Surgery of Malignant Gliomas Using Modern Technology

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Therapy of Malignant Gliomas – A Formidable Challenge

Gliomas of astrocytic, oligodendroglial, and ependymal differentiation comprise with an incidence of 6/100,000/year about 70 % of all intrinsic brain tumours [1]. The WHO classification system distinguishes 4 grades of malignancy [2] characterized by morphologic features such as mitotic activity, microvascular proliferation, and intratumoural necroses. The most frequent glioma of the adulthood, the glioblastoma multiforme, is a highly malignant neoplasm which displays an exceptionally poor prognosis with a median survival time of 15 months [3]. Two years after diagnosis, only 8.2 % of all patients are still alive [4]. The management of glioblastoma consists of 3 main elements: (1) microsurgical resection is followed by (2) concomitant treatment with radiotherapy plus (3) temozolomide chemotherapy [5]. In this context, the extent of surgical resection (EOR) has increasingly been recognized as an important prognostic factor in this patient population [6]. A prospective, randomized multicentre trial in glioblastoma patients has demonstrated that complete resection of the contrast-enhancing tumour leads to an overall survival of 16.7 months compared to 11.8 months after subtotal resection [7]. However, there are 2 major limitations to radical surgical resection: (1) glioblastomas display a highly infiltrative growth pattern [8] which renders complete resection virtually impossible. Careful histological studies revealed a tumour cell spread into the contralateral hemisphere in about 30 % of all patients at the time of diagnosis [9, 10]. Thus, even the most radical surgical approach will not lead to curative treatment [11]. (2) The functional anatomy of the brain consists of cortical and subcortical structures such as the primary motor cortex, Wernicke and Broca speech centres, or the internal capsule, which need to be preserved during surgical resection to avoid serious postoperative neurological deficits. Since patients with permanent neurological deficits have a significantly worse survival prognosis [12], the avoidance of any damage to these eloquent structures is mandatory in the surgical treatment of glioblastoma [13].

Preoperative Work-Up

Traditionally, surgery planning was conducted utilizing anatomical landmarks [14]. In the past, the identification of eloquent areas was performed in a generalized, rigid fashion based on the functional studies by Wilder Penfield, frequently leading to an inadequate assessment of the surgical risk in the individual patient [15]. The major reason for this inaccuracy is the significant individual variability of cortical organization [16]. In addition, recent studies have demonstrated a high degree of functional plasticity of the brain, which causes a significant shift of eloquent areas to distant sites especially under the condition of intracerebral tumour growth [17]. Preoperative application of functional MRI (fMRI) and Diffusion Tensor Imaging (DTI) allows the detection of eloquent cortical and subcortical structures with high sensitivity and specificity [18, 19]. With the advent of computer-based analysis tools allowing the fusion of patho-anatomical, functional, and metabolic imaging data, it is now possible to plan and execute a precise and safe resection trajectory, thus achieving maximal EOR with minimal surgical morbidity (Figure 1). In the case of a large, infiltrative tumour, which needs to be biopsied in order to establish a histological diagnosis, it is of paramount importance to target the area of the lesion with the suspected highest grade of malignancy. In a study conducted in 81 patients who received stereotactic biopsy followed by resection of the tumour within 60 days, the biopsy-based diagnosis was incorrect in 38 %, emphasizing the limitations of stereotactic biopsy as a diagnostic tool [20]. The application of Positron Emission Tomography (PET) scanning utilizing tracers such as \(^{18}F\)fluorodeoxyglucose allows to detect metabolically active areas within a larger tumour mass. The integration of these molecular imaging data into the target planning process can significantly increase the diagnostic yield of stereotactic biopsies in patients with diffuse gliomas [21, 22]. In addition, the differentiation between tumour progress and radiation-induced necrosis or pseudoprogression can be facilitated by PET scanning, supporting adequate clinical management and avoidance of unnecessary treatment measures.
such as repeated surgical resection [23]. Finally, detailed neuropsychological evaluation is helpful in unmasking subclinical tumour-related impairments to improve the prognostication of the postoperative course of the disease [24].

**Intraoperative Technique**

One of the most substantial obstacles to an extensive resection of gliomas is the infiltrative growth pattern of these tumours. The development of 5-aminolevulinic acid (5-ALA) as a tumour-specific fluorescence marker has caused a breakthrough in the resection of malignant gliomas [25]. The substance leads to an intracellular accumulation of fluorescent porphyrins which can be detected intraoperatively using a microscope equipped with a violet-blue excitation light source (Figure 2). A prospective, randomized controlled multicentre trial has demonstrated a significantly better EOR in the 5-ALA group compared to the control arm resected with conventional light [26]. The intraoperative localization of the tumour in addition to the adjacent, eloquent areas of the brain is greatly facilitated by the use of neuronavigation, which has also been termed frameless stereotaxy [27]. This technique is based on MRI imaging conducted with fiducial markers placed on particular landmarks of the patient’s skull. Prior to craniotomy, an LED-emitting detection system linked to a computer containing the imaging data set is used to calibrate the surgical instrument set, which then allows the visualization of the resection process intraoperatively. This approach has significantly improved the safety and extent of resection in glioma patients [28, 29]. However, the accuracy of neuronavigation-based resection, which is solely based on preoperative imaging, decreases during the course of the procedure due to “brain shift” caused by the release of cerebrospinal fluid, brain swelling, and surgical manoeuvres [30]. To account for this aspect, real-time intraoperative imaging is required. Consequently, intraoperative MRI (iMRI) has been developed as an advanced technique for imaging-based resection control in glioma surgery [31]. A recent, controlled, prospective clinical trial has demonstrated that the use of iMRI leads to a better extent of resection and improved 6-month survival rates in the iMRI group compared to the control population. Interestingly, the occurrence of postoperative neurological deficits was not significantly different between the 2 study groups [32]. However, iMRI is complex, requiring either transport of the patient to the scanner during the operation or a completely antimagnetic setting in the operating room. Surgery time is prolonged due to the scanning procedure and iMRI systems are expensive and not available in the majority of neurosurgical centres [33, 34]. A valid alternative is the use of intraoperative ultrasound (IOUS), which allows real-time detection of infiltrative tumour margins [35]. However, IOUS-based resection control, albeit possible, is influenced by surgery-related artefacts and depends significantly on the experience of the surgeon [36]. As an alternative to image-based surgery, awake craniotomy with intraoperative cortical and subcortical stimulation has been established as “gold standard” to achieve maximal EOR with minimal morbidity [37]. The procedure involves tumour resection in the awake patient, allowing serial neurocognitive tests concerning motor or language function combined with direct electri-
cal stimulation of the brain to unmask eloquent cortical and subcortical structures. Using this approach, a better EOR can be achieved while avoiding damage to functionally relevant brain structures [38, 39]. In order to avoid stress for the patient and to gain the best surgical results, a team of highly trained and experienced physicians consisting of anaesthesiologists, neuropsychologists, and neurosurgeons is mandatory [40]. In addition, especially if awake craniotomy is not an option, intraoperatively evoked potential monitoring is highly useful to detect damage to eloquent structures early during the procedure, allowing to correct the surgical trajectory in a timely fashion [41].

**Results from a Single Centre – High-Tech Surgery, Is It Worthwhile?**

Although it is self-evident to embrace the concept of high-tech surgery, limited resources in today’s medical practice may prompt the question of whether this multimodal approach is of any clinical benefit to glioma patients. Employing the entire armamentarium outlined in this review except for iMRI, we volumetrically analyzed the EOR and clinical outcome in 44 patients with malignant gliomas (5 anaplastic astrocytoma, 39 glioblastoma) receiving surgical resection at our department. Mean age was 62.5 years, 61.4 % of all patients presenting with focal neurological deficits. Preoperative tumour size and EOR were quantified volumetrically based on MRI imaging (Iplan Cranio, Brainlab, Feldkirchen, Germany; Figure 3). In addition, surgical morbidity and mortality as well as the improvement of neurological performance were registered. There was no perioperative mortality, surgical morbidity was recorded in 9 % of all cases, caused by wound infection and CSF fistula, respectively. Complete resection (ie, no residual contrast enhancement in the postoperative scan) was achieved in 62 % of all cases, in 93 % of the patients an EOR > 90 % was accomplished. Of all patients presenting with neurological impairment, 52 % showed significant improvement. Only one patient developed transient double vision postoperatively, which completely dissipated after one week. These data confirm that the employment of advanced pre- and intraoperative technologies allows a safe and extensive resection in malignant glioma patients with a low rate of surgical morbidity.

**Conclusion**

Basic science research efforts during the decade of the brain has created an enormous gain of knowledge regarding function, biology, and pathophysiology of the brain [42]. This has caused a shift of paradigm in clinical neurosciences, including the surgical treatment of malignant gliomas. The advent of modern technology has revolutionized the preoperative workup, surgical trajectory planning, and intraoperative monitoring with significant benefits for the patients regarding neurological improvement and overall survival. In the treatment of malignant glioma, combined efforts of all involved medical specialties are mandatory to achieve the best results for the individual patient [43, 44]. Modern neurosurgery can contribute to this treatment strategy by providing maximal EOR combined with minimal morbidity.

**Conflict of Interest**

The authors report no conflict of interest.

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**References:**


