Personalized surgical therapy

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Gliomas are more or less diffuse tumours with the ability to infiltrate surrounding functional brain tissue. Thus, curative surgical treatment generally cannot be achieved. Despite these limitations, open tumour resection represents one of the mainstays in glioma treatment settings. Beyond tissue sampling for accurate histological and molecular genetic evaluation, decompressive effects in the case of space occupying tumours and oncologically relevant cytoreductive effects of microsurgery have been reported in selected patients with glioma of different grades. This paper provides practical considerations in order to integrate the concept of a personalized surgical therapy into the prognostic network of low- and high-grade gliomas, covering both microsurgery and stereotactic biopsy techniques.

Key words: brachytherapy, glioma therapy, microsurgery, molecular neurooncology, stereotactic biopsy

general remarks

Diffuse gliomas represent a broad diagnostic category that also include glioblastomas, the most common and most malignant primary brain tumour in adults. Glioblastomas account for ∼50% of all gliomas and their incidence is estimated to lie in the range 3–5 newly diagnosed cases per year [1, 2]. Even though considerable advances have been achieved since the introduction of concomitant radiochemotherapy followed by adjuvant chemotherapy with temozolomide, a median survival not longer than 15 months can currently be expected for glioblastoma patients [3]. In contrast, patients with grade 2 gliomas can exhibit years of clinical and radiological stability without any applied therapy. However, even these low-grade gliomas generally cannot be achieved. Despite these limitations, open tumour resection represents one of the mainstays in glioma treatment settings. Beyond tissue sampling for accurate histological and molecular genetic evaluation, decompressive effects of microsurgery in the case of space occupying tumours and oncologically relevant cytoreductive effects with favourable influence on outcome measurements have been reported in selected patients. However, uncertainties continue to exist particularly regarding the role of open tumour resection when compared with stereotactic biopsy procedures. The following paragraphs are dedicated to practical considerations in order to integrate the concept of a personalized surgical therapy into the prognostic network of low- and high-grade gliomas.

the problem of radicality in glioma surgery

The highly infiltrating growing characteristics of grade 2–4 gliomas and their frequently broad vicinity of eloquent brain areas limit the extent of resection for a considerable number of patients. Whereas complete tumour resection—which means the removal of the visible tumour part as defined by magnetic resonance imaging (MRI)—is generally considered...
prognostically favourable as demonstrated in numerous prospective and retrospective observational studies [14–17], the influence of incomplete resection (when compared with biopsy) has never been analyzed adequately. As there is no evidence for any favourable effect of incomplete tumour resection, indication for surgery should be done extremely cautiously [18]. Patient- (age, KPS) and tumour-related (tumour grade, size, location, delineation) factors have been shown to influence surgical radicality [12,19]. For potentially not completely resectable tumours, stereotactic biopsy should be considered a valuable alternative surgical approach [20,21]. The grading system of the World Health Organization (WHO) reflects not only the presumptive clinical course of the patient under consideration, but also to a certain extent the degree of resectability with grade 1 being the least and grade 4 tumours being the most invasive tumour entities [1]. Accordingly, gangliogliomas WHO grade 1, neurocytomas WHO grade 1, pilocytic astrocytomas WHO grade 1 and some ependymomas WHO grade 2 are generally good candidates for ‘radical’ resection and this approach should be regarded as the treatment of choice in the case of accessibility of these lesions. The emerging role of the molecular biomarker and their association with prognosis has recently been emphasized [22–25]. Hence, the specific treatment strategies such as chemotherapy, for example, in glioma with oligodendrogial differentiation might increasingly modify the indication for open tumour resection particularly in those with not completely resectable lesions. Given the fact that even for complete tumour resection no level 1 evidence exists, the preservation of neurological function is of utmost importance. Thus, the paradigm for glioma surgery in functional relevant areas remains to be ‘do not harm!’ There is usually no trade-off between the loss of function as a price to be paid for cure—which remains particularly true for malignant glioma patients: any delay in the initiation of adjuvant post-operative radiotherapy and/or chemotherapy due to surgery-related morbidity could additionally harm the patient and worsen his overall prognosis [26,27]. In consideration of these issues, the individual patients’ condition, surgical and non-surgical risk factors, localization and extent of the tumour as well as its presumptive biology will determine the surgical strategy in the sense of a personalized concept.

malignant glioma

In malignant gliomas, WHO grade 4 external beam radiation with concomitant and adjuvant temozolomide is the most important factor for prolonged survival with superior efficacy in MGMT promoter methylated tumours [3,28]. The role of microsurgery is less well defined. Usually, open tumour surgery is considered to be the initial step within the treatment algorithm of malignant gliomas [12]. Even though open tumour resection might add some additional benefit to the patients, the risk of the procedure should not be underestimated. Surgery-related perioperative morbidity rates in the range 10%–20% or even more have been reported [29]. Notably, those patients with complications were less likely to receive radiotherapy and chemotherapy and exhibited substantially shorter survival. Only one prospective randomized trial of biopsy versus resection in glioblastoma patients over the age of 65 has been published so far [30,31]. In that trial, patients undergoing biopsy only did substantially worse (3 months median survival advantage in the resection group). However, errors in the trial design and under-powering have substantially biased study results, which therefore could not be used to support a concept of aggressive surgery in elder glioblastoma patients. As further prospective randomized trials have not been conducted as a consequence of ethical considerations, the evaluation of surgical treatment effects has to rely on data collected in prospective and retrospective observational studies [14,16]. Proponents of surgical treatment have to reconsider, that relatively strict definitions exist what one has to understand by the term ‘complete tumour resection’. In the retrospective study of Lacroix et al. [14], for example, only resections of 98% or more of the initial tumour volume were associated with the prolonged survival. In the randomized, controlled multicentre phase III trial on fluorescence-guided surgery with 5-aminolevulinic acid (5-ALA) of malignant glioma surgical radicality was even stricter defined using the absolute values for residual tumour volume estimation [32]: any gadolinium enhanced volume on the early postoperative MRI (done within 3 days after surgery) larger than 0.175 cm³ was classified as residual tumour. It is important to note that this strict classification scheme could be translated in substantially worse outcome measurements for those harbouring residual tumours. However, given the fact that complications did occur substantially more often in the 5-ALA group [27], a ‘risk-adjusted’ approach is warranted. Intraoperative monitoring of neurological functions has proven to be helpful in both the preservation of functional integrity and the increase of ‘radicality’ [33].

In the case of close proximity to functionally eloquent brain regions, the determination of the exact extent of the tumour might be crucial for the decision whether microsurgical tumour removal might be warranted. In addition to sophisticated MRI sequences, amino acid positron emission tomography (PET) imaging helps to better delineate the true extension of glioma tissue [34]. The volume of contrast enhancement in MRI can be considerably smaller than the volume of active tumour being depicted by (11)C-methionine PET imaging [35]. In the case of a mismatch with the extension of the PET-positive lesion into functional relevant brain areas, a ‘complete’ removal is no longer possible and the surgical strategy should be re-evaluated. When microsurgical resection is not safely feasible (e.g. due to the location of the tumour or impaired clinical condition of the patient), a molecular stereotactic serial biopsy should be carried out. Histology and molecular markers can reliably be analyzed even in small samples of serial stereotactic biopsies. Since the most frequent requested markers (methylation status of the MGMT promoter, LOH 1p/19q, p53 mutation, IDH1/2 mutation) are homogeneously distributed throughout the tumour, the probability of obtaining a ‘false-negative’ result or a misclassification of the molecular status is very low [20,21,36]. Caution, however, is required not to obtain biopsies with a high amount of necrosis or out of the infiltration zone with ‘contamination’ of the specimen by normal brain tissue, both potentially leading to false-negative results. To avoid this
pitfall, an experienced neuropathologist has to review all specimens before molecular analysis.

Since the inauguration of concomitant and adjuvant radiochemotherapy, an effective treatment is now available especially for patients with a methylated MGMT promoter [28]. This benefit can also be expected for those patients with not completely resectable glioblastomas undergoing stereotactic biopsy only and, indeed, has been reported: progression-free survival and overall survival after radiotherapy plus concomitant and adjuvant temozolomide have been shown to be completely in line with the results of the prospective randomized trial carried out by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group. These data should be used to avoid therapeutic nihilism in the case of non-resectable glioblastomas [37].

low-grade glioma

Low-grade gliomas (in particular astrocytomas, oligodendrogliomas and oligoastrocytomas) have an incidence of 0.8 to 1.2 per 100 000 patient-years [2, 38]. This heterogeneous group of primary brain tumours usually affect young adults who frequently become symptomatic with a new onset of seizure [13, 39]. The clinical outcome is highly influenced by treatment-independent factors and ranges from a 5-year survival rate as high as 85% for those of the ‘best’ prognostic group (young patients, no neurological deficits, small tumour volume) to as low as 40% or even worse for those harbouring an unfavourable prognostic profile including three or more risk factors [40, 41]. The group of WHO grade 2 gliomas is very heterogeneous with regard to their growth pattern. Most surgical series focus on rather well-delineated lesions with clear, sharp borders in both T1- and T2-weighted MRI without a substantial difference in volume in either sequence and a matching lesion in fluid attenuated inversion recovery (FLAIR) images. These tumours are, depending on their localization, suitable candidates for microsurgical removal. Extensive resection improves seizure control in patients presenting with epilepsy [39].

In contrast, tumours with poorly delineated borders in both T1- and T2-weighted MRI, being much larger on FLAIR and T2-weighted images than on T1-weighted images, typically grow along the U-fibres which connect different gyri. These lesions are no good targets for microsurgery, since there is a considerable amount of normal brain tissue nestling in among the tumour cells restricting usually extensive resections which will still be ‘subtotal’ [1, 13]. These lesions should undergo a molecular stereotactic serial biopsy to verify the histology and obtain additional information about the molecular profile [20]. As up to 45% of suspected low-grade gliomas turn out to be malignant gliomas, sometimes with only small anaplastic foci within otherwise low-grade tumours, a histological diagnosis is mandatory before any therapeutic decision [42]. As even these partially anaplastic lesions may not display contrast enhancement in MRI, additional imaging information is warranted. Dynamic PET imaging using amino acid tracers such as 18FET has been shown to reliably identify anaplastic foci within the tumour with high sensitivity and specificity and helps to provide valuable information for the target selection of a stereotactic biopsy [34, 42]. Moreover, the information about the localization of a presumed anaplastic focus will also be helpful during microsurgical removal allowing the separate resection of the presumed most malignant tumour part thereby enabling selective histological and molecular genetic analyses of biologically distinct tumour parts. The integration of molecular (metabolic) data in the imaging dataset for biopsy and resection planning will certainly decrease the risk of under-grading and under-treatment in suspected low-grade gliomas.

As many patients harbouring a low-grade glioma are young and the oligosymptomatic preservation of the neurological integrity is a key factor in low-grade glioma surgery. Neurophysiological mapping including awake craniotomy for language monitoring is safe and effective helping to maintain the function even when operating in very close vicinity of eloquent functional areas. Indeed, mapping of cortex and white matter tract additionally helps to extend radicality of resection, since many cortical functions, e.g. language, display an individual variation of both localization and spatial organization [33, 43–45].

For well-delineated, circumscribed tumours with a maximum diameter of ≤3.5 cm, which cannot be removed safely (even with the aid of functional mapping during awake craniotomy) stereotactic I 125 brachytherapy is an attractive minimal invasive highly localized treatment modality, which could be used as an alternative to surgery with a similar or even identical treatment efficacy. The implantation of a low-energy radioactive source such as I 125 enables both the application of a high necrotizing dose within the tumour and maximum sparing of the surrounding non-neoplastic tissue [46]. As a consequence of the favourable radiobiological characteristics of brachytherapy, subsequent external beam radiation is still possible at the time of tumour recurrence/tumour progression without an increased risk of radiogenic complications, which means that the treatment spectrum is not narrowed by interstitial irradiation. In the case of larger eloquently located tumours the combination of tumour resection with the subsequent interstitial irradiation of the residual tumour has been shown to be effective in terms of tumour control with long progression-free and overall survival as well as the preservation of functional integrity [47, 48]. Hence, stereotactic brachytherapy is an attractive therapeutic concept and a valuable addition to the therapeutic armamentarium. Either alone or in combination of microsurgery, it helps to tailor the surgical strategy according to the individual situation of the patient in the sense of ‘personalized surgical treatment’.

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references


