Neuro-Oncology

20(1), 6–7, 2018 | doi:10.1093/neuonc/nox218 | Advance Access date 3 January 2018

Extent of surgery in low-grade gliomas: an old question in a new context

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See the article by Wijnenga et al on pages 103–112

The value of surgery to establish histological diagnosis and define the molecular profile of low-grade gliomas to inform further management (i.e. observation with MRI vs radiotherapy and/or chemotherapy) is clear. Moreover, there is an almost general agreement that maximal safe resection should be attempted early on in patients presenting with neurological symptoms (more commonly seizures) and a suspected low-grade glioma on MRI.[1] Even if there has been no randomized controlled trial that evaluated the extent of resection in these tumors, several retrospective studies have suggested that a significant improvement in both progression-free (PFS) and overall survival (OS) is associated with an increasing amount of tumor removal.[2,3] However, only a minority of studies have analyzed the importance of extent of resection based on a more precise volumetric assessment of the residual tumor after surgery.[4–6] Following the new World Health Organization (WHO) Classification of Brain Tumors in 2016, a new question has arisen: whether the feasibility and value of the extent of resection are influenced by the molecular profile.

In this issue of *Neuro-Oncology* Wijnenga et al[7] from the Netherlands report the results of a retrospective study on 228 adult patients with WHO II supratentorial glioma in whom they evaluated the impact of the postoperative tumor volume, corrected for molecular profile, on OS. Pre- and postoperative tumor volumes were assessed with semi-automatic software on T2-weighted MRI images, and a targeted next-generation sequencing was used for a molecular classification of tumors. Complete or near complete resection was achieved in 39% of patients. Overall, after multivariable analysis, postoperative tumor volume, as primary measure of the extent of resection, was significantly associated with OS with HR of 1.01 (95% CI 1.002-1.02, p=0.016) per cm^3 increase in volume. Notably, a strong effect on OS was seen in patients with no detectable tumor after resection. These findings are in line with the results of a previous smaller post-hoc analysis performed by a University of California, San Francisco (UCSF) group,[8] that reported a significant association of postoperative tumor volume with OS after stratification by molecular factors (1p/19q codeletion and IDH 1 mutation). In particular, every 10 cm^3 of increase in postoperative volume was associated with shorter OS.

Interestingly, in the Wijnenga study[7] the negative effect on OS of any residual tumor after surgery was more evident in IDH mutated astrocytomas compared with IDH-mutated and 1p/19q-codeleted oligodendrogliomas. An explanation could be that the amount of residual tumor cells is more critical in astrocytomas, due to an inherent risk of malignant progression toward glioblastoma, than in oligodendrogliomas, which conversely are intrinsically more indolent and responsive to chemotherapy with alkylating agents. However, this hypothesis needs confirmation in prospective datasets with a duration of follow-up longer than that of the present study (5.79 years). Due to the retrospective nature of the Dutch study, the MRI protocol, postoperative treatments and timing of follow-up evaluations were heterogeneous, thus precluding a reliable analysis of the influence of the extent of resection on PFS.

Two important questions need to be answered by future studies. First, what is the value of the extent of resection in IDH wild-type grade II gliomas? These tumors are more aggressive than IDH-mutated counterparts but somewhat heterogeneous in terms of prognosis.[9] Both the UCSF and Dutch studies were not able to investigate this issue due to the small sample size. A second, more general question is whether the same considerations in terms of the importance of the extent of resection can apply to IDH-mutated grade III gliomas, whose outcome seems similar to that of IDH-mutated grade II tumors.

The modern tools in neurosurgical oncology (intraoperative mapping, awake surgery, intraoperative MRI) have increased the feasibility of more radical resections, and thus new concepts of management have been hypothized.[10] Supratotal resection, i.e. resection extending beyond the MRI signal abnormalities, for tumors in non-eloquent areas has been proposed with the aim of avoiding potentially toxic adjuvant therapies. Moreover, reoperation either at progression after initial observation with MRI or even as a second-look surgery following an initial incomplete resection, is increasingly used in neurosurgical centers with specific expertise in lower-grade gliomas. However, only well-designed prospective studies with uniform techniques and methodology can answer some critical questions, such as whether a total/supratotal resection is better in terms of survival compared with a near total/subtotal resection, and whether the clinical benefit of the different types of resection is the same or not in the different molecular subgroups.

Finally, it will be crucial when designing new studies to be aware that the preservation of cognitive functions and quality of life is at least as important as the improvement of survival.

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