Astrocytoma IDH-mutant treatment

Maximal surgical resection, if safely feasible, is the best initial therapeutic approach [1)]

Early radiotherapy (as opposed to radiotherapy after disease progression) has been shown to prolong progression-free survival (PFS) but not OS [2)]

The use of chemotherapy alone as frontline therapy remains investigational but might be an option if radiotherapy is not feasible, for example, in patients with large tumours. However, the PFS is probably shorter with temozolomide than with radiotherapy in patients with IDH-mutant, grade 2 diffuse astrocytomas [3)]

The RTOG 9802 trial reported a major prolongation of OS with the addition of PCV polychemotherapy to radiotherapy (54 Gy), from 7.8 years to 13.3 years in patients with high-risk WHO grade 2 gliomas who were 18–39 years of age and had undergone a subtotal resection or biopsy or in those aged ≥40 years [4)]

This benefit was reported across histological subgroups and, although cohort sizes were small, benefit was observed in patients with either IDH-mutant astrocytomas or oligodendrogliomas but not in those with IDH-wild-type tumours [5)].

The management of low-grade glioma (LGG) still remains controversial because the effectiveness of early and extensive resection is unclear, and the use of radiation therapy or chemotherapy is not well-defined.

The relatively long survival compared to other brain tumors makes consideration of treatment toxicity, and thus timing of potentially damaging interventions such as surgery, radiation, and chemotherapy, crucial. Moreover, the rarity of these tumors makes clinical trials to ascertain optimal care challenging.

The discovery that most low-grade gliomas harbor isocitrate dehydrogenase (IDH) mutations that confer a favorable prognosis has improved diagnosis and risk stratification of these tumors. Although Level of evidence 1 is still lacking, increasing data support the concept of maximal safe tumor debulking as a first step in tumor management. Preliminary results from a large randomized trial suggest chemotherapy is of comparable effectiveness to radiation therapy for one molecular subtype of low-grade glioma. Importantly, however, the final results of a phase 3 trial comparing radiation with or without procarbazine, CCNU (lomustine), and vincristine (PCV) chemotherapy indicate a large survival advantage to combined chemotherapy and radiation, raising questions about using chemotherapy alone as an initial treatment strategy.

While the combination of radiation and PCVprovides the best proven overall survival with low-grade gliomas, important questions remain. These include whether the better-tolerated temozolomide is as effective as PCV in conjunction with radiation therapy and whether the use of initial chemotherapy as a strategy to defer the potential delayed cognitive toxicity associated with radiation will yield acceptable survival results with a favorable toxicity profile [6].

Choosing the best treatment strategy for each patient with a diffuse low-grade glioma, in other words optimizing the oncologic and functional balance, implies not only a full knowledge of the natural history of this chronic disease, but also an understanding of the adaptation of the brain in response to growth and spread of the glioma [7].

The ideal management of suspected low-grade gliomas (LGGs) has historically been controversial in neurosurgery and neurooncology [8] [9] [10].

Surgery

see Low-grade glioma surgery.

Chemotherapy

see low-grade glioma chemotherapy.

Radiosurgery

see low-grade glioma radiosurgery.

Radiotherapy

see low-grade glioma radiotherapy.

Immunotherapy

Low-grade glioma immunotherapy.

[1] Jakola AS, Skjulsvik AJ, Myrmel KS, Sjåvik K, Unsgård G, Torp SH, Aaberg K, Berg T, Dai HY, Johnsen K, Kloster R, Solheim O. Surgical resection versus watchful waiting in low-grade gliomas. Ann Oncol. 2017 Aug 1;28(8):1942-1948. doi: 10.1093/annonc/mdx230. PMID: 28475680; PMCID: PMC5834105.

[2] van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, Malmström PO, Collette L, Piérart M, Mirimanoff R, Karim AB; EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council. Long-term efficacy of early versus delayed radiotherapy for low-grade

astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet. 2005 Sep 17-23;366(9490):985-90. doi: 10.1016/S0140-6736(05)67070-5. Erratum in: Lancet. 2006 Jun 3;367(9525):1818. PMID: 16168780.

3)

Baumert BG, Hegi ME, van den Bent MJ, von Deimling A, Gorlia T, Hoang-Xuan K, Brandes AA, Kantor G, Taphoorn MJB, Hassel MB, Hartmann C, Ryan G, Capper D, Kros JM, Kurscheid S, Wick W, Enting R, Reni M, Thiessen B, Dhermain F, Bromberg JE, Feuvret L, Reijneveld JC, Chinot O, Gijtenbeek JMM, Rossiter JP, Dif N, Balana C, Bravo-Marques J, Clement PM, Marosi C, Tzuk-Shina T, Nordal RA, Rees J, Lacombe D, Mason WP, Stupp R. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. Lancet Oncol. 2016 Nov;17(11):1521-1532. doi: 10.1016/S1470-2045(16)30313-8. Epub 2016 Sep 27. PMID: 27686946; PMCID: PMC5124485.

4)

Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, Coons S, Ricci P, Bullard D, Brown PD, Stelzer K, Brachman D, Suh JH, Schultz CJ, Bahary JP, Fisher BJ, Kim H, Murtha AD, Bell EH, Won M, Mehta MP, Curran WJ Jr. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. N Engl J Med. 2016 Apr 7;374(14):1344-55. doi: 10.1056/NEJMoa1500925. PMID: 27050206; PMCID: PMC5170873.

5)

Bell EH, Zhang P, Shaw EG, Buckner JC, Barger GR, Bullard DE, Mehta MP, Gilbert MR, Brown PD, Stelzer KJ, McElroy JP, Fleming JL, Timmers CD, Becker AP, Salavaggione AL, Liu Z, Aldape K, Brachman DG, Gertler SZ, Murtha AD, Schultz CJ, Johnson D, Laack NN, Hunter GK, Crocker IR, Won M, Chakravarti A. Comprehensive Genomic Analysis in NRG Oncology/RTOG 9802: A Phase III Trial of Radiation Versus Radiation Plus Procarbazine, Lomustine (CCNU), and Vincristine in High-Risk Low-Grade Glioma. J Clin Oncol. 2020 Oct 10;38(29):3407-3417. doi: 10.1200/JCO.19.02983. Epub 2020 Jul 24. PMID: 32706640; PMCID: PMC7527157.

6)

Schiff D. Low-grade Gliomas. Continuum (Minneap Minn). 2017 Dec;23(6, Neuro-oncology):1564-1579. doi: 10.1212/CON.0000000000000537. PubMed PMID: 29200111.

7)

Duffau H. Diffuse low-grade gliomas and neuroplasticity. Diagn Interv Imaging. 2014 Sep 10. pii: S2211-5684(14)00220-4. doi: 10.1016/j.diii.2014.08.001. [Epub ahead of print] PubMed PMID: 25218490.

8)

Keles GE, Lamborn KR, Berger MS: Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurg 95:735–745, 2001

9)

Lang FF, Gilbert MR: Diffusely infiltrative low-grade gliomas in adults. J Clin Oncol 24:1236–1245, 2006

10)

Wessels PH, Weber WE, Raven G, Ramaekers FC, Hopman AH, Twijnstra A: Supratentorial grade II astrocytoma: biological features and clinical course. Lancet Neurol 2:395–403, 2003