Surgery of IDH-mutated grade 2 glioma: continually setting the bar higher
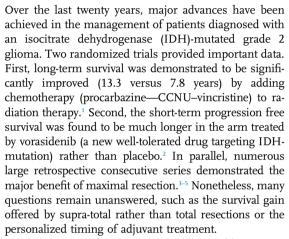
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Over the last twenty years, major advances have been achieved in the management of patients diagnosed with an isocitrate dehydrogenase (IDH)-mutated grade 2 glioma. Two randomized trials provided important data. First, long-term survival was demonstrated to be significantly improved (13.3 versus 7.8 years) by adding chemotherapy (procarbazine—CCNU–vincristine) to radiation therapy.[1] Second, the short-term progression free survival was found to be much longer in the arm treated by vorasidenib (a new well-tolerated drug targeting IDH-mutation) rather than placebo.[2] In parallel, numerous large retrospective consecutive series demonstrated the major benefit of maximal resection.[3–5] Nonetheless, many questions remain unanswered, such as the survival gain offered by supra-total rather than total resections or the personalized timing of adjuvant treatment.

In this issue of *The Lancet Regional Health—Europe*, Ng and colleagues[6] leveraged a retrospective series of 600 patients to address some of these questions. Multivariate analysis demonstrated a better survival for supratotal versus total and total versus partial resections, while patient's functional status was mostly unaffected by the surgery. Ng and colleagues' work[6] does more than confirm the prominent survival advantage of extensive resection in IDH-mutated grade 2 glioma (even without early adjuvant therapy); it is, in many ways, one of those rare practice-changing studies.

First, considering the very large median survivals found in their series (15.2 years for astrocytoma, not reached for oligodendroglioma), it is important to realize that only retrospective consecutive series with innovative methodologies—such as propensity scores used by the authors—can give a comprehensive overview of the treatment effects. The data they provided over three decades are in a way much more robust than the vorasidenib randomized trial, with its 14.2 months of follow-up. More than that, this retrospective design is the only way to analyze simultaneously overall survival *and* functional outcomes. In this regard, authors provided highly convincing data demonstrating that function-based resections under awake neuropsychological monitoring warrants an excellent cognitive outcome, in addition to the survival gain. Such a long-term and holistic approach should be the new methodological standard in IDH-mutated glioma clinical research.

Second, Ng and colleagues[6] provide the most convincing analysis demonstrating the benefit of supratotal versus total resections. This is all the more important since the chances of achieving supratotal resections are expected to increase in the coming years, as the rate of incidental discovery of small tumors should continue to increase, thanks to easier access to magnetic resonance imaging.

Moreover, as the median survival in the high-risk group (astrocytoma with postoperative residual tumor greater than 15 cc) is around 10 years, the long-term adverse effects of early radiation therapy are less concerning. Hence, high-risk patients could benefit from upfront postoperative chemo-radiotherapy, especially if the tumor growth rate exceeds 8 mm/year.[7]

The impressive results presented by Ng and colleagues raise the issue of its reproducibility around the world. Indeed, given the hard learning curve of this ultra-specialized awake surgery and the rarity of IDH-mutated grade 2 glioma, it seems mandatory to organize the care of these patients in quaternary neurosurgical and neurooncological referral centers, to reach an annual case volume close to 40 new cases/year and to offer patients all the required resources and multidisciplinary expertise, including neuropsychologists, speech therapists, rehabilitation teams, and more.

This is the necessary condition to tackle the next challenges. Regarding the surgical outcomes, there is still room for improvement in functional outcomes, which are already excellent albeit not perfect (see for example the slight deterioration in executive functions). The understanding that complex cognitive functions are widely distributed and highly plastic recently enabled to develop new machine-learning methods to preoperatively determine the maximal (supratotal) resection that would warrant full recovery of cognitive status.[8,9] In this perspective, potentiation of neuroplasticity by pharmacological or brain stimulation interventions would be a great ally on the path towards optimal recovery, but much remains to be done to understand the plasticity-induced changes of brain functional networks at the mechanistic level and foster their reshaping. Ultimately,

DOI of original article: https://doi.org/10.1016/j.lanepe.2024.101078
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even if objective evaluations testifies within-normal-range scoring, many patients complain of persisting fatigability following their glioma resection. Efforts should be devoted to better evaluate this fatigability, to understand its neural basis,[10] and to find means to relieve this debilitating symptom.

All in all, the study of Ng and colleagues concludes the 30 years of Duffau's pioneering work in the field of IDH-mutated grade 2 glioma awake surgery, definitively establishing the major contribution of functional-controlled maximal resections for improving both survival and functionality of these patients. We are now entering an exciting area in which the adjunct of vorasidenib to our armamentarium combined with neuroscience advances for controlling neuroplasticity should allow to render the life of these patients even longer and better.

Declaration of interests
None.

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