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Emerging Imaging and Operative Techniques for Glioma Surgery

Claude-Edouard Chatillon and Kevin Petrecca
Montreal Neurological Institute and Hospital, McGill University
Canada

1. Introduction

Malignant gliomas are the most common adult primary brain cancers and are amongst the most devastating of human malignancies. These cancers are characterized by high proliferation and invasion into normal brain. Treatment consists of a combination of surgery, radiotherapy, and chemotherapy. Despite years of experience and refinement of these treatments, patients suffering from World Health Organization grade four gliomas have a mean survival of 14 months (Stupp et al., 2005).

The goal of surgery is to remove the entirety of the tumor as strong emerging evidence suggests that completeness of resection improves cancer control and lengthens survival. Extent of resection, for malignant gliomas, is based on gadolinium-enhanced magnetic resonance imaging (MRI). In cases of complete resection, radiotherapy is then delivered to a 2 cm border along the resection cavity. In cases of incomplete resection, radiotherapy is delivered to the residual tumor and a 2 cm border along the residual tumor and resection cavity. The rational for this radiotherapy strategy is that invasive cancer cells can be found up to 2 cm distant from the main tumor mass.

Studies examining the location of malignant glioma recurrence following surgery and adjuvant radiotherapy and chemotherapy have found that most cancers recur within a 1 cm border along the surgical resection cavity, even in cases in which no residual gadolinium-enhancing tumor was evident on immediate post-operative MRI. This suggests that gadolinium-enhanced MRI does not sufficiently reveal the entire tumor resulting in residual tumor post-operatively. Other common MRI sequences, including FLAIR and T2, do not adequately distinguish non-gadolinium enhancing cancer cells from peritumoral edema. The inability to accurately visualize the whole tumor, including invasive cells, on imaging decreases the likelihood of complete resection. Recently, attempts to visualize malignant gliomas with newer imaging techniques, including metabolic labeled positron emission tomography (PET), have identified tumor borders beyond those seen with gadolinium-enhanced MRI. These technologies may have profound implications regarding surgical planning in malignant glioma surgery.

Historically, extent of tumor resection has been determined by the surgeon's qualitative assessment at the time of operation, often reporting a gross total resection. More recently, the use of immediate post-operative MRI has revealed that complete resection of the gadolinium-enhancing portion of the tumor is achieved at a much lower rate. This overestimation by surgeons is, in part, owing to the difficulty distinguishing cancer cells

from normal brain. Since malignant gliomas are highly invasive tumors, the margin between tumor and normal brain is typically not obvious. Reluctant to cause an irreversible neurological deficit, surgeons will error on the side of caution. The downside is that malignant cancer cells will remain. Since adjuvant radiation and chemotherapies are only modestly effective (Stupp et al., 2005), these cancer cells that remain along the border of the original tumor mass will recur. Intraoperative tools designed to help surgeons distinguish cancer cells from normal brain include ultrasound and fluorescence guided surgical resection. Comparative studies using these tools have shown higher rates of complete resection compared to standard operating techniques.

Here we review current and emerging imaging technologies designed to better visualize the tumor on preoperative imaging. We also review developing surgical technologies to help surgeons distinguish cancer cells from normal brain intraoperatively. The development of these technologies will lead to an increased rate of complete resection and thus improved cancer control.

2. Preoperative glioma imaging

2.1 Tumour delineation in glioma

The accurate characterisation of tumour size and location is crucial to decisions in diagnosis, presurgical planning and adjuvant therapy, as well as assessment of treatment response or failure in patients with a glioma. The diagnostic and tumour delineation gold standard remains the MRI using T1 with and without gadolinium-enhancement, T2 and fluid attenuation inversion recovery (FLAIR) sequences. However, classical MRI sequences provide an indirect assessment of tumour grade by relying on tissue density, fluid content and blood-brain barrier breakdown patterns. Advanced MRI techniques aim to measure water molecule diffusion patterns (diffusion weighted imaging), cerebral blood volume (perfusion-weighted MRI) and metabolic tissue composition (magnetic resonance spectroscopy), which are more direct measures of tumour metabolism. Furthermore, PET using the classical metabolic tracer fluorodeoxyglucose (FDG) or novel amino acid tracers have been shown to provide complimentary information to MRI in presurgical planning and improve outcome in low and high grade gliomas.

2.2 Conventional MRI

Since its first clinical use in the 1980s, MRI rapidly became the imaging modality of choice in cerebral tumors, owing to its resolution, grey-white matter distinction and radiation sparing advantages over computed tomography (CT). To image glioma invasion, changes in tissue density, fluid content and blood brain barrier breakdown underlie the abnormalities seen on classical MRI sequences. Tumour delineation in low grade gliomas (LGG) is usually determined by the extent of hyperintense signal on a T2 sequence. Edema is usually absent in LGGs and should therefore not be a confounder of T2 hyperintensity. Areas of enhancement after gadolinium enhancement are typically not seen in LGG and are, in fact, a marker of anaplastic transformation. In contrast, tumour delineation in high grade gliomas (HGG) cannot rely on the T2 sequence, due to the often significant edema surrounding the lesion. The area of enhancement on the gadolinium-enhanced T1 sequence is usually used for pre-operative planning, post-operative extent of resection assessment and evaluation of progression, treatment response or recurrence.

The reliability of classical MRI to fully delineate the tumour has been questioned in low and high grade tumours. In particular, the absence of enhancement after gadolinium injection does not exclude the presence of high grade cancer cells. This has been shown within non-enhancing, T2 hyperintense lesions suspected of being LGG (Kunz et al., 2011) and outside the enhancement perimeter in HGG (Pauleit et al., 2005). Furthermore, the effects of various treatments on the blood-brain barrier, at times independent of their anti-tumoural effects, have highlighted the need for imaging modalities more directly linked to metabolic tumoural activity. For example, radiation alone or combined with chemotherapy can lead to a regional blood-brain barrier breakdown in 20 to 50% of treated patients, leading to new or increase in size of exisiting areas of enhancement on gadolinium-injected T1 sequences in treated patients, an entity known as pseudoprogression (de Wit et al., 2004; Brandsma et al., 2008; Taal et al., 2008; Brandsma et al., 2009). Conversely, novel anti-angiogenic treatments have led to the radiological concept of pseudoresponse, whereby the anti-vascular endothelial growth factor treatment affects vascular permeability but may not significantly alter tumour progression, as evidenced by continued enlargement of hyperintensity signal on FLAIR and rapid relapse after interruption of treatment (Norden et al., 2008; Brandsma et al., 2009). In order to improve preoperative glioma grading and delineation, as well as to improve treatment response assessment, research in glioma imaging has focused on direct detection of biological tumoural changes by targeting local changes in metabolite composition, glucose metabolism, amino acid uptake and hypoxic markers.

2.3 Advanced MRI techniques

The use of advanced MRI techniques has the advantage of being available in most clinical settings and does not require additional, and often expensive and with limited half-lives, radioactive tracers. MRI can currently provide information on water mobility within tissue (diffusion imaging), chemical composition (proton MR spectroscopy) as well as cerebral blood volume (CBV) and permeability (perfusion MR) (Cao et al., 2006).

2.3.1 Diffusion imaging

Diffusion imaging exploits the variation of micromotion properties of water protons in different environments. Pathological changes such as increased cellularity, necrosis, cytotoxic and vasogenic edema, osmolarity and active transport mechanisms affect these properties. These changes have an impact on proton diffusivity and mobility, which can be measured by diffusion imaging (Bammer, 2003). Diffusion imaging consists of standard diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC) map and diffusion tensor imaging (DTI). DTI is a measurement of diffusion along different axes and can be used to determine fractional anisotropy (the preferential movement of water protons in certain direction), from which white matter tractography can be extrapolated.

Although DWI has established its clinical use in the diagnosis of several cerebral pathologies, including acute stroke (Warach et al., 1992; Adams et al., 2007) and in differentiating necrotic tumours from cerebral abscesses (Kim et al., 1998; Desprechins et al., 1999), its role in glioma grading and delineation is uncertain. Kono et al. (2001) found an inverse relation between tumour cellularity and the ADC value in astrocytic tumours, but the DWI and ADC imaging values were unable to discriminate between non-enhancing tumour invasion and peritumoural edema.

Early cellular changes following treatment, such as cytotoxic edema and necrosis, can be measured using DWI and have been shown to predict clinical efficacy (Moffat et al., 2005).

Indeed, in twenty glioma patients undergoing radiotherapy, chemotherapy or combined treatment, the percentage of tumour volume having undergone a change in ADC signal after three weeks of treatment (compared to a pre-treatment MRI) was compared between the different radiographic outcome groups after completion of treatment. These values were found to be significantly different between the partial response (n = 6), stable disease (n = 6) and progressive disease (n = 8) groups. Although survival statistics were not provided, the early identification of response to treatment might allow the treatment team to offer therapeutic alternatives to non-responders at an earlier timepoint in the course of the disease.

Using measurements of mean diffusivity (MD) and fractional anisotropy (FA), DTI has a potential role in delineating tumour margins within white matter. A tumour infiltration index (TII), derived from MD and FA values, was presented as a potential tool to discriminate "pure" vasogenic edema from tumour infiltrated edema (Lu et al., 2004). They observed that peritumoural edema FA values were lower (relative to MD values) in glioma patients than in meningioma and metastasis patients. They hypothesized that this was due to concomitant white matter disruption by tumoural invasion. This suggestion was not confirmed pathologically in the study, and a more recent study failed to replicate this hypothesis (Kinoshita et al., 2010), although a positive correlation was found between the TII and the standard uptake value (SUV) on ^{11}C-methionine PET imaging (a marker of tumour infiltration) in peritumoural hyperintense T2 areas.

2.3.2 Perfusion MR

Dynamic MR imaging during intravenous injection of gadolinium can be used to calculate regional CBV and vascular permeability with a spatial resolution similar to DWI (Cao et al., 2006). Both CBV and vascular permeability have been shown to correlate with glioma histological grade, but with significant overlap between grades (Roberts et al., 2000; Law et al., 2004). The use of perfusion MR in delineating tumour margins or response to treatment has not been explored.

2.3.3 Proton MR Spectroscopy (MRS)

The resonance frequency of hydrogen atoms in a magnetic field varies in function of their chemical microenvironment (the molecule that contains them). MRS expresses these differences as a chemical shift. Various metabolites commonly detected in brain tissue have relevance in glioma imaging because they correlate with specific metabolic events. These include choline-containing compounds (cell membrane turnover), creatine (energy metabolism), lactate (hypoxia), lipids (necrosis), and n-acetyl-aspartate (neuronal cell integrity).

The MRS choline peak may provide information to delineate gliomas. The choline/NAA ratio has been shown to correlate with the degree of tumoural invasion (tumour cell density)(Croteau et al., 2001), and a cutoff choline/NAA index (CNI) of 2.5 has been suggested to differentiate tumour from non-tumour MRI changes in untreated patients (McKnight et al., 2002). However, the role of MRS in pre-operative tumour delineation is limited by the poor spatial resolution of the technique (0.8 to 1 cm^3 voxel size). This limitation might eventually be resolved with development of higher resolution MRIs.

MRS may also play a role in treatment outcome prediction. In 28 glioblastoma patients undergoing combined radiotherapy and chemotherapy, the volume of metabolic

abnormality (determined as areas of CNI > 2.5) within the tumour correlated negatively with survival. Another retrospective study of 26 glioblastoma patients undergoing radiosurgery (following previous radiation) demonstrated increased survival when more than 50% of the MRS tumour volume (CNI > 2) was included in the radiosurgery target (Chan et al., 2004). The latter finding suggests that MRS may be of benefit in defining radiosurgical (and perhaps conventional radiation) target volumes.

MRS, more specifically the Cho/NAA and NAA/Cr ratios, has shown some diagnostic value in differentiating tumour recurrence from radiation necrosis (Rock et al., 2004; Weybright et al., 2005; Sundgren, 2009). However, MRS is unreliable in the common cases of mixed recurrent tumour and radiation change (Sundgre, 2009). In a recent report, Zhou et al. (2011) observed that viable glioma could be differentiated from normal tissue and radiation necrosis using a novel amide proton transfer (APT) MRI technique in an irradiated U87MG glioma rat model.

2.4 Positron emission tomography
2.4.1 The choice of radioactive label
The most common radioactive labels used in PET are ^{18}F and ^{11}C. Although comparative studies of ^{18}F and ^{11}C labels using the same tracer were not found, studies comparing SUVs of O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) (Weber et al., 2000) or [^{18}F]fluorodopa(FDOPA) (Becherer et al., 2003) with L-[methyl-^{11}C]methionine (MET) in patients with intracerebral lesions found similar uptake values in normal brain and tumour between the two tracers. Therefore, the main advantage of ^{18}F labelled tracers seems to be the longer half-life (110 minutes) compared to ^{11}C (20 minutes), which allows centers without on-site cyclotrons to perform PET studies.

2.4.2 The choice of labelled tracer
The most commonly used PET radioactive tracer remains FDG. However, the physiologically high glucose metabolism of normal brain produces a high background FDG uptake which decreases the signal-to-noise ratio in FDG-PET imaging, decreasing the detectability of low-grade or recurrent gliomas (Chen & Silverman, 2008; Klasner et al., 2010). In the search for alternative tracers, amino acids were found to be ideal because most CNS tumours show high uptake of amino acids compared to normal brain tissue, which has much lower amino acid requirements due to its low proliferative potential. Many different amino acids, such as ^{11}C-methionine (MET), ^{11}C-leucine and ^{11}C-tyrosine, as well as amino acid analogs (^{18}F-FDOPA, ^{18}F-FET), have been synthesized (Klasner et al., 2010). As noted earlier, comparative studies showed similar uptake values between the ^{11}C-MET, ^{18}F-FET and ^{18}F-FDOPA tracers (Weber et al., 2000; Becherer et al., 2003). Other tracers, such as ^{18}F-fluoromisonidazole (FMISO), specifically target hypoxic cells (Bruehlmeier et al., 2004), while nucleotide analogs, such as [^{18}F]fluorothymidine (FLT), target cell proliferation.

2.4.3 PET in tumour diagnosis and grade
Various amino acid PET studies have demonstrated increased tracer uptake in tumours compared to non-tumoural lesions, but the differential diagnosis between tumour types could not be made (Herholz et al., 1998; Jacobs et al., 2005; Pauleit et al., 2005). An increased uptake of 1.5-1.6 compared to the contralateral hemisphere was suggested as a threshold for viable tumoural tissue (Jacobs et al., 2005). Some studies observed a significantly higher

uptake in HGGs compared to LGGs using ^{11}C-MET PET[32,34], whereas other groups identified a non-significant trend of higher tracer uptake in higher glioma grades using ^{18}F-FET[2] and ^{18}F-FET PET[35]. Fueger et al. (2010) recently demonstrated that ^{18}F-FDOPA PET SUVs were significantly different between all grades in newly diagnosed gliomas, but not in previously treated gliomas. They calculated an SUV_{max} of 2.72 to discriminate between LGG and HGG. Furthermore, the ^{18}F-FDOPA values correlated with Ki-67 values in pathological samples. Identifying metabolic "hot spots" within non-enhancing lesions was shown to accurately target higher grade areas in suspected LGGs (Kunz et al., 2011). As well, combining PET findings with gadolinium-injected images increase the diagnostic yield of stereotactic biopsies in HGG (Pauleit et al., 2005).

2.4.4 PET and tumour delineation

Tumour margins determined by conventional MRI and PET tracer uptake often yield different but overlapping tumour volumes. In a report of 103 consecutive cases, Pirotte et al. (2006) used combined FDG-PET, MET-PET and MRI to define the planned surgical resection in 63 LGGs and 40 HGGs. They observed that the PET-defined tumour volume complemented the MRI-defined tumour volume in 96% of cases. PET imaging data altered the planned resection volume in 80% of cases. One of two trends was usually observed: either the planned resection volume was increased to achieve a complete removal of the tumour, or the resection volume was decreased in cases where the aim was to resect only the metabolically active (anaplastic) portion of the tumour. In LGG, PET imaging increased the planned resection volume in 57% of cases and decreased it in 27% of cases. In HGG, the resection volume was increased in 28% and decreased in 48% of cases. Unfortunately, pathological data regarding tissue in areas with discordant PET/MRI findings was not documented.

Importantly, in a subsequent study using the same combined PET/MRI to plan the resection, the same group reported an increased survival in HGG patients when a complete resection of the area of increased tracer uptake on PET had been achieved (mean = 32.5 vs 17.6 months, p = 0.0001) (Pirotte et al., 2009). Complete resection of the planned metabolically active volume was achieved in 70% of cases. Nariai et al. (2005) observed a similar survival advantage in their cohort of patients with HGGs when there was no residual area of elevated PET uptake.

2.4.5 PET and evaluation of response to treatment

An important aspect of imaging follow-up during the treatment of patients with glioma is the early identification of response to treatment. This allows the treating team to continue current treatment when it is appropriate, or to offer different treatment options as early as possible to non-responders. PET imaging using the nucleotide tracer ^{18}F-FLT has shown promise in this respect. In a group of twenty patients with recurrent glioma treated with bevacizumab and irinotecan, significant tracer uptake decreases in previous metabolically active areas at 2 weeks and 6 weeks following initiation of treatment were only observed in patients surviving > 12 months (Schiepers et al., 2010).

Another important aspect of glioma treatment follow-up is the ability to differentiate tumour recurrence from radiation-induced changes. In a series of 45 patients, Rachinger et al. (2005) report 93% specificity and 100% sensitivity for ^{18}F-FET PET in detecting tumour recurrence (compared to 93.5% specificity and 50% sensitivity for MRI). In this study, the

ultimate diagnosis of radiation change was determined histopathologically in only 2 of 14 patients. Similarly, Nariai et al. (2005) found a significant difference in SUVs between recurrent glioma (n = 47) and radiation changes (n = 4, as defined histopathologically or by resolution of radiological findings) using ^{18}F-DOPA PET.

In summary, PET imaging provides complementary information to MRI in the diagnosis, tumour delineation and treatment follow-up of gliomas. Amino acid tracers are better suited to study brain cancers due to the greater signal to noise ratio compared to normal cerebral tissue. Nucleotide tracers such as FLT might be more sensitive to tumoural proliferation and may play an important role in the identification of treatment response and the discrimination of tumour recurrence from radiation-induced changes.

3. Intraoperative tools in glioma surgery

3.1 Extent of resection

The usefulness of aggressive resection of malignant gliomas has not been established. Many studies have shown no lengthening of progression free survival or overall survival with aggressive resection versus limited resection. The major limitation of these studies is that they relied on surgeon opinion to quantify the extent of resection; using qualitative terms such as gross total resection, subtotal resection, debulking, and biopsy. In fact, many of the studies predate MRI. Since malignant gliomas are highly invasive, the distinction between tumor and normal brain is typically not obvious. Thus, the intraoperative impression is often not concordant with the actual degree of resection.

More recent studies using early postoperative MRI, less than 48 hour postoperatively, to accurately quantify extent of resection have shown an advantage to aggressive resection. In fact, not only do patients with complete resection experience long survival, patients with incomplete but larger resection fair better than patients with incomplete but smaller resections (Stummer et al., 2006; McGirt et al., 2009).

Based on these findings and others there is a growing consensus that the extent of resection should be a primary concern, even where full resection is not possible, as the degree of tumor resection is associated with better patient outcomes when combined with chemotherapy and radiotherapy (Stummer et al., 2008). However, even for experienced surgeons, it can be difficult to define the tumor margins, as in many cases there is no demarcation between tumor and normal tissue.

3.2 Image guided surgery: Neuronavigation

Image guided surgery refers to a technique in which a point in a patient's space can be located on preoperative imaging. In neurosurgery, image guided surgery, or neuronavigation, refers to the ability to use a probe to locate a particular scalp, skull, or brain region on the preoperative MRI or computed tomography (CT) image. Advantages of neuronavigation include tailored craniotomy planning, and direct correlation of cortical anatomy with preoperative imaging. Neuronavigation is also useful in guiding the initial stages of resection, close to the cortical surface. Its usefulness in accurately identifying deeper tumor boundaries is dependent upon maintained accuracy with preoperative imaging. Since the preoperative imaging is static, and brain positioning is dynamic throughout an operation, there can be, and often is, a loss of accuracy over the course of the operation. Brain movement during surgery, or brain shift, can be caused by tumor removal, intracranial pressure reduction manoeuvres such as diuretic administration, cerebrospinal

fluid evacuation and gravity. Since malignant gliomas tend to be large and invade along deep white matter tracts, the utility of navigation to accurately locate deep tumor borders is limited by a loss of accuracy during the surgery.

Wirtz et al. (2000) studied the impact of navigation in 52 patients with grade four glioma. Early post-operative MRI was used to quantify the extent of resection. They found that a complete resection was achieved in 31% of cases in which navigation was used, whereas a complete resection was achieved in only 18% of cases without navigation. In contrast, Litofsky et al. (2006) reported that in 486 patients, the use of navigation resulted in fewer gross total resections. Willems et al. (2006) conducted a prospective randomized study in which 45 patients, each harbouring a solitary contrast-enhancing intracerebral tumor, were randomized for surgery with or without neuronavigation. Quantification of the extent of resection was determined using magnetic resonance imaging. They found that the mean amount of residual tumor tissue was 28.9% when navigation was not used and 13.8% when navigation was used. The corresponding mean amounts of residual gadolinium enhancing tumor tissue were 29.2 and 24.4%, respectively. These differences were not significant. They also found that gross total resection was achieved in five patients who underwent surgery without navigation and in three who underwent surgery with navigation. They concluded that there is no rationale for the routine use of neuronavigation to improve the extent of tumor resection.

Although a consensus has not been reached, most neurosurgeons agree that neuronavigation is valuable in surgical planning and the early stages of resection and that its accuracy is dependent on the dynamics of brain positioning throughout the operation. Developing techniques to update the navigation system during the operation, accounting for brain shift, will be increase the utility of navigation in glioma surgery.

3.3 Intraoperative MRI

Although not actually used as a guidance tool during the time of surgical resection, intraoperative MRI (iMRI) can be considered a tool to increase the extent of resection since it is performed within the same operative setting. Typically, the surgery is taken to the point at which the surgeon believes the resection has been completed. The dura and skin are then closed in a temporary fashion and the patient is then transferred into the adjacent iMRI or the iMRI is brought to the patient. Upon imaging, the decision is then made if residual resectable tumor remains, and if so, the skin and dura are reopened and the resection completed.

Advantages of this technique are that the image quality is excellent, neurosurgeons are familiar with this mode of imaging, and residual tumor is readily identifiable. Disadvantages of iMRI include the significant upfront infrastructure costs and additional surgical time required. Hirschberg et al. (2005) reported that the average operating time using iMRI was 5.1 hours and was significantly longer than in the conventional OR (3.4 hours). Importantly, iMRI is not an online technique, it does not guide the surgery or help to distinguish tumor from normal brain, it is used to evaluate the extent of resection at a surgeon defined time point.

Over the last 10 years, many centres have acquired, used, and are now reporting their experience with iMRI. Senft et al. (2010) reported their experience in using an iMRI system in glioma surgery. Between July 2004 and May 2009, a total of 103 patients harbouring gliomas underwent tumor resection with the use of a mobile low field iMRI. All patients underwent early postoperative high field MRI to determine the extent of resection. They

found that all tumors could be reliably visualized on intraoperative imaging. Intraoperative imaging revealed residual tumor tissue in 51 patients (49.5%), leading to further tumor resection in 31 patients (30.1%). Importantly, extended resection did not translate into a higher rate of neurological deficits. When analyzing survival of patients with glioblastoma, patients undergoing complete tumor resection did significantly better than patients with residual tumor (50% survival rate at 57.8 weeks vs. 33.8 weeks, log rank test p=0.003). Hatiboglu et al. (2009) studied the impact of iMRI on the decision to proceed with additional glioma resection during surgery and to maximize extent of resection. Patients who underwent craniotomy for glioma resection with high-field iMRI guidance were prospectively evaluated over a 1 year period. Volumetric analysis and extent of resection were assessed with iMRI, using gadolinium enhanced T1-weighted images for tumors showing contrast enhancement and T2-weighted images or nonenhancing tumors. Surgery was terminated after iMRI in 23 patients (52%) because gross total resection was achieved or because of residual tumor infiltration in an eloquent brain region. Twenty-one patients (47%) underwent additional resection of residual tumor after iMRI. For enhancing gliomas, the median extent of resection increased significantly from 84% (range, 59%-97%) to 99% (range, 85%-100%) with additional tumor removal after iMRI (P < 0.001). Gross total resection was achieved after additional tumor removal after iMRI in 15 of 21 patients (71%). Overall, 29 patients (65%) experienced gross total resection, and in 15 (52%), this was achieved with the contribution of iMRI.

To examine whether iMRI combined with neuronavigation contributes to a significantly improved extent of resection in glioma surgery Kuhnt et al. (2011) analysed 293 glioma patients who underwent craniotomy and tumor resection with the aid of 1.5 T iMRI and integrated multimodal navigation. In cases of remnant tumor, an update of navigation was performed with intraoperative images. Tumor volume was quantified pre- and intra-operatively by segmentation of T2-abnormality in low-grade and contrast enhancement in high-grade gliomas. They found that in 25.9% of all cases examined, additional tumor mass was removed as a result of the information provided by iMRI. This led to complete tumor resection in 20 cases, increasing the rate of gross-total removal from 31.7% to 38.6%. In 56 patients, additional but incomplete resection was performed due to close location to eloquent brain areas.

Leuthardt et al. (2011) recently reported their experience with the combination of awake craniotomy and iMRI for resection of gliomas in close proximity to eloquent cortex. They studied 12 patients undergoing this procedure. They found that the extent of resection was limited because of proximity to eloquent areas in 5 cases: language areas in 3 patients and motor areas in 2 patients. Additional tumor was identified and resected after iMRI in 6 cases. Average operating room time was 7.9 hours (range 5.9 - 9.7). They concluded that awake craniotomy and iMRI can be safely performed to maximize resection of tumours near eloquent language areas.

In summary, many centres have now reported significant improvements in extent of resection, without increased rates of neurologic deficit, using iMRI in glioma surgery. Most importantly, this surgical improvement has lead to longer survival.

3.4 Ultrasound co-registered with MRI

The first reports of the use of intraoperative brain ultrasonography (US) to image the brain were published well over 50 years ago (French et al., 1950; Ballantine et al., 1950; Balantine et

al., 1950). Reports using real-time B-mode 2D US imaging, as we know it today, were published in the early 80s (Voorhies & Patterson, 1980; Rubin et al., 1980). 2D US can be used at the beginning of the operation, while on dura, to image the tumor and its relationship to brain structures including ventricles, blood vessels, gyri, sulci and rigid structures such as the falx and tentorium. Such imaging, prior to dural opening, is similar to the preoperative MRI since tumor resection has not yet taken place and brain shift is minimal. US can also be used on the surface of the brain or within the resection cavity provided an adequate probe-fluid interface can be maintained. US is useful as an intraoperative imaging tool since it can be used throughout the operation to update the surgeon with respect to residual tumor and help identify the surgical location. Imaging in real-time compensates for the problem of brain shift which compromises neuronavigation techniques since they are based on the static preoperative images. A major drawback of 2D US is that the real-time images are displayed in a plane corresponding to probe positioning and not the conventional axial, sagittal and coronal planes commonly used by neurosurgeons. Such arbitrary orientation can be confusing and unsettling for many neurosurgeons.

To address this issue, tracked US or 3D US was developed. In this technique, the US probe is registered to the neuronavigation system and the 2D images are acquired and reformatted into 3D. These images can then be displayed with the corresponding MR images to better orient the user, an attractive solution for most neurosurgeons. To assess the usefulness of 3D US in detected tumor, Unsgaard et al. (2005) compared 3D ultrasound with preoperative MR images in 28 tumor cases and found that ultrasound was at least as good as MRI in identifying tumor borders. Other studies have also validated the accuracy of US in brain tumor surgery. Gerganov et al. (2008) compared 3D US reconstructions with iMRI during brain tumor resection procedures and found that the image quality before the resection to be of similar quality with both modalities. Similarly, van Velthoven et al. [23] found that ultrasound is as reliable as MRI to delineate gliomas, metastases and meningiomas. In fact, it may even be superior to MRI in defining low-grade tumor boundaries (Unsgaard et al., 2005).

Three dimensional US may be useful in identifying tumor, but does its lead to an increased extent of resection? To answer this question, Unsgaard et al. (2002) reported on their series of cases in which the operation was taken to the point at which the impression was that no residual tumor remained. At this time 3D US imaging was used and revealed previously unidentified residual tumor was found in 53% of cases.

More recently, 3D US has been improved to take into account brain shift during the course of the operation. Using a non-linear algorithm, Mercier et al. (2011) have shown that they are able to fit the US taken during and at the end of the operation with the preoperative MRI taking into account brain shift so as to provide the surgeon with real-time imaging referenced to the preoperative MRI. They found that interpreting the post-resection ultrasound is easier when properly registered with the preoperative MRI and with the pre-resection ultrasound. Further studies are necessary to determine if this translates into increased extent of resection.

3.5 Fluorescence guided resection

The ability to visualize the tumor intraoperatively, and distinguish it from normal brain would present an ideal situation allowing for maximal resection of brain cancers. Such a technique would require high sensitivity and specificity.

5-aminolevulinic acid (5-ALA) is a natural biochemical precursor of hemoglobin that elicits synthesis and accumulation of fluorescent porphyrins in various epithelia and cancerous

tissue (Mlkvy et al., 1998). The topical form of this agent is FDA approved for and has been employed for dermatologic surgery (Roberts & Cairnduff, 1995; Lang et al., 2001; Sadick, 2010). 5-ALA is produced at the cytosolic surface of the mitochondrial membrane and then transported to the cellular cytosol for hemebiosynthesis (Kennedy et al., 1990; Kennedy & Potter, 1992; Henderson et al., 1995; Kloek et al., 1996). The availability of 5-ALA in the cell cytoplasm is the rate limiting factor in heme biosynthesis in all but erythopoetic cells. Heme biosynthetic enzymes are more active in brain cancer than in normal brain tissue. As a result, addition of ALA (the rate-limiting agent and precursor) to malignant glial cells leads to an increase in the intracellular accumulation of protoporphorin IX, a fluorescent intermediary in heme biosynthesis (Kennedy et al., 1990; Kennedy & Potter, 1992; Henderson et al., 1995; Kloek et al., 1996). As a result, malignant glial cells fluoresce red relative to normal brain tissue when visualized under ultraviolet light.

Stummer et al. (1998) reported on the sensitivity and specificity of 5-ALA. Intraoperatively detected areas of weak or strong fluorescence are tumor-cell positive in the majority of cases [84.8% (90% CI: 70.7% - 93.8%)], and only a low number of fluorescent (all weakly) biopsies are tumor cell negative (3.8% of all biopsies taken). The minimum tumor cellularity of 4.5% is requried for 5-ALA detectable under fluorescence light. Approximately two thirds of non-fluorescent biopsies taken from normal adjacent tissue are tumor-cell positive, demonstrating the invasive growth pattern of malignant glioma. 5-ALA-induced fluorescence detection sometimes fails to identify areas that show contrast-enhancement in postoperative MR, especially in those areas that are not accessible by the blue light source.

Several European centers have investigated the role of 5-aminolevulinic acid in fluorescence guided resection of newly diagnosed Grade III/IV astrocytomas (Stummer et al., 1998; Stummer et al., 2000; Stummer et al., 2006). Stummer et al. (2006) demonstrated in their randomized multicenter phase III trial (n = 322 patients, dose of 20 mg/kg body weight) a gross total resection rate of 63.6% in the experimental arm (5-ALA guided resection) versus 37.6% in the control arm (standard white light resection). Clinically, this translated into a higher 6 month progression free survival than those allocated to white light resection (41.0% versus 21.1%). This trial is the first study that showed prospectively that fluorescence-guidance increases the completeness of resection of malignant gliomas.

In the clinical studies 5-ALA has proven to be safe. Events have been classified according to their relationship to the drug, and those related to the combination of drug and procedure. During the last 2 years in the post marketing studies in Europe under a stringent risk management program, no significant adverse effects have been reported to regulatory authorities in Europe.

In 2006 it was reported that the use of 5-ALA was associated with improved gross tumor resection when used as a fluorescent agent in high grade glioma (Stummer et al., 2006). This European registration trial for 5-ALA as a fluorescent guided probe for tumor visualization, revealed a marked improvement in percentage of patients achieving gross total resection compared to normal operating white light (64% vs 38%, p < 0.001). Randomized control trials in both Canada and United States of America are in the final stages of preparation.

4. Conclusion

Since the routine use of early post-operative MRI to accurately quantify extent of resection has become common, studies are now being reported revealing that increased extent of resection yields improvements in overall survival. However, even in cases of complete

resection of the MRI based gadolinium-enhancing portion of the tumor, tumors always recur and the prognosis is poor.

While MRI based imaging is the current standard for tumor imaging, labelled tracer PET imaging is emerging as a complimentary technique to better visualize the entirety of the tumor. Just as it is difficult to visualize the entirety of the tumor on imaging, it is also difficult to visualize the tumor, and distinguish it from normal brain, intraoperatively. Imaging tools that can be used to increase the rate of resection include iMRI, 3D US, and fluorescence guided surgery.

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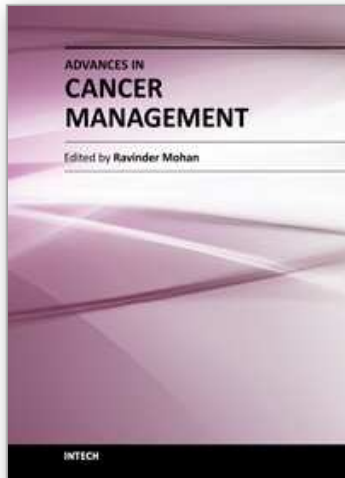
Advances in Cancer Management

Edited by Prof. Ravinder Mohan

Cancer is now the most common cause of death in the world. However, because of early diagnosis, better treatment, and advanced life expectancy, many cancer patients frequently live a long, happy, and healthy life after the diagnosis- and often live as long as patients who eventually do not die because of cancer. This book presents newer advances in diagnosis and treatment of specific cancers, an evidence-based and realistic approach to the selection of cancer treatment, and cutting-edge laboratory developments such as the use of the MALDI technique and computational methods that can be used to detect newer protein biomarkers of cancers in diagnosis and to evaluate the success of treatment.

How to reference

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Claude-Edouard Chatillon and Kevin Petrecca (2012). Emerging Imaging and Operative Techniques for Glioma Surgery, Advances in Cancer Management, Prof. Ravinder Mohan (Ed.), ISBN: 978-953-307-870-0, InTech, Available from: http://www.intechopen.com/books/advances-in-cancer-management/emerging-imaging-and-operative-techniques-for-glioma-surgery

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