly diagnosed patients

Surgery is commonly the initial therapeutic approach for debulking and obtaining tissue for diagnosis. Tumor resection is of prognostic value, and may be beneficial to attempt maximal tumor resection [II, C]. Implantation of chemotherapy-impregnated wafer (BCNU polymer) into the resection cavity has shown only a marginal benefit in malignant glioma versus radiotherapy alone [II, B].

Fractionated focal radiotherapy (60 Gy, 2 Gy × 30, or equivalent doses/fractionations) is the standard treatment after resection or biopsy [I, A]. Escalating doses beyond 60 Gy has not been shown to be of value. In elderly patients or patients with a low performance status, shorter hypofractionated regimens (e.g. 40 Gy in 15 fractions) are commonly proposed [II, B]. Radiotherapy (28 × 1.8 Gy, 50 Gy) in patients >70 years of age was superior to best supportive care alone in a randomized phase III trial [II, B].

Concomitant and adjuvant temozolomide chemotherapy has been demonstrated to significantly improve median and 2-year survival in a large randomized trial in glioblastoma [I, A]. Selecting patients likely to benefit from therapy on the basis of MGMT gene promoter methylation has been suggested [II, B].

Adjuvant chemotherapy with procarbazine, lomustine and vincristine (PCV regimen) has failed to improve survival in prospective randomized studies [I, A]. Nevertheless, based on a large meta-analysis [I, A] nitrosourea-based chemotherapy may marginally improve survival in selected patients.

recurrent disease

Some benefit of chemotherapy has been shown for patients with an adequate performance status who have not received

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland

Approved by the ESMO Guidelines Working Group: December 2004, last update September 2007. This publication supercedes the previously published version—Ann Oncol 2007; 18 (Suppl 2): ii69–ii70.

Conflict of interest: Dr Stupp has not reported any conflicts of interest.

prior adjuvant cytotoxic therapy. Anaplastic astrocytomas are more likely than glioblastoma to respond to chemotherapy [III, B]. For patients failing prior chemotherapy, there is no established chemotherapy regimen available and patients are best treated within investigational clinical protocols. Single-agent nitrosourea therapy may improve tumor control in some patients, while EGFR inhibition with erlotinib has not demonstrated any measurable anti-tumor efficacy in a randomized phase II trial [II, C].

Repeat surgery and implantation of chemotherapy-impregnated polymers may prolong survival in selected patients [II, B].

anaplastic oligodendroglioma

Oligodendroglioma carries a somewhat better prognosis. In particular, the subgroup of patients with a deletion on chromosome 1p and 19q seem to have a longer survival and better response to chemotherapy compared with patients without deletion. In patients with recurrent oligodendroglioma, chemotherapy should be considered [II, B], while (neo)adjuvant PCV chemotherapy [procarbazine, lomustine (CCNU), vincristine] has failed to improve survival in patients in addition to radiotherapy in newly diagnosed anaplastic oligoastrocytoma and oligodendroglioma [I, B].

response evaluation

If response is evaluated, it should be done with MRI. Contrast enhancement and presumed tumor progression on imaging 4–8 weeks after the end of radiotherapy may be an imaging artefact (pseudoprogression) and should be re-evaluated 4 weeks later with a second MRI.

Response to chemotherapy is evaluated according to the WHO criteria, but should also include an assessment of neurological function and corticosteroid use (Macdonald criteria). The rate of patients alive and progression free at 6 months (PFS_{6mo}) has been recognized as a valid endpoint and also includes patients who benefit from therapy by disease stabilization.

follow-up

Follow-up consists of a clinical evaluation with particular attention to neurological function, seizures or seizure equivalents and corticosteroid use. Patients should be tapered off steroid use as early as possible. Venous thrombotic events occur frequently in patients with unresected or recurrent tumors.

Laboratory tests are not indicated unless the patient is receiving chemotherapy (blood count), corticosteroids (glucose) or antiepileptic drugs (blood count, liver function tests).

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were

considered justified standard clinical practice by the expert authors and the ESMO faculty.

literature

- Brandes AA, Tosoni A, Basso U et al. Second-line chemotherapy with irinotecan plus carmustine in glioblastoma recurrent or progressive after first-line temozolomide chemotherapy: a phase II study of the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). *J Clin Oncol* 2004; 22: 4727–4734.
- Cairncross G, Berkey B, Shaw E et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 2006; 24: 2707–2714.
- DeAngelis LM. Medical progress: brain tumors. *N Engl J Med* 2001; 344: 114–123.
- Hegi ME, Diserens AC, Gorlia T et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005; 352: 997–1003.
- Jaecckle KA, Ballman KV, Rao RD et al. Current strategies in treatment of oligodendroglioma: evolution of molecular signatures of response. *J Clin Oncol* 2006; 24: 1246–1252.
- Keime-Guibert F, Chinot O, Taillandier L et al. Radiotherapy for glioblastoma in the elderly. *N Engl J Med* 2007; 356: 1527–1535.
- Kleihues P, Louis DN, Scheithauer BW et al. The WHO classification of tumors of the nervous system. *J Neuropathol Exp Neurol* 2002; 61: 215–225.
- Lacroix M, Abi-Said D, Fournier DR et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 2001; 95: 190–198.
- Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990; 8: 1277–1280.
- Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine and vincristine in the adjuvant treatment of high-grade astrocytomas: Medical Research Council trial. *J Clin Oncol* 2001; 19: 509–518.
- Roa W, Brasher PM, Bauman G et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol* 2004; 22: 1583–1588.
- Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002; 359: 1011–1018.
- Stummer W, Pichlmeier U, Meinel T et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2006; 7: 392–401.
- Stupp R, Hegi ME, Gilbert MR, Chakravarti A. Chemoradiotherapy in malignant glioma: standard of care and future directions. *J Clin Oncol* 2007; 25: 4127–4136.
- Stupp R, Hegi ME, van den Bent MJ et al. Changing paradigms—an update of the multidisciplinary management of malignant glioma. *Oncologist* 2006; 11: 165–180.
- Stupp R, Mason WP, van den Bent MJ et al. Concomitant and adjuvant temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme. *N Engl J Med* 2005; 352: 987–996.
- van den Bent M, Brandes A, Rampling R et al. Randomized phase II trial of erlotinib (E) versus temozolomide (TMZ) or BCNU in recurrent glioblastoma multiforme: EORTC 26034. *ASCO Ann Meet Proc Part I. J Clin Oncol* 2007; 25: 76S (Abstr 2004).
- van den Bent MJ, Carpentier AF, Brandes AA et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: A randomized European Organization for Research and Treatment of Cancer phase III trial. *J Clin Oncol* 2006; 24: 2715–2722.
- van den Bent MJ, Taphoorn MJ, Brandes AA et al. Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglioma

- tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971. *J Clin Oncol* 2003; 21: 2525–2528.
20. Westphal M, Hilt DC, Bortey E et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-oncol* 2003; 5: 79–88.
 21. Westphal M, Ram Z, Riddle V et al. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; 148: 269–275.
 22. Wong ET, Hess KR, Gleason MJ et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol* 1999; 17: 2572–2578.
 23. Wood JR, Green SB, Shapiro WR. The prognostic importance of tumor size in malignant gliomas: a computed tomographic scan study by the Brain Tumor Cooperative Group. *J Clin Oncol* 1988; 6: 338–343.
 24. Yung WK, Albright RE, Olson J et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer* 2000; 83: 588–593.