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REVIEW

Is it all a matter of size? Impact of maximization of surgical resection in cerebral tumors

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Abstract
The oncological impact of cytoreductive surgery for malignant glioma has been analyzed in a few prospective, randomized studies; however, the impact of different cytoreductive surgical techniques of cerebral tumors remains controversial. Despite retrospective analyses revealing an oncological impact of complete surgical resection in cerebral metastases and low-grade glioma, the oncological impact of further extension of resection to a supramarginal resection remains disputable lacking high-grade evidence: supramarginal resections have yet to be analyzed in malignant glioma. Although extension of resection towards a supramarginal resection was thought to improve outcome and prevent malignant transformation in low-grade glioma, the rate of (temporary) deficits was higher than 50% in recent retrospective studies, and the oncological impact and long-term results have to be analyzed in further (prospective and controlled) studies. Cerebral metastases show a growth pattern different from glioma with less and more locally limited brain invasion. Therefore, local control may be achieved by extension of resection after complete lesionectomy of cerebral metastases. Therefore, supramarginal resection may be a promising approach but must be evaluated in further studies.

Keywords Low-grade glioma · Malignant glioma · Glioblastoma · Cerebral metastasis · Supramarginal resection · Surgery · Resection

Introduction

For many solid systemic tumors, histopathological evaluation of the degree of surgical tumor resection (R0 vs. R1, R2 resection status) is an aspect of the TNM classification known to be of prognostic relevance. However, the TNM classification is not applicable for brain tumors, and a histopathological confirmation of tumor cell-free resection margins is not useful for malignant glioma and not established for cerebral metastases. The degree of surgical resection is therefore routinely evaluated by early postoperative magnet resonance tomography (MRI). A preoperative contrast-enhancing lesion in the MRI T1 sequences usually serves as surrogate for malignant glioma and cerebral metastases and the T2/Flair lesions as surrogate for low-grade glioma. Complete surgical resection is usually defined as lesionectomy in the postoperative MRIs but not as complete biological tumor removal. Complete biological tumor removal may not be possible for many intracerebral tumors due to their widespread infiltration of eloquent cerebral tissue, and thus the impact of cytoreductive surgery of cerebral tumors has been questioned. Therefore, the present review aims to discuss the impact of a maximization of surgical resection in low- and high-grade gliomas and cerebral metastases.

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Resection concept developed for treatment of low-grade gliomas

Low-grade gliomas are associated with a heavy personal burden and have a high socio-economic relevance. Their optimal treatment is part of an ongoing debate, and as prospective randomized trials comparing different therapeutic strategies are lacking, recommendations with high-level evidence are not available.

Low-grade gliomas remain clinically silent until they are incidentally discovered or elicit specific symptoms, usually epileptic seizures [34]. After a period of continuous growth of 4–5 mm per year in average, they show a more aggressive behavior with neoangiogenesis and malignant transformation. Another characteristic feature of low-grade glioma is their infiltrative growth pattern with a diffuse tumor infiltration of still functional brain areas. The majority of low-grade glioma patients are young adults without major neurologic deficits who enjoy normal life. The specific biology of low-grade glioma addresses a challenge of the actual therapeutic concepts based on the biology of "benign" glioma. Two different therapeutic concepts are common: a "watch-and-wait" strategy with or without a diagnostic biopsy as opposed to aggressive treatment by surgical resection. The "watch-and-watch" strategy with MRI-based serial tumor observation avoids the risk of surgery-associated morbidity and mortality. As low-grade glioma may infiltrate eloquent and functional cerebral tissue, surgery harbors the substantial risk of neurological deterioration. This approach does not adequately address the potential property of low-grade glioma (LGG) of continuous slow growth, invariably progressing to high-grade gliomas (HGG). The opposite approach is a surgical resection. Surgery of LGG requires identification and preservation of relevant and eloquent cortical and subcortical brain areas. Identification of functional tissue involves neurophysiological monitoring, planning surgery as awake surgery, and extensive pre- and intraoperative neurological and psychological testing. In this scenario, neurosurgeons require an extensive theoretic and practical knowledge about the functional anatomy of the brain. This strategy may help to prevent surgery-associated morbidity: a recent meta-analysis of 90 studies with over 8000 patients rated the frequency of severe neurologic deficits following LGG resection when using intraoperative neurophysiological mapping [11]. In this cohort, rate of radiologically confirmed gross-total resection was 75% compared to 58% gross-total resection and use of intraoperative brain mapping significantly prevented serve neurological deficits [11]. Therefore, risk for neurologic complication following low-grade surgery is comparable to other neurosurgical procedures.

Nevertheless, the main question remains whether radical resection of low-grade glioma translates into improved neurological symptoms and a better prognosis. Several retrospective studies suggest a significant benefit of low-grade glioma resection: a frequently cited study analyzed survival in population-based parallel cohorts of low-grade glioma patients in two different Scandinavian hospitals with different surgical strategies. Early surgical resection resulted in better overall survival as compared to a biopsy and a "wait-and-watch" strategy [21, 22]. A second retrospective "near-randomized" trial from Freiburg also revealed a benefit of early resection on survival (5-year OS 82% after early resection vs. 54% after biopsy and observation) [42]. The largest retrospective series of low-grade glioma patients came from the French glioma consortium and demonstrated a significantly increased malignant progression-free and overall survival following extensive surgical resection [9, 38]. Several further retrospective studies demonstrated a clear benefit of low-grade glioma resection [14, 19, 20, 35, 46, 47, 60, 63, 64]. Extent of resection and residual tumor volume serves as predictor of malignant transformation and the progression-free survival [5, 50]. However, next to these retrospective studies, high-level evidence based on prospective randomized studies is lacking. Actual guidelines such as the "Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force" advocate a maximal resection of low-grade glioma as first therapeutic option. Extension of the resection towards a supramarginal resection may additionally improve the outcome and prevent malignant transformation [62]. However, rate of temporary deficits in the last study was 60% [62].

The potential benefit of gross-total resection and possibly the additional benefit of a supramarginal resection of low-grade glioma led to the development of a new surgical concept, which induced a paradigm shift: as low-grade gliomas are highly infiltrative tumors and as their biological extent cannot be completely resolved by standard MRI imaging, French neurosurgeons headed by Hugges Duffau advocated to tailor the extent of surgical resection to the individual functional cortical and subcortical borders instead of to radiological delimitation. Therefore, resection should be extended as far as possible until the functional brain areas and the subcortical fiber tracks are reached. This concept entitled as "functional surgical neuro-oncology" was defined by an operation in the central nervous system "according to cortico-subcortical individual functional boundaries made visible by the use of intraoperative mapping in awake patients" [13]. Therefore, the neurosurgeon needs to be the surgeon and neuroscientist in one person with an extensive knowledge of functional anatomy and the brain connectome. From a neuro-oncological view, the neurosurgeon's task is to ensure the neurologic and functional integrity of tumor patients and to extend the resection as far as possible—if possible far beyond the radiologic boarders of the tumor. Recent retrospective data suggest a correlation between extent of resection and rate of malignant progression, progression-free, and overall survival. Though the impact of GTR on overall survival (OS) and time of malignant transformation has been demonstrated, the additional benefit of a supramarginal resection is yet not proven. As high-quality studies (e.g., randomized and controlled trials) on supramarginal resection are lacking, recent studies do not allow high-level recommendation and further high-quality studies are required.

High-grade glioma

Low- and high-grade gliomas are highly infiltrating tumors. Therefore, the same considerations as for low-grade glioma may be applicable for malignant glioma.

The impact of cytoreductive surgery of malignant glioma has been discussed controversially [51]. First, evidence for the impact of cytoreduction in patients suffering from glioblastoma was published as early as the 1950s: extensive surgical resection resulted in superior survival compared to biopsy alone [55]. More recently, a beneficial effect on the median survival of tumor resection over biopsy alone was demonstrated in a prospective observational study with 565 patients and in a study with a limited number of patients with malignant glioma over the age of 65 years [32, 56]. Later, two prospective, randomized, and controlled studies on malignant glioma offered further high-level evidence for the impact of extent of surgical resection on survival: The multicenter 5-ALA study with 270 glioblastoma patients compared the surgical technique of 5-ALA-fluorescence-guided resection with the conventional white-light-assisted technique. The 5-ALA technique was associated with a 29% higher rate of complete surgical resections of the contrast-enhancing tumor parts on an early postoperative MRI within 72 h after surgery and subsequently with improved 6-month progression-free survival [52]. As it was not powered for an analysis of OS, the 5-ALA trial did not demonstrate a better OS in the 5-ALA-group [52]. An additional post hoc analysis of the data from the 5-ALA study including imbalances and bias demonstrated the impact of extent of surgical resection on survival [53]. The single-center iMRI study with 58 glioblastoma patients compared the conventional white-light-assisted resection technique with the intraoperative MRI guidance on extent of resection. Again, patients with complete tumor resections had longer progression-free survival than patients with residual tumor after surgery [48]. The study was neither designed nor powered for a further analysis of a potential effect of extent of surgical resection on overall survival [48]. Nevertheless, both the 5-ALA and the iMRT studies demonstrated the impact of complete surgical resection on the (progression-free) survival and provided high-level evidence that complete surgical resections of contrast enhancement should be attempted whenever possible. Next to 5-ALA and iMRT techniques, other surgical techniques may aide in achieving more complete surgical resections: Similar to 5-ALA fluorescence, staining of malignant tumor by fluorescein may facilitate a complete surgical resection: Recently, the results of the multicentric, prospective FLUOGLIO Phase II study with totally 56 malignant glioma patients underwent fluorescein fluorescence-guided resection were published: In this trial, degree of surgical resection ranged between 83 and 100% (median 100%), and median progression-free survival (PFS) was 7 months and median OS of 12 months, respectively [1]. Forty severe adverse events were observed in 56 patients of whom none was related to the fluorescein administration [1]. Fluorescein staining of malignant glioma and cerebral metastases was analyzed for stereotactic needle biopsy as well as surgical resection in several further retrospective studies [e.g., [10, 44, 45, 54]]. However, fluorescein staining of malignant brain tumors may be unspecific as fluorescein staining might be detected not only in tumors but also in areas of surgical injury and any zone of brain edema [16].

Does extension of surgical resection to a supramarginal resection beyond the contrast enhancement on MRI have an additional beneficial effect on overall survival? This question cannot be answered yet as (high-quality) studies are lacking. Recently, a prospective uncontrolled study analyzed the impact of a technique entitled dual intraoperative visualization approach (DiVA) with a "supra-complete" resection on overall survival [17, 18]: This technique includes intermittent projection of functional neuronavigation data, a complete 5-ALA fluorescence-guided tumor resection, intraoperative evaluation of the extent of surgical resection by an intraoperative MRI, and in case of residual tumor resection, a further resection and re-evaluation of the 5-ALA signal. Malignant glioma cell infiltration within the resected tissue was intraoperatively analyzed by an experienced neuropathologist. The authors described a proportional correlation between the extent of surgical resection and overall survival: The greater the extent of surgical resection over the control group undergoing conventional gross-total resection, the more significant the extension of overall survival time [18]. Rate of perioperative deterioration was 3% in the DiVA group and therefore lower as compared to that in the control group (11%). However, the study suffers from several weaknesses and biases including its uncontrolled and partially retrospective study design. Furthermore, it remains unclear whether DiVA leads to higher probability of a complete tumor resection and how far resection was extended beyond the MR contrast-enhancing boarders of the tumor. Another retrospective study reported long-lasting local control in about 10% of glioblastoma patients—almost exclusively in patients with complete (and probably supramarginal) resection of small glioblastoma and an unmethylated MGMT promoter [41].

Another question is whether other MRI sequences than contrast-enhancing parts on the MRI T1 sequences may serve as better surrogate parameters for the extent of surgical resection in high-grade glioma. For low-grade glioma, the T2-/FLAIR sequences usually are accepted as tumor correlates and are used for the evaluation of the extent of surgical resection [15, 29]. Abnormalities in MRI diffusion tensor imaging (DTI), apparent diffusion coefficient (ADC), or T2-/FLAIR sequences may inversely correlate with cell density and serve therefore as surrogate for the infiltration zone of malignant glioma beyond the solid tumor parts. As compared to the contrast enhancement on the T1 sequences, a longer PFS and OS were observed in a retrospective series of 31 glioblastoma patients in whom more DTI-documented abnormality was resected [59]. A further large retrospective single-center analysis with 1229 glioblastoma patients of "The University

of Texas MD Anderson Cancer Center" evaluated the impact of T2/FLAIR abnormality resection. Complete surgical resection of T1 contrast-enhancing tumor parts was achieved in 71%. Resection of at least 53.2% of T2/FLAIR abnormalities in addition to complete surgical resection of T1 contrast-enhancing tumor parts resulted in significantly improved overall survival [33]. The beneficial effect of T2/FLAIR abnormality resection was even evident in multivariate analysis. In this study, the rate of overall complications was 23% and the rate of neurological complications was 18%. Interestingly, resection of at least 53.2% of T2/FLAIR abnormalities was associated with less frequent complications (overall complication rates 26 vs. 18%, $p = 0.04$) [33].

In conclusion, a high-level evidence supports that complete surgical resections of contrast enhancement should be attempted where possible. Further resection beyond the borders of the contrast-enhancing tumor parts on MRI T1 sequences may improve progression-free and overall survival.

Cerebral metastasis

Cerebral metastases are the most common cerebral neoplasms with an increasing incidence [12]. About 50% of cerebral metastases arise from lung cancer (from either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)) and each about 20% of cerebral metastases from breast cancer or malignant melanoma [7, 31]. Cerebral metastases were often believed to be sharply delimitated from the surrounding brain tissue. However, different growth patterns of cerebral metastases can be distinguished, and only about 30% of cerebral metastases are well delineated [3, 6, 25, 28, 49]. The vast majority of cerebral metastases show an irregular tumor-brain interface with perivascular protrusion of tumor cells, nests of tumor cells in the adjacent normal brain tissue, or angio-cooptive infiltrations [28]. Therefore, cerebral metastases should be treated like infiltrating brain tumors.

A local brain invasion by cerebral metastases was considered as one reason for the high local recurrence rate after surgical resection alone. In fact, standard surgery alone was not sufficient to achieve local control in about 50% of cerebral metastases in prospective randomized and controlled studies [30, 39]. Does increasing radicalism of surgical metastases resection translate into a better local control? To date, this question has not been analyzed in prospective randomized and controlled studies. However, few retrospective studies revealed that extension of surgical resection may improve local control of cerebral metastases. Two recent retrospective studies analyzed the impact of an early postoperative MRI after metastectomy and demonstrated small residual tumor parts after intended gross-total resection in 5.4 and 20%, respectively [4, 26]. In the later study, detection of residual tumors within 72 h after surgery significantly correlated with local in-brain progression and was considered as one risk factor for a later local in-brain progression [26]. However, standard surgical procedure is aimed at gross-total tumor resection but not at extension into the surrounding normal appearing tumor bed.

The concept of a "microscopic-total" or "supramarginal" resection was initially introduced by Yoo and co-workers for cerebral metastases in 2009: resection was extended to a depth of about 5 mm after complete gross-total resection of non-eloquently situated cerebral metastases, and margins of the resection cavity were histologically confirmed to be tumor-free by frozen section [61]. In a retrospective analysis with 94 patients, supramarginal resection resulted in significant improved 2-year local control rate (70.1%) in the uni- and multivariate analysis as compared to standard gross-total resection. Interestingly, the 2-year overall survival but not the median and the 1-year survival were improved after supramarginal resection [61]. Next, supramarginal resection of eloquently localized cerebral metastases was shown to be feasible without an increased risk of perioperative complications if surgery is performed as awake surgery and /or with neurophysiological guidance [24]. The temporary morbidity was 14.7% in a further retrospective study analyzing the impact of supramarginal resection of eloquent metastases in 34 patients [27]. In this study, local tumor control could be achieved in 85% suggesting a higher local control rate as in the previously published prospective and controlled studies (e.g., 27% in the surgery/whole-brain radiation arm of the EORTC 22952-26001 study) [27, 30]. Recently, the impact of supramarginal resection of cerebral metastases was studied by the Milan workgroup in a retrospective study of 69 patients suffering from single large brain metastases (more than 21 mm in diameter). Surgery was performed with intraoperative functional and neurophysiological mapping, and resection was extended at least 5 mm beyond the contrast-enhancing tumor in the T1-weighted MRI sequences [40]. Adjuvant radiation therapy was standardized with an irradiation of the tumor bed with 3 × 10 Gy. New neurological deficits following resection were not observed and the 1- and 2-year local control rate was 100% [40].

In conclusion, prospective and randomized studies analyzing the impact of the resection degree in cerebral metastases. If possible, complete lesionectomy of cerebral metastases is standard and documented by retrospective studies. To date, four retrospective studies analyzed the impact of supramarginal resection in cerebral metastases: These studies reveal that a limited extension resection beyond the borders of the contrast-enhancing tumor parts on MRI T1 sequences is safe and may translate into a significant lower recurrence rate.

Limitations

Estimation of the impact of maximization of surgical resection is confounded by several limitations and methodical problems.

Firstly, the impact of complete surgical resection is well documented by prospective, randomized, and controlled studies for malignant glioma but not for low-grade glioma and for cerebral metastases. Therefore, recent evidence is gained from few studies with several biases. A further extension of the surgical resection towards a supramarginal resection has yet to be analyzed in studies with a high methodical quality.

Secondly, potential oncological impact of extension of surgical resection towards a supramarginal resection remains disputable, and the biological behavior of gliomas and cerebral metastases is hardly comparable: Low- and high-grade gliomas are highly invasive and infiltrative tumors. For low-grade glioma, it was recently documented that IDH-positive tumor cells can be detected within the whole brain of glioma patients and the tumor has therefore to be considered as a systemic disease of the brain [43]. Disseminated tumor cells interconnect over long distances and form a highly functional and resistant cellular network that connects over long distances [37]. Interconnection of glioma cells via tumor microtubules is crucial for tumor progression, network communication, and resistance to adverse events [37]. Therefore, extension of surgical resection will likely not lead to a complete removal of all tumor cells and subsequently not enable a local cure of gliomas. In contrast, cerebral metastases are sharply delimitated or show only a limited local infiltration of the adjacent brain tissue not exceeding 10–15 mm [28]. Therefore, extension of resection of cerebral metastases towards a supramarginal resection may lead to a biological complete removal of all malignant cells and subsequently enable a local cure.

Thirdly, their infiltrative and invasive growth pattern is one reason for the beneficial effects of an adjuvant treatment in malignant brain tumors. A prolongation of the PFS and OS by an adjuvant therapy is well documented for gliomas and cerebral metastases [e.g., [8, 30, 39, 58]]. The effects of different adjuvant therapy strategies have been taken into account as a potential bias when discussing studies without standardization of the adjuvant treatment. Patients with supramaximal resection can only be compared to patients with only maximal resection, if adjuvant treatment is equally distributed between the two groups. However, several studies cited in the present overview do not report the following adjuvant therapy, and recommended adjuvant treatment protocols have changed during the last years.

Fourthly, the potential oncological benefit of more aggressive resection strategies is associated with a higher risk of permanent and at least transient neurological deficits. This conflict has to be discussed with patients, and the decision regarding a more aggressive or more restrained surgical approach should individually be made. In this view, the actual EANO guideline recommends a maximum safe resection "whenever feasible in all patients with newly diagnosed gliomas" but also states that "the prevention of new, permanent neurological deficits is more important than extent of resection as gliomas are not cured by surgery" [58]. Permanent postoperative deficits were considered as being a negative prognostic factor. In this view, the guideline emphasizes a high priority of the quality of life for patients and caregivers. The impact of the patients' and caregivers' quality of life and of quality of life assessments is part of the ongoing further debate [36, 58]. However, one problem of the recent studies analyzing supramarginal resections is that these studies often focus more on a potential beneficial oncological effect than on a differential testing of neurological deficits and quality of life. Therefore, further studies should address these aspects.

Fifthly, extension of surgical resection beyond a supramarginal resection cannot really be verified by standard radiological evaluation. For most malignant tumors such as malignant glioma or cerebral metastases, contrast-enhancing parts on the MRI T1 sequences serve as surrogate parameters for tumors. Complete surgical resection is defined as complete removal of these contrast-enhancing tumor parts. A "surgeon-independent" confirmation of supramarginal resection beyond a complete surgical resection is hardly possible for several reasons: cerebral masses such as brain metastases not only cause brain shift but also may induce compression of the surrounding brain parenchyma which resolves during surgery. Changes of the cavity volume geometry after surgical resection are well documented [2, 23], and together with lesser compression of the surrounding brain, parenchyma may prevent accurate MRI-based segmentation of the cerebral tissue. Differences of pre- and postoperative manual or automatic MRI-based segmentation and volumetry of the brain parenchyma do not represent the degree of supramarginal resection. Therefore, an objective quantification of the degree of supramarginal resection is yet not established.

Furthermore, extension of resection towards a supramarginal resection requires an extensive knowledge of functional neuroanatomy and of the brain connectome. The functional borders have to be identified intraoperatively and preserved. The technique of supramarginal resection should therefore involve detailed intraoperative electrophysiological, neurological, and neuropsychological testing and the ability to perform awake surgery. These requirements may restrict this technique to highly specialized neuro-oncological centers.

Finally, an incomplete surgical resection and residual tumor tissue might be beneficial for subgroups of patients or for certain special therapy protocols. In the recent ACT IV study (rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma), treatment with rindopepimut did not increase overall survival. A post hoc subgroup analysis suggested that patients with significant residual disease might benefit from a treatment with rindopepimut plus temozolamide [57]. However, potential beneficial effects of residual tumor for patients receiving immune-modulatory treatments have to be evaluated in further studies.

Conclusion

The oncological impact of a complete surgical resection of malignant tumors is well documented by prospective randomized and controlled trials. Retrospective analyses also reveal an oncological impact for complete surgical resection of cerebral metastases and low-grade glioma. The oncological impact of a further extension of resection to a supramarginal resection remains disputable: the impact of supramarginal resection has not been analyzed in malignant glioma. Extension of the resection towards a supramarginal resection was believed to improve outcome in low-grade glioma and to prevent malignant transformation. However, rate of (temporary) deficits exceeded more than 50% in recent retrospective studies, and the oncological impact and long-term results have to be analyzed in further (prospective and controlled) studies. Cerebral metastases show a different growth pattern with less and locally limited brain invasion. Therefore, local control may be achieved by extension of resection after complete metasectomy. To date, four retrospective studies analyzed the impact of supramarginal resection in cerebral metastases: Local control ranged between 29.1 and 100%. Rate of temporary neurological deficits ranged between 0 and 14.1%; permanent deficits were not observed. Supramarginal resection may represent a promising approach for cerebral metastases but has to be evaluated in further studies. However, extension of surgery towards a supramarginal resection requires a detailed knowledge of functional neuroanatomy and requires intraoperative orientation along cortical and subcortical individual functional boundaries. As optimal supramarginal resection requires detailed electrophysiological, neurological, and neuropsychological monitoring, this technique may be restricted to highly specialized neuro-oncological centers.

Compliance with ethical standards

Conflict of interest Prof. Sabel is a consultant for Johnson & Johnson Company and Integra Company. Dr. Dibué-Adjei is an employee of LivaNova PLC, manufacturer of vagus nerve stimulators. All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interests; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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