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Clinical applications of imaging biomarkers. Part 2. The neurosurgeon's perspective

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ABSTRACT. Advances in imaging, including multivoxel spectroscopy, tractography, functional MRI and positron emission spectroscopy, are being used by neurosurgeons to target aggressive areas in gliomas, and to help identify tumour boundaries, functional areas and tracts. Neuro-oncological surgeons need to understand these techniques to help maximise tumour resection, while minimising morbidity in an attempt to improve the quality of patient outcome. This article reviews the evidence for the practical use of multimodal imaging in modern glioma surgery.

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What are the aims of glioma surgery? Despite exciting advances in MRI biomarkers, surgery is still needed to provide representative specimens for histological and molecular examination, for tumour debulking and sometimes chemotherapeutic access. Multimodal MRI can have a role in all surgical aspects of tumour management.

Gliomas are heterogeneous tumours that can lead to inaccuracies in diagnosis [1]. Areas of normal brain, inflammation, oedema, necrosis and active tumour of varying grades may coexist in a single patient [1–3]. Appropriate treatment requires representative sampling of the most aggressive part of the tumour. In enhancing tumours on CT or MRI, a portion of the contrast-enhanced section is targeted, whereas in unenhancing lesions perfusion, diffusion and spectroscopy can aid objective selection.

There continues to be debate regarding the role of debulking surgery for glioma [4–15]. There is Class 2 evidence that resectional surgery (as defined on post-operative MRI) in high-grade glioma correlates with improved prognosis [4–9]. In low-grade gliomas, the evidence is less convincing, but many authors contend that macroscopic resection does provide benefit [10–12]. A significant reduction in tumour burden without morbidity is the surgical aim.

Tumour boundaries are not clearly demonstrated by current clinical imaging techniques. McKnight et al [2] studied 68 patients with high-grade glioma using magnetic resonance spectroscopy (MRS) and targeted biopsies, and suggested that between one-third and one-half of the altered T_2 weighted signal seen on MRI is tumour. Price et al [16] have shown that tumour is present outside the T_2 weighted boundary. Silbergeld and Chicoine [17] were able to culture malignant glioma cells from histologically normal brain taken 4 cm from the contrast-enhancing edge of high-grade gliomas. Spectroscopy, perfusion, diffusion and positron emission tomography (PET) imaging can help define tumour presence not seen on conventional imaging [2, 3, 16, 18].

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Compounding factors for surgery include anatomical functional variability and, the distorting and infiltrating effects of tumours. The surgical procedure produces distortions. Coenen et al [19] demonstrated up to 12 mm of brain shift during surgery. Image guidance, with pre-operative conventional MRI, can be helped by tractography, functional MRI and intraoperative real-time ultrasound or MRI.

Conventional MRI has superseded CT as the investigation of choice for operative planning and for aiding intra-operative resection. Multimodal MRI [diffusion, perfusion, spectroscopy and functional MRI (fMRI)] and PET imaging provide significant advantages over conventional MRI. Pre-operative imaging assessments allow informed decisions on operative planning and the role of surgical resection. Each technique has specific advantages over standard imaging.

Multivoxel spectroscopy

Spectroscopy can be used to aid biopsy target identification and to help define tumour boundaries. Croteau et al [3] looked at 31 patients and correlated MRS Choline with biopsy samples and showed ratios comparing choline on the tumour side with choline or creatine levels on the contralateral normal side correlated with the degree of tumour infiltration in both high- and low-grade gliomas. McKnight et al [2] used three-dimensional spectroscopy on 68 patients and found a Cho/*N*-acetylaspartate ratio >2.5 correlated with tumour on co-registered biopsy samples with a sensitivity of 0.9 and a specificity of 0.86. McKnight et al [2] suggested that tumour was present in 30–50% of the T_2 signal abnormality outside the contrast-enhanced area. A normal spectroscopic pattern could be seen if only small islands of tumour were present within normal brain tissue. Croteau et al [3] felt that MRS was more accurate than conventional MRI in defining tumour boundaries. Limiting factors of spectroscopy-aided surgery include the relatively large voxel size ($1 \times 1 \times 1$ cm), the associated difficulties with co-registration and intra-operative shift.

Perfusion

Perfusion imaging has been used to identify biopsy targets and provide indices of histologically aggressive activity. Maia et al [20] examined 21 patients and used relative cerebral blood volume (rCBV) maps to target sample collection. Maia et al [20] found that high rCBV correlated with histological findings of oligodendroglioma or anaplastic astrocytoma, with oligoastrocytomas having intermediate values. When compared with the contralateral side, a rCBV ratio $\geq$1.2 was 80% sensitive and 100% specific for these tumours [20]. Maia et al [20] concluded rCBV improves selection of targets by reducing sampling error. Sadeghi et al [21] looked at 14 patients with MRI, PET and co-registered biopsy and found that both MR-derived CBV and methionine PET gave similar information and correlated with endothelial proliferation and mitotic activity ($p<$ 0.01), suggesting they both provide indices of focal malignant activity. The limiting factors with perfusion imaging are similar to those encountered with spectroscopy, and include the relatively large voxel size, intra-operative shift and a greater problem with image co-registration.

Diffusion

Significant surgical interest currently centres on tractography, but diffusion imaging has also been used to outline tumour boundaries. Price et al [16] examined 20 patients with World Health Organization (WHO) grade II, III and IV gliomas with diffusion tensor imaging (DTI) correlated to biopsy specimens. Tumour was indentified in all grades outside the T_2 weighted signal change and was predictable with diffusion imaging [16]. A study of 11 paediatric patients with DTI suggested low-grade gliomas in children did not infiltrate, but this small case series did not have tumour histology for 7 of the 11 cases, limiting the validity of this statement [22].

DTI or tractography can help to outline the functional anatomy of subcortical white matter. Current interest rests with the corticospinal tract, but the technique has also been used for language and visual tracts. This is being used for intra-operative guidance in tumour cases and dominant temporal lobectomy [23–25]. Tractography is non-invasive and, unlike other non-invasive functional techniques, provides information on subcortical white matter pathways [26].

DTI tractography images are usually acquired as echo planar images [23, 27]. These are distorted at the skull base and near air-filled spaces [23]. Stimulated echo acquisition mode (tSTEAM) gives less distortion but provides only half the signal intensity, so requires four times as many averages, increasing signal time significantly [27]. Using tSTEAM or other sequences may help in using tractography for brain stem tumours or functional stereotactic methods [27].

A number of clinical studies have attempted to examine accuracy. Berman et al [26] compared tractography with intra-operative stimulation mapping and magnetic source imaging in 9 patients and found up to 15 mm between stimulation and DTI fibre tracts. They explained this as a consequence of using a 5-mm-wide stimulating bipolar within the resection margin, with its range being 5–10 mm [26]. Bello et al [24] looked at 64 patients with fibre tracking for motor and language pathways and correlated these with intra-operative subcortical mapping. Bello et al [24] charted the corticospinal tract, superior longitudinal fasciculus, inferior fronto-occipital fasciculus and uncinate fasciculus and found a high correlation with intra-operative electrophysiology. Interestingly, all patients had a worse deficit initially but, by 1 month, 88% were normal [24]. Nimsky et al [23] examined 19 patients who had pre-operative fMRI with fibre tracking and intra-operative DTI, and electrophysiology looking at phase reversal to indentify the central sulcus. In only 6 of the 19 was a gross total resection possible, but these were tumours adjacent to the primary motor cortex where a very low gross total resection rate would be expected [23]. They found up to 8 mm of brain shift intra-operatively [23]. A number of investigators suggest, even without brain shift, a safety margin of 5 mm when approaching the pyramidal tract appears appropriate [23, 27].

There are problems with fibre tracking. Fibre tracking is a user-defined process and is dependent on the size and location of the seed and the experience of the individual processing the data [22, 27]. Multiple algorithms are used as there is currently no accepted gold standard [22]. Intra-operative updating of fibre tracking is currently time-consuming [19, 23]. Crossing fibres, multiple principle directions and oedema can affect the eigenvector and the tract produced [22, 26]. Nilsson et al [22] used fibre tracking in two cases, and suggested that, with their methods, fibre tracking identified the bundle site but not its size. Finally, clinical series that demonstrate a conversion of tumour cases from subtotal into gross total excisions are needed [23]. Despite these problems, diffusion imaging provides an exciting avenue for further investigation.

fMRI

fMRI offers pre- and intra-operative prediction of functional cortical areas. Shinoura et al [28] looked at 17 patients, and compared fMRI for identification of the primary motor cortex with intra-operative somatosensory-evoked potentials (SSEPs) and cortical mapping. fMRI was successful in more patients than SSEPs, mainly because, in patients with a hemiparesis, the opposite side could be easily identified and correlated with the affected side [28]. There was a high concordance between the fMRI localised area and that identified intra-operatively [28]. Fandino et al [29] showed in their series of 11 patients, they were able to demonstrate cortical reorganisation of the primary motor cortex on fMRI that agreed with cortical stimulation.

Roux et al [30] examined language and had only three of eight patients with complete agreement between fMRI and intra-operative cortical stimulation, leading them to suggest the technique was not good enough for pre-surgical or intra-operative usage. More recently, Bizzi et al [31] compared 34 patients using fMRI for motor and language with intra-operative electrophysiology. Overall sensitivity was 83%, and specificity was 82% [31]. Interestingly, they found a difference with tumour

grade, with a sensitivity and specificity of 65% and 93%, respectively, for WHO grade IV gliomas, and 93% and 79%, respectively, for grade II gliomas [31].

There remain limitations with intra-operative use. fMRI shows areas of activation, but these areas may not need to be preserved to avoid a neurological deficit [32]. Two separate case studies suggest that the blood oxygen level dependant (BOLD) signal can be lost adjacent to gliomas [33, 34]. At least 5 mm of error should be allowed for, before considering intra-operative brain shift [32]. Finally, it is not always possible to get an fMRI response in all patients owing to patient co-operation and neurological deficit [35]. fMRI appears to be useful in motor mapping, and its use for language mapping is developing [30–32].

PET/SPECT

Operative uses for PET include biopsy targeting and functional cortex identification. Roessler et al [36] looked at 27 patients with PET-targeted biopsies and found anaplastic foci could be recognised to aid biopsy targeting. Sadeghi et al [21] demonstrated in 14 patients that methionine (MET) PET provides an index of focal malignant activity. Other studies have also supported MET PET as being superior to conventional MRI in identifying biopsy targets and differentiating radionecrosis [37–39]. Meyer et al [40] used 12 $^{15}O_2$-labelled water PET scans to identify Broca's and Wernicke's areas for language localisation in 7 patients [40]. Broca's area was identified in five patients, and Wernicke's in six, although there was no intra-operative electrophysiological confirmation [40]. Case reports show inaccuracies in the predictive nature for histological diagnosis [41]. Other disadvantages of PET include the need for radioisotopes and the relatively poor resolution.

Conclusion

There are many exciting developments within multimodal MRI and PET imaging that can be of practical use to the neurosurgeon. Increased information to aid biopsy targeting, and the definition of cortical functional areas and white matter tracts can help make surgery more accurate, more aggressive and less risky and, hopefully, improve patient outcome.

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