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Topic: Brain tumor cell invasion and metastasis: anatomical, biological and clinical considerations

Brain tumor surgery: supplemental intra-operative imaging techniques and future challenges

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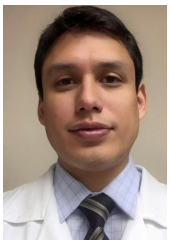

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ABSTRACT

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.

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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

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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 theorical 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), Cl (linear tensor), Cs (spherical tensor), were important for regional DTI tumor analysis.[69] Also, Cortez-Conradis pointed for AD, Cl, 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.[69,70]

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 arterio-venous malformations; however, for surgical borders for high-grade gliomas, it is a novel technique.[71] Eyüpoglu *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-fluorescein areas.[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.[73] Ramakrishna *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.[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.[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.

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Conflicts of interest
There are no conflicts of interest.

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