# Beautiful Eyes Guiding Powerful Hands – The Role of Intraoperative Imaging Techniques in the Surgical Management of Gliomas

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## Abstract

The aims of the surgical management of cerebral gliomas are to achieve the widest feasible resection and preserve the patient's functional integrity. This results in an improved survival rate and a favourable quality of life. When treating this disease, current neuroradiological techniques are important for preoperative depiction and planning, and intraoperative image-guided resection, especially when the tumour involves eloquent cortical and subcortical structures. Knowledge of these techniques and their limitations, and appropriate expertise are therefore necessary to gain the complete benefit of their diagnostic and therapeutic power.

# **Keywords**

Magnetic resonance imaging (MRI), diffusion tensor imaging-fibre tractography (DTI-FT), functional MRI, neuronavigation, glioma

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Gliomas are primitive cerebral tumours representing a heterogeneous group of intra-axial central nervous system neoplasms of glial origin with different histology, behaviour, molecular characteristics, natural history and thus prognosis.<sup>1-4</sup> Four distinct tumour grades have been identified according to the degree of malignancy, as reported in the World Health Organization (WHO) classification.<sup>5</sup> The low-grade gliomas (LGGs) commonly refer to grade 2 astrocytoma, grade 2 oligoastrocytoma and grade 2 oligodendroglioma, while high-grade gliomas (HGGs) refer to the grade 3 anaplastic variants of astrocytomas, oligodendrogliomas and oligoastrocytomas, and to the grade 4 gliomas. LGGs and HGGs differ in terms of epidemiology, clinical features, proliferation rate, mitotic activity and angiogenesis phenomena, and thus require specific treatment protocols.<sup>2-4,6,7</sup>

Several investigations in the past two decades have increasingly supported the role and the oncological efficacy of surgically managing LGGs and HGGs.<sup>1-3,7-13</sup> Current neurosurgical treatment has several aims: to obtain adequate and representative tissue specimens for an effective histological diagnosis and proper genetic and molecular analysis (MGMT methylation status, 1p19q loss of heterozigosity, isocitrate dehydrogenase 1 mutation); to achieve maximum cytoreduction and to avoid or reduce eventual malignant transformation; to relieve the patient's neurological signs and symptoms, including seizure occurrence; to minimize postoperative morbidity and preserve the best achievable quality of life. Indeed, the extent of resection (EOR) is significantly related to overall and progression-free survival, as demonstrated in a series of previous investigations.<sup>37,8,10,14</sup>

To maximise the EOR while minimising postoperative morbidity and preserving the patient's integrity, it is mandatory during surgery to correctly identify functional relevant brain regions, or eloquent areas, which are often infiltrated or dislocated by gliomas, particularly in the case of LGGs. Eloquent supratentorial brain areas are practically defined as areas relevant for the performance of basic neurological functions, such as sensory, motor, language and visual cortical and subcortical structures.<sup>15,16</sup>

A composite setting of neuroradiological,<sup>17</sup> neurophysiological<sup>18</sup> and neuropsychological<sup>19</sup> assets is available at the pre- and intraoperative stage, with so-called functional brain mapping and monitoring techniques allowing the identification of specific cortical and subcortical functional structures. Using these techniques may impact on the EOR and thus on the long-term survival of patients affected by LGGs.<sup>10,15,16</sup>

Contemporary imaging techniques are essential at all stages of managing gliomas.<sup>20</sup> The authors thus aim to explore and critically analyse different imaging technologies currently used in routine clinical practice at the pre- and intraoperative stage in the surgical management of gliomas. The advantages, limitations and the potential of conventional and advanced magnetic resonance imaging (MRI) and ultrasound techniques are discussed.

# The Role of Magnetic Resonance Imaging

MRI is an elective neuroradiological procedure to study gliomas. Several different MRI sequences are applied according to the diagnostic query and clinical hints. T1-weighted imaging (T1w) with and without the use of gadolinium contrast, T2-weighted imaging (T2w) and fluid-attenuated inversion recovery (FLAIR) sequence are referred to as conventional MRI. The primary aim of conventional MRI is to obtain an optimal depiction of the physiological and pathological anatomy, i.e. the morphological features of the lesion of interest *per se* and its relationship with the surrounding structures.<sup>20,21</sup>

Recent advances in MRI techniques provide different types of data: the functional specialisation of an area of interest, with particular emphasis on the eloquent areas (fMRI); the normal and pathological anatomy, and the different degree of involvement of selected subcortical white matter (WM) tracts (diffusion-tensor imaging [DTI], and fibre tractography [FT] reconstruction); the perfusion pattern described by analysing the Brownian motion of water molecules (diffusion-weighted imaging [DWI] and perfusion-weighted imaging [PWI]); the metabolic changes detected non-invasively in vivo through the biochemical tissue variations of a suspect lesion (magnetic resonance spectroscopy [MRS]).

Both conventional and advanced MRI applications are critical for diagnosis of gliomas and help in the preoperative planning of their surgical removal. In fact, they are fundamental in mapping and monitoring individual anatomo-pathological features of patients and lesions.<sup>19</sup> The neuroradiological protocol used at the authors' institution is reported elsewhere.<sup>22</sup>

# **Conventional Magnetic Resonance Imaging**

Morphological T1w, T2w, FLAIR images and post-contrast T1w provide information on the site, location and structural aspect of the tumour and peritumoural abnormalities. These images help to determine the relationship of the tumour with major vessels and to calculate the lesion volume. Macrocalcifications, cystic areas, intratumoural haemorrhages and necrosis may help to define the nature of the lesion. These sequences are relevant in the initial differential diagnosis of a glioma compared with diverse mass lesions, such as lymphomas, brain metastases, abscesses and haematomas, especially when combined with clinical data and advanced imaging. Post-contrast T1w allows better definition of blood vessels and provides information on the blood-brain barrier (BBB) integrity, providing an initial definition of grade: LGGs present an undamaged BBB and they do not usually show enhancement on post-contrast images.<sup>20</sup> Furthermore, repetitive measurement on morphological MRI allows the rate of growth of the tumour to be quantified, which indicates the tendency towards aggressive biological behaviour.23,24 The growth of LGGs is around 4 mm/year, while an increase in diameter greater than 8 mm/year suggests a high tendency towards malignant transformation, even in the absence of contrast enhancement or modification of FLAIR images.

# Advanced Magnetic Resonance Imaging – fMRI, DTI-FT, MRS, PWI

fMRI provides information about the cortical areas active in response to motor or language tasks whereas DTI-FT depicts the connectivity around and inside a tumour by identifying selected WM fibre tracts.

Motor fMRI is used clinically to depict the cortical motor sites and to understand their relationship with the tumour.<sup>25-27</sup> fMRI with different language tasks is used to build a map of the cortical areas mainly involved in object naming, famous face naming, verb generation and verbal fluency.<sup>11,27-29</sup>

## Figure 1: Recurrent Left Temporo-parietal Low-grade Glioma



A: The fluid-attenuated inversion recovery image depicts a recurrent left temporo-parietal low-grade glioma. The morphological study, however, does not fully resolve the relationship between the lesion and the flanking eloquent white matter tracts. B: The corresponding diffusion tensor imaging – fibre tracking study depicts the course of the cortico-spinal tract (red), inferior fronto-occipital (light blue), superior longitudinalis fasciculus (yellow), inferior longitudinalis fasciculus (purple), fasciculus uncinatus (blue) and their relationship with the lesion. When loaded into the neuronavigation system, this dataset is available to the surgeon throughout the procedure.

DTI-FT provides anatomical information on the location of motor tracts and several language tracts,<sup>30</sup> such as the cortico-spinal tract (CST) and tracts involved either in the phonological or semantic components of language, such as the superior longitudinalis fasciculus (SLF), which includes the fasciculus arcuatus, and the inferior fronto-occipital (IFO) (see Figure 1).22,26 The basic DTI-FT map includes the CST for the motor part, and the SLF and the IFO for the language part.<sup>26,31,32</sup> Additional tracts can be reconstructed, such as the uncinatus, the inferior longitudinalis and the subcallosum fasciculus, upon specific clues obtained by extensive preoperative neuropsychological evaluation or for research purposes. DTI-FT depicts the relationship between the WM tracts and the tumour mass, describing these tracts as unchanged, dislocated or infiltrated according to the degree of involvement.33 Critical aspects for obtaining a reliable reconstruction are the raw data quality and an appropriate fractional anisotropy (FA) threshold. Tumour characteristics, such as histology, oedema and location, can also influence tract depiction. According to intraoperative DTI-FT and direct electrical stimulation (DES) correlation data, a FA of 0.1 should be used for optimal visualisation of tracts in LGGs (see Figure 2).31 DTI-FT is particularly useful and hence recommended in LGGs since these tumours are more likely to infiltrate WM fibres than HGGs, for which DTI-FT should be performed in selected cases only.<sup>18</sup>

MRS allows the evaluation of intratumoural areas where the metabolism is more or less pronounced, according to the differential

#### Figure 2: Usefulness of Diffusion Tensor Imaging-Fibre Tractography – An Illustrative Case of a Left Pre-motor Low-grade Glioma



This figure shows T1-weighted imaging with gadolinium (upper row), diffusion tensor imaging – fibre tractography (DTI-FT) reconstructions of the cortico-spinal tract (CST) (middle row) and the face pre-motor fibres (lower row) in a patient affected by a low-grade glioma. DTI-FT enables CST to be visualised as only mildly backward displaced but uninvolved by the left frontal non-enhancing lesion. Yet, the face pre-motor fibres are involved inside the tumour mass. This evidence guides the surgeon in precise functional electrical mapping to correctly identify this fibre bundle intraoperatively.

proton MR-spectral output of the analysed regions of interest.<sup>34</sup> The differential representation of choline, creatinine and their ratio, n-acetilaspartate, lipids, lactic acid and, occasionally, other metabolites such as myo-inositol can provide a presumptive diagnosis and grading of the lesion.<sup>35</sup> This is particularly crucial for tumour-mimicking masses,<sup>36</sup> when refining the differential diagnosis is required to choose an appropriate treatment protocol, for instance when distinguishing between treatment-induced changes and recurrence, or between a glioma and a lymphoma. This is also helpful in guiding tissue sampling during surgery for histological and molecular purposes.

PWI studies the arterial and capillary vascular bed by analysing the paramagnetic effects of the contrast medium on the MR signal. Perfusion maps can be designed using these data, providing information on the biological behaviour of the tumour. LGGs and

HGGs display different behaviours,<sup>37</sup> with hyperperfusion indicating a more malignant nature. These different imaging modalities produce an impressive amount of data that can be used to produce a complex map of the cortical and subcortical eloquent structures, and areas with different metabolic and perfusion properties. This allows the anatomical and functional boundaries, and the metabolic and perfusion assets determined by the tumour to be established. All these data are critical for preoperative surgical planning and evaluation of the risks, but become even more relevant when they are loaded into the neuronavigation system. These MRI applications are also valuable intraoperatively, providing the following advantages: operation time reduced; prompt and accurate choice of site of DES with reduced number of stimulations needed for safe identification of eloquent structures; decreased likelihood of intraoperative seizure occurrence; and a reduction in the awake patient's fatigue.18,19

# The Multimodal Neuronavigation System – From the Preoperative to the Intraoperative Stage

Morphological volumetric T1w, T2w or FLAIR images, in addition to motor and language fMRI and DTI-FT images, are usually loaded into a frameless neuronavigation system. The neuronavigation system comprises computer-assisted technology enabling the integration of three-dimensional anatomical and functional data and preoperative imaging data with the intraoperative identification of a target. It thus helps during surgery to localize the tumour and to establish the relationship between the tumour and the surrounding functional and anatomic structures, both at the cortical and the subcortical level.<sup>22</sup>

fMRI and DTI-FT data are usually loaded into the neuronavigation system and coregistered with anatomical MRI and reference points applied on the skull of the patient. For effective use of fMRI and DTI-FT data in this setting, accurate data transfer to the neuronavigation system is critical, as is the use of adjustments during surgery to maintain global accuracy, as described elsewhere.<sup>22</sup> However, the problem of brain shift has to be addressed, as discussed below.

The reliability of fMRI and DTI-FT, and their sensitivity and specificity in depicting the structures of interest, has been investigated by intraoperative brain DES studies correlating intraoperative findings with MRI data.26 These investigations demonstrated that motor fMRI usually correlates with data obtained from DES. However, the extent of functional activation is larger than the area defined with intraoperative mapping, and can help choose a safe cortical entry point. This larger fMRI representation of a specific motor area means that motor fMRI can be safely used for planning and performing surgery. In the case of language tasks the results are variable, showing suboptimal correlation with intraoperative brain mapping results.<sup>29,38,39</sup> This is due to the extent of activation depicted by fMRI being larger compared with DES, which, conversely, demonstrates only essential language sites. Therefore, the exclusive use of language fMRI cannot be recommended in critical decision-making without using direct brain mapping in the awake surgery setting. However, language fMRI is reliable in establishing language laterality and it can effectively replace the Wada test.

From the senior author's experience, the combined use of DTI-FT and DES is a feasible approach that can be effectively and safely applied in routine clinical practice according to the clinical and surgical needs.<sup>18,22,26</sup> When DTI-FT data are loaded into the neuronavigation system, the operation time is decreased by guiding the surgeon to the point of the tract where stimulation can be started and, then, proceeding to careful resection.<sup>19</sup>

# Multimodal Magnetic Resonance Imaging Neuronavigation

The main limitation of using a neuronavigation system, particularly for large tumours or those at the subcortical level, is the occurrence of brain shift. Brain shift is the displacement of the cerebrum from its normal position, especially in relation to its position when preoperative MRI data were obtained, and subsequently loaded into the neuronavigation system to be used intraoperatively.<sup>25,26,40</sup>

Brain shift is due to intraoperative brain deformation caused by mass removal, brain swelling and cerebrospinal fluid leaks. The

extent of brain shift of major WM tracts can reach up to 8–10 mm.<sup>41,42</sup> To reduce the effects of brain shift during resection, some countermeasures can be adopted.<sup>22</sup>

Other imaging techniques are also available to increase the accuracy of structure identification and therefore of surgical resection, producing an ongoing depiction at the intraoperative stage, such as ultrasound and intraoperative MRI.

# Intraoperative Ultrasound

Ultrasound has been used in a range of neurosurgical procedures,<sup>25,42,43</sup> and is also useful for intraoperative visualisation of gliomas and mapping. Advances in ultrasound technology have improved the image quality.<sup>44</sup> Integrating intraoperative ultrasound with neuronavigation is an efficient, affordable and flexible tool for intraoperative imaging and surgical guidance since it detects brain shift and has a direct impact on intraoperative ultrasound could be used to update preoperative imaging data such as fMRI and DTI-FT to increase the accuracy of this information when used intraoperatively, especially at the subcortical level. However, the ability of these methods to reveal tumour remnants is lower than that of intraoperative MR systems. Overall, initial studies demonstrated the clinical usefulness of ultrasound intraoperatively in updating the neuronavigation system and leading to safer and wider resection.<sup>44,46</sup>

# Intraoperative Magnetic Resonance Imaging

Although all the above-mentioned methods enable the surgeon to correctly identify and preserve the eloquent structures, to complete the operation without tumour remnants is also critical. In the past 15 years, MRI was introduced into the operating room to allow realtime imaging during surgery. Intraoperative MRI has been used to surgically treat LGGs using low (0.2 T, 0.5 T) or high (1.5 T, 3 T) magnetic fields.<sup>45</sup> High-field magnets have the potential to improve image guality and to acquire advanced sequences;<sup>47</sup> these features can thus provide updated data on the EOR,<sup>12,46</sup> the localization of tumour remnants, the depiction of metabolic changes, tumour invasion and on the functional eloquent cortical and deep-seated brain structures. The advantage of intraoperative MRI is precise judgement of surgical performance with the patient still in the operating room. In addition, intraoperative MRI allows detection of brain shift since morphological images can be obtained by performing repeated imaging during surgery, and then loading the data into the neuronavigation system to update the initial dataset.<sup>41</sup> Intraoperative MRI also enables the early detection of intraoperative complications.

The main limitation of the intraoperative MRI system is the substantial cost of the equipment and its maintenance. In addition, especially with high-field magnets, titanium neurosurgical tools are mandatory. Given the gantry sizes, patient positioning can be altered to allow a proper scan, moving the patient during surgery can also increase the operation time and compromise sterility. Finally, artefacts from blood or air can disturb image reading.

# Conclusions

Contemporary imaging techniques have a fundamental role in the diagnosis, treatment and follow-up of patients with gliomas. Their contribution to the pre- and intraoperative stage has been briefly explored in this paper.

Given the relative complexity of the imaging systems described, critical to their use in surgical procedures for gliomas is appropriate training and the dedication of a multidisciplinary team. Robust and mutual co-operation with the neuroradiological team is thus essential when addressing the treatment of these tumours.

However, although most of the imaging techniques described, and tractography in particular, reach a high level of accuracy, because they are based on probabilistic measurements and are affected by brain shift when data are not acquired intraoperatively, they do not represent the gold standard mapping technique when used alone. In fact, intraoperative mapping using DES, as discussed elsewhere, ultimately represents the gold standard for the identification and preservation of eloquent functional structures, the damage of which presents a high risk of permanent neurological deficits.<sup>18,22</sup>

Nevertheless, current imaging modalities can effectively enhance surgical performance, leading to an increased number of patients eligible for surgical treatment with more accurate preoperative planning and risk evaluation. At the intraoperative stage, these techniques can guide the surgeon and DES for brain mapping and monitoring, speed up the identification of functional structures and thus reduce the operation time and the patient's fatigue, especially in the awake setting. This helps to reduce the occurrence of permanent postoperative neurological deficits and to improve intra- and postoperative seizure control. The techniques described also help to guide pathological sampling and advanced imaging techniques could help to identify infiltrated brain tissue in areas appearing normal using conventional imaging modalities, thus further increasing the EOR. Of particular relevance, a total or subtotal resection can be achieved in a greater percentage of patients when current imaging and stimulation techniques are combined.

We therefore believe that the use of modern imaging techniques is fundamental and recommend their use in the treatment of gliomas by a multidisciplinary team with appropriate knowledge of their potential and limitations.

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