ABSTRACT

Modern brain tumor surgery stands in the pillar of maximum safe resection. Tumor borders are always challenging, especially infiltration zones in malignant brain tumors. Novel technologies are designed for a better delineation and to increase the extent of resection (EOR) in brain tumor surgery, such as: cortical and sub-cortical mapping strategies with somatosensory-evoked potentials, awake stimulation mapping and cortical/sub-cortical stimulation for motor pathways, important for resection in eloquent areas; intra-operative imaging as functional and intra-operative magnetic resonance imaging, diffusion tensor imaging and intra-operative ultrasound are important for the tumor borders and to achieve the gross total resection; neurochemical navigation methods as 5-aminolevulinic and sodium fluorescein are important for the non-contrast-enhanced tumor border; future methods can be achieved with augmented reality surgery, new intra-operative chemical markers, and visualization methods. Nevertheless all these techniques seem to be promising, the real challenge in the future will be held in how to apply them and how they really affect the prognosis of the patients. Also, new concepts in tumor genetics will provide knowledge for the tumor behavior and will guide resection. Despite all limitations, the increasing importance of safe EOR shows the possible benefits of the novel technologies and surgical advances in brain tumor surgery, taking it to a new step of the neuronavigation era.

Key words: Brain tumor; fluorescein; intra-operative; neuronavigation; novel; technology

INTRODUCTION

Neurosurgery went through several changes over the past 50 years; technology has been applied to all fields, since the introduction of microscope and the microsurgical technique by Yasargil, until endoscopes, minimally invasive spine surgery and functional neurosurgery with deep brain stimulation implants. As we see, the neurosurgery has two important arms in this modern era: the equipment and the surgical expertise.

New imaging technologies are applied to other two different manners, pre-surgical moment and intra-operative imaging.[1]

Modern neurosurgery lives a paradigm of concepts. Although there are insufficient proves of the real benefits and impacts of the aggressive image-guided neurosurgery,[2] evidences show the importance of gross total resection (GTR) in the quality of treatment and the effectiveness

Access this article online

Quick Response Code:  
Website: www.jcmtjournal.com
DOI: 10.4103/2394-4722.172249

How to cite this article: Belsuzarri TAB, Sangenis RMA, Araujo JFM. Brain tumor surgery: supplemental intra-operative imaging techniques and future challenges. J Cancer Metastasis Treat 2016;2:70-9.

Received: 29-09-2015; Accepted: 30-11-2015.
increase of adjuvant therapy.[3-5]

Neuroimaging has been playing an important role in neurosurgery in the last century and technology has come to provide details in neuroanatomy, neurological function, metabolic and metabolism, which augments the ability to increase the extent of resection (EOR) while simultaneously, minimizes the risk of damage in eloquent brain.[1]

Increasing evidences show the importance of GTR for glioblastoma multiforme (GBM’s) and adjuvant radiochemotherapy and demonstrate a 2-8 months survival benefit in patients with GTR compared to sub-total resection.[3-5] Nevertheless, after a first impact, the focus has changed from just increasing the EOR, to increase the quality of life and safe resection; the tumor relationship critical anatomic structures and eloquent areas have become the center of the discussion.

Nowadays, molecular genetics came to open further discussions about tumor behavior, such as isocitrate dehydrogenase mutations (IDH) 1/2, 1p19q codeletion, PTEN deletions, MGMT mutation, telomerase reverse transcriptase (TERTp) mutation, EGFR and TP53.[6-8] The IDH 1 and 2, were first described in GBM’s, nevertheless further research showed that it was more expressive in grade II-III diffuse gliomas (about 70%). IDH 1/2 mutations are important biomarkers for diffuse gliomas, because they behave less aggressively and a better prognosis, than other IDH mutations (IDH wild-types), with a positive predictive value (PPV) for better progression-free survival and overall survival.[8] The 1p/19q codeletion is found in almost 70% of histologically oligodendrogliomas, thus have an indolent progression and might be the molecular defi nition of oligodendroglial lineage. Also, these low-grade gliomas (LGG) tend to respond well for chemotherapy, thus have better prognosis. The MGMT is an enzyme, which repairs the DNA and interferes in temozolamide effect. Mutations in the MGMT have been correlated with improved progression and improved survival rate.[6-7] On the other hand the ATRX/TP53 mutations might be the objective genetical markers of the astrocytic lineage.[6,7]

In GBM’s the most common aberrations are found in the chromosomes 7 and 10, where the PTEN and EGFR are located. Aberrations on the PTEN and EGFR amplifications are found in 80% and 30-40%, respectively, both of them strongly related to poor prognosis and aggressive progression, which reinforces the idea that these tumors with PTEN and/or EGFR amplifications are IDH-wild type tumors.[6,7] Finally, studies points for the association of promoter region of the TERTp mutation and poor prognosis.[8] A recent research was published comparing the TERTp mutation, 1p19q codeletion and IDH mutation in Grade II-III and GBM’s with interesting findings.[8] TERTp mutation only, was found in 347 patients with GBM’s, compared to the TERT and IDH group with 11 patients, IDH mutation only group with 32 patients and triple negative group with 80 patients. This data shows that almost 75% of the patients with GBM have only TERT mutation and have a correlation with aggressive behavior type of gliomas. Also, patients with Grade II-III with TERT mutation only (59 patients), had an aggressive course and were associated with poor survival, which suggest the need of early adjuvant therapies and special follow-up. Also only IDH mutation, was associated with lowest age of diagnosis (37 years) and the highest rates were found in the only TERT mutation group (59 years), between all the gliomas. This study opens for further research between the association of TERTp and other previously discussed mutations.[8]

The genetic studies and imaging findings have become allies in the understanding of tumor behavior; nevertheless have also pointed questions on the efficiency of the surgical techniques to improve patient prognosis and the natural history of these tumors.

METHODS

A literature search of the Ovid Medline and PubMed databases for the period January 1980 to September 2015 was conducted using the following key words: brain tumor, borders, technology, neuronavigation, intra-operative, fluorescein, novel. Main novel technologies were selected by their relevance and were analyzed by categories.

RESULTS

Neurosurgery has rapidly changed in the past years due to new technologies and new different possible surgical approaches. These changes have modified neurosurgical concepts, from an aggressive vision to a safe EOR with good function. Since the beginning of the microsurgical era, the surgical planning has improved from an anatomy-planned surgery to an optimal non-visible tumor borders resection.[1,2]

Several technologies were introduced in the intra-operative field such as functional monitoring with cortical and sub-cortical mapping, imaging technologies as neuronavigation, intra-operative magnetic resonance imaging (iMRI), intraoperative ultrassound (iUS), chemical biomarkers as 5-aminolevulinic acid (5-ALA), and sodium fluorescence.[2]

Some of these advances were possible not only for the technology, but also due to anesthetic advances and better neurofunctional knowledge.[9,10]

Nevertheless, even with the standard care in neurosurgery, the 2-year survival rate in GBM’s still is about 38.4% and the 5-year rate is below 5%.[11-13] Also, past reports have shown that even with hemispherectomies, patients could not be cured.[14,15] Even though, the surgical technology has improved the past years, there are no consistent evidences
of improving survival rate.[2]

In this point we have two arms, the technologies to improve resection and to increase the knowledge of tumor nature. By now it is clear that just improving resection won’t provide the best result, but better understanding of the different diseases and tumor natures, will provide direction for optimal resections and better outcomes.

**Awake craniotomy**

Anesthetic advances permitted safer awake craniotomies to obtain brain mapping and better neurosurgical borders. However, it has a series of challenges to be analyzed before such as integration of different types of knowledge, imaging, multidisciplinary team, cooperation from several clinics sectors, application of protocols, application of specific technical adjustments, and a multidisciplinary approach. The integration of the pre-operative functional MRI (fMRI) and neuropsychological tests are the key for a good planning and patient selection. Not all tumor patients should undergo awake craniotomy, but patients with lesions close relationship with eloquent areas, in special for motor and speech.[16,17] Talacchi et al. stated that intra-operative complication can vary from anesthetic (inadequate or excessive sedation, pain, nausea, vomiting); respiratory (oxygen saturation < 90%, increased CO₂, hypoventilation < 8 breaths/min, airway obstruction); hemodynamic (hyper- or hypotension, tachy- or bradycardia); and neurological (convulsions, brain swelling, new neurological deficit). From these complications, hyper- and hypotension are the most frequent in awake surgery (11% and 56%, respectively).[16,17]

The main purpose of awake surgery is the monitoring of speech and motor pathways. This way, the physical pre-operative imaging/clinical examinations and intra-operative positive tests are important. Patients with aphasias and language disturbance seen at the physical examination, have higher risk of post-operative neurological deterioration. Intra-operative positive tests for stimulation in motor areas have also higher risk of motor deterioration, probably due to the proximity of the tumor lesion to the cortical tracts.[16]

Shinoura et al. studied motor worsening after 102 motor areas glioma surgery; they have encountered motor worsening immediately after surgery and after 1 month were related to awake surgery failure and intra-operative complications. The main causes of failure of awake surgery are severe somnolence, epilepsy, air embolism, no wake up and motor neglect.[18]

In order to analyze the hemisphere dominance, the Edinburgh, Wada or fMRI (with verb generation tasks) can be done. Also, multiple tests are applied to the language task with visual object naming tests such as the Boston naming test, Snodgrass and Vanderwart Test, DO80, and Aachner Aphasia Test. They are done to map the dominant hemisphere and localization of speech areas. The pre-motor areas of the face are always tested to identify possible motor causes of the aphasia. Even with all protocols, intra-operative positive sites errors can range from 4.6% to 22%.[16] The counting test is used to document a speech arrest during electrocortical stimulation and also auditory naming, verb generation and reading are commonly used tests. Additional tests can be applied such as calculation, visuospatial functions, working memory, visual pathways, eye movements, and writing.[16,17]

One important point is that function can be found at the edge of high-grade gliomas and also within the tumor in low-grades, so it has to be analyzed for a safe EOR.[19,20]

Awake surgery has been used for some time, but new tests and anesthetic evolution have permitted a better understanding of functional areas and also the mapping of complex brain areas.

**Cortical and sub-cortical mapping**

During the past years, the increase importance of the EOR and the relationship with increased overall survival has made the neurosurgeons push to the limits of the glioma surgeries, even in eloquent areas. Nevertheless, without intra-operative monitoring, morbidity increasing became fact. The objective of increasing overall survival with good functional status made the neuronavigation era a reality.[1,21]

As imaging has increased its accuracy over the past years, neuroanatomy studies have shown a better knowledge of the sub-cortical tracts and the new mapping technologies have shown the real cortical and functional mapping, which most of the times can be changed by the lesion.[9,22]

Intra-operative monitoring has been studied by several different methods, using somatosensory-evoked potentials (SSEP), awake stimulation, and cortical/sub-cortical direct motor stimulation. SSEP uses sub-dural electrodes to evoke potentials of gyri and to localize the central core (pre-central and post-central gyr) [Figure 1]. Awake stimulation is a...
good approach for the language function and its multiple association areas, which could be more complex and even specific for different languages/cultures. Language function is the most complex and superior level function, with multiple localizations and spread connective areas. The exact language-related cortical area is not mathematical and is individual related, especially in patients with intracranial lesions. Patients with intracranial tumors can have very atypical language areas related to their brain mapping conformation and compliance to the tumor.\[22\] The key for brain surgery of the dominant hemisphere is the central core and language function, which has become possible.\[22,23\]

Brain mapping usually needs large craniotomies and longer time of surgical/anesthetic exposure, but provides multiple functional areas.\[21,24\] Li et al. analyzed 91 cases of brain functional area glioma surgery under direct electrical stimulation (DES) and noticed that the most commonly observed areas of counting interruption were distributed on the posterior part of the left anterior central gyrus (47.7%), the operculum of the left inferior frontal gyrus (24.4%), the triangular part of the left inferior frontal gyrus (12.8%), and even the posterior part of the superior frontal gyri (4.7%). After surgery, 46% had no post-operative dysfunction, 42.9% a brief language dysfunction, 29.7% limb movement disorder, and 1 case had a permanent disability; this shows that DES is a non-invasive accurate method.\[22\] Another positive point of DES is the mapping of the sub-cortical areas because it does not have influences on brain shift or other positioning errors.\[22\]

Even though fMRI is satisfying for motor/sensitivity areas, its sensitivity is only of 59-100% and specificity of 0-97% for language areas.\[22\]

De Witt Hamer et al. reviewed and made a meta-analysis of surgical situations of 8,091 glioma cases and found that the rate of long-term severe neurological dysfunction sub-sequent to DES was 3.4%, while the long-term severe disability rate of patients that underwent surgery without DES was 8.2%. In addition, for the patients undergoing DES, the overall resection rate and the rate of involvement of the language functional area in the resection were significantly increased.\[23\]

Event thought DES is a relative novel technology, is also an important research method for higher cognitive functions, such as music, calculation, memory, complex speech processes, hemispheric ignorance, perception, visual pathways and more.\[25-29\]

**Neuronavigation and intra-operative magnetic resonance imaging**

Magnetic resonance has changed the course of anatomical marks in neurosurgery; since its beginning in the early 80’s, the pursuit of high field technologies for better images has become a challenge.\[9\]

In the neuronavigation era, planning surgery has become not only a decision on craniotomies and different approaches, but also a way to prevent and predict the final surgery with minimal injuries. This way, fMRI, positron emission tomography (PET), and diffusion tensor imaging (DTI) are important technologies.\[1\]

PET utilizes H$_2$\textsuperscript{15}O as a blood tracer to measure flow or ($^{18}$F)-fluorodeoxglucose uptake to measure cerebral metabolism.\[10\]

fMRI measures blood oxygen level dependency changes due to alterations in the ratio of the oxyhaemoglobin and deoxyhaemoglobin in the most metabolically active regions\[30\] [Figure 2].

Another image technology is the DTI, which visualizes the fiber tracts with the thermally driven motion, or diffusion of water and molecules through fibers.\[31,32\]

DTI and fMRI allow neurosurgeons to have functional/eloquent areas and sub-cortical fibers related to the lesions in their pre-operative planning; therefore, functional

![Figure 2: Functional magnetic resonance imaging and glioma: Red spots of the functional areas for the speech test near/between the tumor](image-url)
neuronavigation has become part of the clinical decision-making, surgical approach, and EOR\textsuperscript{[33]} [Figure 3].

Nevertheless, the functional neuronavigation has not shown its clinical utility due to a lack of high evidence studies. Wu \textit{et al.} carried out the only randomized controlled trial with an established protocol in functional neuronavigation and demonstrated a reduced post-operative motor deterioration, a higher Karnofsky Performance Scale, and an increased overall survival in study patients.\textsuperscript{[33]}

![Figure 3: Tractography magnetic resonance imaging. In blue: the white fibers tracts. In red: tumor](image)

One of the worst problems in neuronavigation is the brain shift; it is the change of tissue/lesion during surgery due to cerebrospinal fluid drainage, tumor resection, and brain swelling; with estimated to be around 1 cm after opening the dura,\textsuperscript{[42]} and more than 1 cm after initial resection of tumor. Therefore, the iMRI technology has come to solve this problem and also increase the EOR. The first iMRI was performed in 1994; it presented several benefits and showed that a considerable part of patients had resectable residual tumor.

In special for LGG treatment, iMRI has led to favorable results in several studies. Reports show 30-60% of return to surgery after initial resection with iMRI\textsuperscript{[35-38]}

Even though iMRI is an interesting method, nowadays there is only one randomized controlled trial comparing iMRI to conventional surgery; the trial found that iMRI was associated with higher rate of complete resection (96\% vs. 68\%) and increased progression-free survival without additional morbidity.\textsuperscript{[5,39]} Kubben \textit{et al.} held a systematic review and showed just an evidence level II of iMRI being more effective than conventional neuronavigation in increasing EOR, quality of life or prolonging survival after GBM resection.\textsuperscript{[38,39]}

In practical analysis, iMRI has some issues for global implementation regarding costs and time. This method requires special implementation; most of the times not only the equipment, but also revision of the local of implementation, making it a high cost technology.\textsuperscript{[40,41]}

In addition, the time for image acquiring and the need of stop the surgery for it, prolong time of surgery and anesthesia.\textsuperscript{[42-44]}

Roder \textit{et al.} studied retrospectively 117 patients after conventional surgery, after 5-ALA, and after iMRI they found that mean residual tumor volume after iMRI-assisted surgery (0.5 [0.0-4.7] cm$^3$) was significantly smaller compared to the residual tumor volume after 5-ALA-guided surgery (1.9 [0.0-13.2] cm$^3$; $P = 0.022$), which was significantly smaller than in conventional surgery (4.7 [0.0-30.6] cm$^3$; $P = 0.007$). Total resections were significantly more common in iMRI (74\%) than in 5-ALA-assisted (46\%, $P = 0.05$) or conventional surgery (13\%, $P = 0.03$). Also, the iMRI time of surgery was significantly higher compared to pre-iMRI period (213 vs. 354 min). Improvement of the EOR using iMRI was safely achievable and post-operative morbidities were comparable between cohorts. Total resections increased 6 months progression free survival from 32\% to 45\%. In follow-up analysis, the neuronavigation had new or worsened neurological deficits at 3 months in 18.2\% of patients, compared to 45.5\% of the control group. Non-neurological complications were present in both groups, 31.8\% in the control group and 30.4\% in the neuronavigation group. Also, the progression-free survival and survival rate was better in the neuronavigation/iMRI groups vs. control groups.\textsuperscript{[5]}

Despite it is a retrospective study with a short period of time and limited patients in different chronologic times, the great outcomes and promising results should open for new prospective studies.\textsuperscript{[45]} Further, the quality of iMRI images remains an issue; pre-operative MRI images are usually acquired by high-fields MRI with DTI and fMRI; thereby the surgery plan for critical and eloquent areas is difficult and questionable after tumor resection and brain shift. Also, studies related to contrast dosage/timing and the local of resection have been done. The main challenge is to differentiate tumor border from blood brain barrier brakes and surgical tissue changes, which also have contrast-enhanced borders.\textsuperscript{[43,44]} The Cochrane review point for different patients’ baselines with heterogeneous lesions and the current studies do not provide quality evidences of benefits. Also, there is no standard protocol for its use and most of the time it is used in single centers.\textsuperscript{[5]}

**Intra-operative ultrasound**

Intra-operative ultrasound is a dynamic method that can provide dynamic images with brain shift corrections and also the correlation between the tumor and normal brain, just as the tumor vascular nutrition and borders. In the past decades, the iUS increased the quality of images, from poor-quality images to three-dimensional (3D) imaging.
Intra-operative ultrasound is more effective with heterogeneous lesions, with cystic compartments, and lesions with different echogenicity from the cortex, important in deep lesions, more than 1 cm from the cortex. Several reports support the use of iUS with good results such as good visualization of tumor borders with 3D iUS in 88% of patients and had led to an EOR in 55%, numbers compared to the use of iMRI and 5-ALA. Therefore, the use of US contrast in brain tumor surgery, called intra-operative contrast-enhanced US (ICEUS), is to determine better tumor visualization and also vascularization, is in study. The contrast agents containing microbubbles hit by low-acoustic power US waves resonate with a specific value that can be read by a US algorithm for contrast. There is a good correlation between the pre-operative MRI and iUS and can reach a small difference of 2 mm with the advantage of being intra-operative and dynamic. Nevertheless, neither iUS nor ICEUS can provide good borders for all LGG because of the similar echogenicity between the tumor and normal tissue. Differently from the contrast-MRI, the ICEUS depends on intra-vascular micro bubbles resonance, which will not provide the interstitial aspects. Fluorescence-guided surgery such as the use of 5-ALA can highlight tumor borders, but only in high-grade gliomas. Compared with 5-ALA and iMRI, the iUS has the advantage of providing borders images not only for high grade gliomas, but also for other types of tumor such as metastasis, meningiomas and some LGG, and the relationship to normal/vascular tissue with the non-stop surgery advantage.

Fewer studies have shown the capability of the iUS and MRI; further studies are needed to evaluate the real aspect of the ICEUS and the use of combined methods with hybrid probe with MRI neuronavigation and iUS.

**Fluorescence guidance**

Even though intra-operative image guidance has evolved in the past decades, the interface between tumor borders, remaining tumor cells, and normal tissue is challenging.

Despite several substances have been studied, there are two major promising fluorescences: 5-ALA and sodium fluorescein.

The administration of 5-ALA leads to differential accumulation of protoporphyrin in the malignant tissues, via heme-biosynthesis pathway.

The 5-ALA administration has proved to increase the GTR of glioblastomas (65% vs. 36%; P < 0.0001), smaller volume of the residual tumor (medians 0 cm³ vs. 0.7 cm³; P < 0.0001), and better progression-free survival in 6 months after intervention (41% vs. 21%; P = 0.0003) [Figure 5].

Recent studies with fluorescence guidance combined with neuronavigation and brain mapping shows rates up to 98% of GTR in selected cases. In addition, the fluorescence guidance may reach beyond contrast-enhanced tumor borders and infiltrative zones that might be shown in the fluid attenuation inversion recovery (FLAIR) sequences of MRI. Although 5-ALA might be promising, it has some issues to be considered. First, we have to consider its high sensitivity and a low-specificity, in special the non-high intensity pigmentations areas of fluorescein such as in tumor border and the hyperpigmentation in non-tumoral areas (necrosis, fibrosis, astrocytes infiltration) and also other non-glial lesios as lymphoma and metastasis. Furthermore, the absence of tissue fluorescence is common in LGG due to its relatively unruptured blood-brain-barrier and other intrinsic mechanisms of fast elimination of the drug; this makes it useless for LGG surgery. Moreover, the studies with...
fluorescence guidance have not studied the tumor genes and the good results could be genetically related. Further studies are needed to direct correlate the genetically aggressive tumors and the use of 5-ALA.

Another substance used for guidance is the sodium fluorescence, which accumulates in high neovascularization areas, also seen in high-grade lesions. Recent studies point to an increase of EOR and GTR, but without increasing of the overall survival rate.[64] After review, 5-ALA had 91% sensitivity, 59% specificity, 85% PPV, and 71% negative predictive value for histopathological identification of malignant glioma.[65] Future objectives in fluorescence guidance may lead to better microscopic visualization methods for the fluorescein such as filters, special masks or lens.[66]

**Current evidences**

The Cochrane group has reviewed all the reports of image-guided surgery for brain tumor resection and found some issues. Most of the studies are not controlled and randomized; also patients’ baselines and tumor aspects were heterogeneous in most of the groups and the resecability of them was different between intervention and control groups.[2] Despite limitations and low quality of evidence, the analyses from the classical reports from Senft 2011, Stummer 2006 and Wu 2007 showed a trend for better results.[2] Complete tumor resection was achieved with iMRI in 23/24 (96%) of participants in the intervention arm group compared with 17/25 (68%) of participants in the control arm (relative risk [RR] for incomplete resection 0.13, 95% confidence interval [CI]: 0.02-0.96, low quality evidence).[2]

Using 5-ALA, complete resection was performed in 90/139 (65%) of the intervention arm vs. 47/131 (36%) of the control arm (RR for incomplete resection 0.55, 95% CI: 0.42-0.71, low quality evidence). Finally, neuronavigation with DTI was achieved among the 85 participants with high-grade glioma and complete tumour resections were achieved in 32/42 in the DTI arm vs. 14/43 in the control arm (RR for incomplete resection 0.35, 95% CI: 0.20-0.63, very low quality evidence). Among 129 participants with LGG, complete tumor resections were achieved in 40/61 in the DTI arm vs. 42/68 in the control arm (no significant difference).[2] In survival analysis, the 5-ALA groups had a median survival of 15.2 months (95% CI: 12.9-17.5) in intervention group and control with 13.5 months (95% CI: 12.0-14.7). The neuronavigation-DTI arm was 21.2 months (95% CI: 14.1-28.3) vs. 14.0 months (95% CI: 10.2-17.8). Only in World Health Organization grade IV tumors analysis, neuronavigation-DTI arm was 19.3 months (95% CI: 15.2-23.5) vs. 11.1 months (95% CI: 7.3-15.2) in the control arm.[2] In time to progression, the median time in iMRI group was 226 days (95% CI: 0.0-454) vs. 154 days (95% CI: 60-248) in control. With 5-ALA, it was 5.1 months (95% CI: 3.4-6.0) vs. 3.6 months (3.2-4.4 months) in control.[2] It is clear that the group analysis was not homogeneous and it might be due to a lack of protocols and a standardized approach to all lesions. Furthermore, there is need for standardization of reports for a systematic-review analysis and for future trends. Even though, the theoretical benefits of the novel techniques should impulse more randomized, controlled trials with better baselines.

**Future technologies**

Neuronavigation has become more popular and the localization of tumors has come to practice with the navigation instrument and the monitor. Even though, what if we had the images seen in the surgical field continuously, without navigators? The augmented reality has come to time with the objective of sending information to surgical field without monitors.

Augmented reality technique has four steps: virtual image creation; real environment; projection and registration. Thus, image can be seen in the surgical field and the virtual interface can be used. The augmented reality is important in planning surgery and having the lesion visible in the skin since the beginning of the surgery. The augmented reality can be applied not only to the surgical field to prepare a better surgical incision and approach, but also to the surgical view in the microscope, which is important when the surgeon cannot take his or her eyes/instruments from the microscopic field.[67,68]

Moreover, the augmented reality could also include other parameters such as fiber tracts or important structures that should not be approached. As an innovation in neurosurgical surgery, there are few studies but promising applications.[67]

Also other interesting concept is the regional vs. global DTI biomarkers for glioblastoma. Most of this lesions are heterogeneous with multiple histological features and can lead to different degrees of malignancy, thus biopsies can be different in multiple areas. DTI is routinely used to locate high-grade areas, but the development of a sensitive and specific biomarker, remains an issue. Also, the role of DTI-derived tensor metrics in normal brain and infiltrated brain is important for the distinction of tumor infiltration in non-contrast-enhanced areas. As the GBM been considered as a whole brain disease, DTI analysis of the whole brain might be more interesting than studying just the lesion areas. Roldán-Valadéz et al. showed that relative anisotropy, axial diffusivity (AD), CI (linear tensor), Cs (spherical tensor), were important for regional DTI tumor analysis.[69] Also, Cortez-Conradis pointed for AD, CI, Cs and introduced the whole brain concept. The advantages of whole brain DTI analysis are: Decrease of bias associated with the analysis of just one region of interest; the tumor and edema regions are included; lesions not perceived by the radiologist’s eye on conventional sequences would be included in a global assessment; it may avoid problems associated with partial volume effects, and inaccurate image coregistrations.[70]
Furthermore, these biomarkers could also been applied for other tumors and even other neurological diseases, without any contrast addition and increase of costs.\textsuperscript{[73,74]}

For high-grade lesions with increased neo-vascularization, there was a report with use of indocyanine green (ICG) for detection of tumor borders. It is classically used by ophthalmologists for retinal vasculature and more recently for vascular neurosurgeries for aneurysms and arteriovenous malformations; however, for surgical borders for high-grade gliomas, it is a novel technique.\textsuperscript{[71]} Eyüpoglu \textit{et al.} reported the ability of demonstrating the hypervascular areas with ICG that were not visible with the 5-ALA use. This technique was called dual intra-operative visualization approach (DIVA) with the initial approach using 5-ALA; after all initial tumor was resected, ICG was administered for visualization of remaining hypervascularization areas, with good initial results. Further studies are needed, but DIVA technique could be an interesting approach for further resection of non-fluorescence areas.\textsuperscript{[72]}

One of the most difficult tasks in glioma surgery is the low-grade lesion. Most of the low-grades have similar density, echogenicity, and macroscopic aspect. Despite the neuronavigation progression, there are few MRI methods for low-grade tumor visualization, and most of the times the lesion is not contrast-enhanced and there is just the FLAIR sequence for tumor borders.\textsuperscript{[73]} Ramakrishna \textit{et al.} showed improvement of overall survival with aggressive resection of FLAIR tumor limits, not only in the first attempt, but also in reoperation, regardless of patient age, pathology, chemotherapy, and radiation.\textsuperscript{[74]}

The 5-ALA for LGGs is usually reported as non-visible, but it is not true for all of them. Valdés showed that 5/12 patients had at least 1 instance of visible fluorescence during surgery and 45% of the non-visible fluorescence had a higher and detectable concentration of PpIX in the tumor tissue after the 5-ALA administration. With this idea, other researches were made to accurate the visibility of the fluorescein, or guide the elevated concentration in tissue with special probes of light visualization or high-resolution microscopic techniques, but with few results by this date.\textsuperscript{[75]}

**CONCLUSION**

Evidences of the correlation between tumor removal and increase of survival rate have an impulse in novel technologies for safe resection and EOR. The uses of iMRI, DTI, PET, IUS, and fluorescence guidance have come to establish the neuronavigation era in neurosurgery.

Also, there is an increasing importance of the tumor genetics and behavior, which will provide crucial information and will guide tumor resection and adjuvant treatment. Despite all limitations of each technology and the lack of clear evidences, it is clear that this neurosurgeon/technology interface has come tighter and promising. However, the best result will come with the integration between technology for resection and tumor nature knowledge.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**


