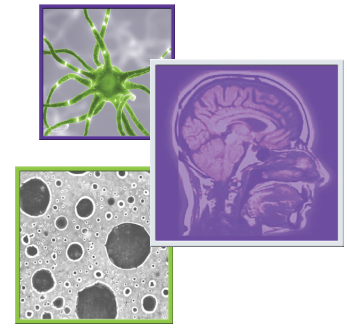
PERSPECTIVE
Special Focus: Oligodendrogliomas

CNS Oncology



The role of surgery in grade II/III oligodendroglial tumors

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Supratentorial gliomas WHO grade II and III with an oligodendroglial phenotype are highly infiltrative lesions that preferentially originate in lobar location. Open tumor resection represents one of the mainstays of management as beneficial decompressive effects for large space-occupying lesions and oncologically relevant cytoreductive effects from complete resection can be expected. In patients not eligible for safe tumor resection meticulous histological and molecular-genetic evaluation can be obtained from advanced stereotactic biopsy techniques. In this perspective, important aspects of open tumor surgery and stereotactic biopsy are discussed within the context of diagnosis, prognosis and treatment of oligodendrogliomas and oligoastrocytomas WHO grade II and III. Practical considerations are provided in order to integrate the place of surgery into an increasingly personalized management concept. For highly selected patients interstitial brachytherapy is introduced as an alternative surgically performed treatment option.

KEYWORDS
• astrocytoma • brachytherapy • eloquent location • extent of resection • high-grade glioma • imaging • iodine-125 seeds • low-grade glioma • microsurgery • molecular-genetic markers • oligoastrocytoma • oligodendroglioma • prognosis • resectability • stereotactic biopsy

The individual course of oligodendrogliomas can be highly variable: patients frequently present with years of stable tumor formations and physical wellbeing (WHO grade II tumors), others show a more aggressive course of the disease despite an oligodendgrolial tumor cell component (WHO grade III tumors) [1]. Treatment considerations should be based on a meticulous diagnostic and prognostic characterization. Open tumor resection is considered one of the mainstays within the glioma treatment algorithm [2,3]. The traditional view is that maximal safe resection improves outcome. This could particularly apply to oligodendroglial tumors as they originate preferably in surgically more accessible lobar localization [4]. There is some evidence, however, that the prognostic benefit from complete resection might be less pronounced than in pure astrocytic tumors [5]. Moreover, complete resection cannot always be obtained. The oncologic benefit from incomplete resection – as compared with biopsy only or even careful observation – has not been systematically evaluated yet. In the following review the place of surgery either alone or within a combined treatment concept will be critically discussed. Particular focus is set on a staged management concept that bases treatment decisions (including open tumor resection) on a precise characterization of each individual tumor.

Management considerations

Oligodendroglial gliomas are characterized by more favorable biomarker profiles, increased sensitivity to chemotherapy and superior outcome scores – facts that should be considered within the framework of personalized medicine [6–8]. Accordingly, a meticulous preoperative diagnostic workup and representative tissue sampling procedure for accurate histological and molecular-genetic evaluation are key elements within the management cascade.

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Preoperative diagnostic workup

• Magnetic resonance imaging

Conventional MRI is the gold standard for differential diagnosis, treatment planning and monitoring of treatment response in diffuse gliomas. Lesions with sharp borders and similar volumes in both T_1-and T_2-weighted sequences must be separated from those formations with poorly defined delineations and tumor extensions in T_2/fluid attenuated inversion recovery (FLAIR) images that extent beyond hypointense areas in T_1-weighted images [9]. The latter type of diffuse gliomas typically grows along the U-fibers, which connect different gyri. Thereby, tumor cells and normal brain tissue are intimately mixed with each other, which makes a clear separation impossible. The distinction circumscribed versus diffuse lesion is clinically important since it has major impact on resectability and prognosis [9,10].

Conventional MRI suffers from low sensitivity and specificity to identify an oligodendroglial tumor cell component. Sharp delineations on MRI might be more common in oligodendroglial tumors but do not exclude broad infiltration of adjacent brain areas [11]. Moreover, intratumoral calcifications and a patchy contrast enhancement may be seen; the latter does not necessarily indicate high-grade histology [12]. In turn, nonenhancing tumors are not always low-grade lesions with increased chance of anaplasia in older patients (~50% above 40 years of age) [13,14].

Perfusion MR imaging and proton MR spectroscopic imaging have the potential to provide strong information about histological diagnosis, have the potential to identify local brain invasion outside of the volume readily identifiable by conventional MRI, and may indicate more aggressive behavior [15–17]. Increase in relative cerebral blood volume (rCBV), as being assessed by dynamic susceptibility contrast MRI (DSC-MRI), has been shown to predict high-grade transformation in astrocytic tumors before gadolinium enhancement occurs [18]. In oligodendroglial tumors, this distinction is less reliable as these tumors inherently exhibit higher rCBV values [19]. Diffusion tensor imaging (DTI) can be used to differentiate normal white matter and oedematous brain tissues from neoplastic tissues and may help to determine if fiber-tracts are displaced, infiltrated or disrupted by tumor formations [20]. Functional MRI (fMRI) can be used for noninvasive delineation of eloquent cortex areas and might be helpful to further estimate the tumors' resectability [21,22]. However, due to limits and loss of accuracy of spatial resolution in the process of data fusion of fMRI with the anatomical imaging dataset, this information has to be used only very cautiously for intraoperative identification of functional areas.

• Positron emission tomography

Integration of novel metabolic/molecular imaging techniques has additionally improved diagnostic accuracy: in PET imaging oligodendroglial tumors are characterized by higher uptake of radiolabeled amino acid tracers such as ^{11}C-methionine (^{11}MET) and more importantly O-(2-[^{18}F] fluoroethyl)-L-tyrosine(^{18}FET) [23–27]. ^{18}FET-PET allows better delineation of true glioma extensions and has been shown to improve the differential diagnosis between pure astrocytic and oligotumors [26–28]. Moreover, pattern of intratumoral ^{18}FET uptake kinetics can be exploited to identify focal anaplasia in MRI non enhancing astrocytomas and oligoastrocytomas and to define distinct biological subgroups with different clinical courses in suspected WHO grade II gliomas [29].

Histology & molecular-genetic markers: surgical considerations

Gliomas are histologically heterogeneous lesions with various molecular profiles. Mixed oligoastrocytomas encompass about 40–65% of all grade II and grade III gliomas whereas pure oligodendrogliomas WHO grade II and particularly grade III are much less frequent [30–32]. In mixed tumors, astrocytic and oligodendroglial tumor cells components can either be closely intermingled or distributed in a biphasic pattern [33]. This might contribute to a high interobserver variability in histological diagnosis (up to 30% discordant findings), which is typical for studies in grade II and III glioma [8,34,35]. Moreover, anaplasia can either be seen in tumor samples collected throughout entire tumor volumes or might occur only focally embedded within otherwise low-grade histology [13]. Hence, accurate histological diagnosis critically relies on the biopsy sampling procedure.

Assessment of molecular-genetic markers considerably increases diagnostic accuracy, subclassification and prognostic evaluation. Important biomarkers are loss of heterozygosity (*LOH*) on chromosomes *1p* and *19q*, a mutational status of the gene encoding for *IDH1*, and methylation

of the promoter of the gene that encodes for O^6-methylguanine-DNA methyltransferase (*MGMT*) as the result of a genome-wide CpG island hypermethylated phenotype profile [36]. There is high evidence that these factors correlate with favorable outcome and increased treatment response [8,37,38]. Hence, any surgical treatment has to provide representative tumor tissue allowing histological and molecular-genetic evaluation.

The role of open tumor resection & stereotactic biopsy

• Stereotactic biopsy

The only aspect of glioma surgery with high-level evidence is that histological diagnosis should be obtained before active treatment commences [2,3]. Tissue samples for histological evaluation can either be harvested from open tumor surgery or achieved by the aid of minimal-invasive stereotactic biopsy procedures. Stereotactic biopsy is indicated for lesions with unclear differential diagnosis, complex location in highly eloquent areas or in cases where the patients conditions or intentions exclude open surgery [39]. Moreover, in terms of open question whether and how treatment should be applied, a serial stereotactic biopsy provides histology and molecular diagnosis of the tissue for a sound management decision. Both alternatives, biopsy and microsurgery, critically depend on an extensive experience, excellent technical conditions and optimized logistic processes, which can only be ensured by highly specialized neuro-oncology centers.

In recent years, preoperative multimodal imaging techniques and their integration into open and stereotactic biopsy procedures have certainly increased diagnostic efficacy and reduced the risk of misclassification and undergrading (and consecutive undertreatment) [13,40,41]. Heterogeneous tumor compositions can sufficiently be unmasked, for example, by generating spatially precise maps of dynamic ^{18}FET uptake covering entire tumor volumes [13].

Determination of important biomarkers should be implemented into clinical routine. Accurate molecular-genetic characterization can be sufficiently obtained from biopsy samples as small as 1 mm³ in size [13,40,42]. Biopsy specimens taken from different sites throughout the tumor have indicated that the status of important biomarkers, such as *LOH1p/19q, IDH1* mutation, *MGMT* promoter methylation and *TP53* mutation, always was unchanged within the tumor [13,40]. This also concerns heterogeneous tumor compositions with focal anaplasia, indicating that these molecular markers are early events in glioma genesis [13,43]. The probability of obtaining 'false-negative' results or a misclassification of the respective biomarker status is considered low in experienced hands. Significant contamination of the biopsy probe by normal brain or necrotic tissues, however, might cause false-negative results; thus a highly controlled tissue sampling technique is mandatory [40,42]. Given the powerful prognostic/predictive importance, for example, of *1p/19q* codeletion, biopsy technique should always try to achieve both a proper histological and molecular diagnosis. Hence, the term of 'molecular stereotactic biopsy' has been generated for this refined technique [40]. Under these considerations biopsy can be regarded as an important element for tailored treatment concepts particularly in complex located oligodendroglial tumors [39].

• Microsurgical resection

Beyond tissue sampling for accurate histological and molecular-genetic diagnosis, surgical resection is considered as one of the mainstays in the treatment [2,3]. In large-space-occupying lesions surgical resection helps to reduce intracranial pressure and mass shift hereby stabilizing the patient for any further adjuvant treatment regimen. In case of neurological deficits due to tumor-related compression (not infiltration!) of eloquent areas, surgical removal of the tumor mass may ameliorate neurological symptoms. Corticosteroids are a reliable tool that helps to distinguish tumor related compression with concomitant edema from tumor infiltration as the underlying cause of the neurological deficit: lack of symptom relief after some days of steroid treatment indicate profound tumor infiltration of functional relevant areas with an even higher risk of functional deterioration in case of resection [44]. Moreover, tumor resection has been shown to control seizures in patients with pharmaco-resistant epilepsy [45].

Open tumor resection can either be performed alone (grade II gliomas) or within a combined treatment regime (grade III gliomas). In asymptomatic grade II gliomas timing of surgery remains controversial, as these tumors can be stable for years even without any specific applied therapy. However, recent MRI studies have shown, that an annual growth rate of

3–4 mm in diameter must be considered even in clinically stable patients [46]. Ultimately, diffuse gliomas, including those with an oligodendroglial phenotype, may undergo more or less delayed malignant transformation with rapid clinical decline later on. However, it remains yet unclear, to which extent early resections can delay this fate [47,48].

The highly infiltrative growth and frequent involvement of functionally important brain tissue explains why in general surgery cannot cure the patient. However, there is broad consensus that complete tumor removal (as being defined by MRI criteria) improves overall survival [49,50]. Some authors even promote a concept of 'supratotal' resection for noneloquent gliomas in order to account for the highly infiltrative growing behavior beyond MRI-defined volumes [51].

Postoperative imaging should be performed as a MRI within 48–72 h after surgery with T_1-weighted images with and without contrast medium plus T_2-weighted and FLAIR images [52]. Diffusion weighted images help to delineate asymptomatic ischemic areas in conjunction with the resection – as these regions may show (unspecific) contrast enhancement within the next 3 months, this information helps upfront to distinguish early progression from treatment related phenomena [53].

The number of patients with gross total resection may be significantly increased by the aid of sophisticated imaging techniques (e.g., intraoperative MRI) and intraoperative mapping techniques including awake craniotomy for language monitoring during surgery [54–59]. However, there is only one randomized trial about the impact of intraoperative MRI [59]. This study revealed that progression-free survival was statistically not significantly different in both groups with and without intra-operative MRI. However, the proportion of patients with complete removal of the solid tumor tissue was higher in the MRI cohort. The only significant factor for prolonged PFS was complete removal of the solid tumor parts irrespective of the technique being used.

As noncontrast enhancing tumors may harbor malignant foci which can be detected by ^{18}FET-PET (see above), intraoperative PET-based neuronavigation might help to selectively sample tissue from these areas in order to avoid histological misgrading and subsequent inappropriate adjuvant therapy. Accordingly, if open surgery planning is based on conventional MRI alone, one has to be aware that any residual tumor that has been left *in situ* may remain poorly characterized [39].

The prognostic impact of partial resection in grade II and III gliomas, however, has not been systematically analysed yet. *Post hoc* analyses of prospective randomized trials originally designed to analyze the prognostic relevance of chemotherapy and radiotherapy (in WHO grade III oligotumors) and numerous retrospective observational studies have frequently found a powerful prognostic impact of open tumor resection as compared with biopsy only [6–8]. These data, however, should be regarded cautiously due to their inherent uncontrolled heterogeneity: patients receiving incomplete tumor resection or biopsy only usually were older, had a lower pre-treatment clinical score, suffered more often from deep-seated and/or poorly delineated tumors, and cannot be compared with those receiving complete resection [2,3,50,60,61].

There is some indication that the impact of surgical resection on clinical outcome might differ in anaplastic gliomas harboring an oligodendroglial phenotype and pure astrocytic tumors [5]. In one study the impact of gross total resection was less pronounced in grade III oligoastrocytomas as compared with pure astrocytic tumors although gross total resection was achieved more frequently. This was also confirmed in grade II gliomas: increased extent of resection (EOR) resulted in better PFS for diffuse astrocytoma but not for oligodendroglioma [62]. The authors concluded that if surgery resulted in EOR <90%, patients with astrocytoma should undergo second-look surgery, whereas patients with oligodendroglioma or oligoastrocytoma should rather be transferred to chemotherapy. Given these uncertainties and the possibility to treat oligotumors effectively independent of open tumor resection, high-risk surgery should be avoided particularly in this tumor entity. In case of surgical accessible and completely resectable tumors, open tumor resection continues to be a valuable and important treatment modality. Otherwise, for complex located tumors with lack of space occupying effect and an increased functional risk in case of a microsurgical procedure, a molecular stereotactic biopsy should be considered as alternative surgical procedure.

Interstitial iodine-125 brachytherapy

Interstitial implantation of a radioactive source such as iodine-125 is designed to deliver a high radiation dose to a well-defined tumor volume

while minimizing the dose to the surrounding normal brain [63,64]. Low-dose rate interstitial iodine-125 brachytherapy can be successfully used for highly selected patients with small and circumscribed grade II oligodendroglial gliomas in any location of the brain either as initial treatment instead of high risk open tumor resection or for small sized recurrences after previously performed surgery and/or multimodal treatment [65]. Tumor size is considered the most important risk factor of this treatment option: Tumors with a diameter >3.5 cm are usually not suitable for brachytherapy. In case of larger complex located circumscribed tumors brachytherapy should therefore be combined with open tumor resection [66]. In these complex cases, usually a planned low-risk partial resection is performed as initial step and iodine-125 implantation is then initiated 3 months later. The combined approach, which has been analyzed in low-grade gliomas, has been shown to be highly effective and not associated with permanent morbidity; It might be also an attractive treatment strategy for large and complex located grade II oligotumors. Whether iodine-125 brachytherapy is more effective in *1p/19q* codeleted tumors remains unknown and deserves further evaluation. Generally, it can be assumed that brachytherapy is similarly effective as open tumor resection. A systematic comparative analysis of these two surgical treatment modalities, however, is still lacking. Given these uncertainties iodine-125 brachytherapy should be preserved for those tumors not accessible for open tumor resection.

Conclusion

Open tumor resection continues to be one of the mainstays of treatment in case of completely resectable oligodendroglioma and oligo-astrocytoma. For complex located circumscribed and small sized tumors iodine-125 brachytherapy is an attractive alternative treatment option. Molecular stereotactic biopsy is a valuable tool to obtain histology and the molecular signature of tumors which are no candidates of a safe and complete resection.

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