

Brain Disorders 2020: Brain tumor resection guided by fluorescence

Gonzalez Escalante P E

Universidad Autónoma del Estado de Hidalgo, Mexico

Abstract:

We present the methods that are being used in the scope of an on-going clinical trial designed to assess the usefulness of ALA-PpIX fluorescence imaging when used in conjunction with pre-operative MRI. The overall objective is to develop imaging-based neuronavigation approaches to aid in maximizing the completeness of brain tumor resection, thereby improving patient survival rate. In this paper we present the imaging methods that are used, emphasizing technical aspects relating to the fluorescence optical microscope, including initial validation approaches based on phantom and small-animal experiments. The surgical workflow is then described in detail based on a high-grade glioma resection we performed.

Introduction:

Neurosurgical guidance has come a long way since its inception. In the past, a rigid frame was mechanically screwed into the patient's head and used to guide the surgeon to the region of interest. However, for tumor resection the physical frame was too obstructive for the surgical procedure, and as a result frameless image guided stereotaxy was quickly adopted into neurosurgery to alleviate this problem. However, this approach relies on pre-operative images (MR or CT) and thus, cannot account for any tissue shift occurring during surgery, i.e., brain shifts due to tissue resection, retraction, gravity effects, CSF loss, etc. These tissue shifts can result in up to 2 cm of registration error during surgery. Surgeons rely heavily upon registration accuracy since tumor tissue can look identical to healthy surrounding tissue during resection. Multiple imaging solutions have been suggested to adjust for brain shift, including intra-operative MRI, CT, or ultrasound. However, incorporating intra-operative imaging equipment can significantly interfere with the flow of the surgical procedure. Additionally, specific types of tumors, such as high-grade gliomas, have ill-defined tissue boundaries with tendrils extending from the main tissue volume. These tendrils are often not seen on the pre-operative (and/or intraoperative) MRI and can be difficult to locate during the surgical procedure.

Therefore, there is a need for new technologies providing specific intra-operative tissue information to the surgeon in a manner that is independent of shifts all the while increasing resolution and sensitivity to tissue features usually missed in surgical procedures guided by the current intra- and/or pre-operative imaging modalities. Every year, worldwide, as many as 5 to 10 people out of 100,000 are diagnosed with a malignant brain tumor, carrying a prognosis of less than one year³. The most common kind of primary malignant glioma is high-grade glioma accounting for approximately 40% of all intracranial

tumors. Since it is the recurrence of high-grade gliomas that ultimately affect survival rate, it is thought that complete removal of all tumor tissue can benefit patients. In fact, there is increasing evidence, in good part due to more quantitative approaches and more accurate imaging systems (e.g., MRI), that completeness of resection is correlated with increased patient survival time. However, a study found that more than 98% of tumor volume must be resected for patient survival to be significantly improved. This study also showed that when traditional surgical procedures are used only 47% (197 out of 416 patients) of cases were above the 98% resection threshold. A limiting factor in improving completeness of resection is the surgeon's ability to differentiate tumor from healthy tissue during brain surgery. The differentiation is usually based on visual inspection through a surgical microscope complemented by intra-operative consultation based on microscopic specimen pathology analysis using cryosection.

There are an increasing number of studies showing the potential of using fluorescence imaging to enhance diseased tissue for brain as well as for other types of surgeries. Depending on the specificity of the underlying biological processes, fluorescence imaging can increase the surgeon's ability to localize malignant tissues during surgery in a manner that does not rely on intra-operative MR or CT imaging. Recent reports have indicated that using Protoporphyrin IX (PpIX) fluorescence to delineate tumor tissue increases the completeness of tumor resection^{7,8,9} and, ultimately, patient survival⁷. In this case the biological mechanism behind fluorescence contrast enhancement relies on the use of the pro-drug 5-aminolevulinic acid (ALA). ALA is a chemical that is naturally found in most mammalian cells. In cells, the nonfluorescing ALA molecule is converted into the fluorescent molecule PpIX through the heme biosynthetic pathway. PpIX has increased absorption in the blue region of the electromagnetic spectrum (around 408 nm) with fluorescence reemission in the red/near-infrared (NIR) part of the spectrum. All nucleated cells have the ability to create PpIX since it is a precursor to heme, which is required in oxidative phosphorylation (ATP production in mitochondria). However, it has been shown that PpIX accumulates in malignant and premalignant tissues. Various properties of tumor cells are thought to cause the accumulation of PpIX including¹⁰ faster active transport system, faster bioprocess mechanisms, low concentrations of iron and low quantities of ferrochelatase, i.e., the enzyme that adds iron to PpIX in order to make heme.

Objective:

To demonstrate that the fluorescence-guided approach allows a better resection of high lesions degree allowing not to compromise functionality patients.

Methods:

Post-operated patients with fluorescein were selected to whom they were made magnetic resonance before and after surgery with volumetry, diagnoses were corroborated by pathology and the post-surgical functionality of the patient taking into account comorbidities.

Results:

It is demonstrated that the fluorescence guided approach is an important treatment method and beneficial for malignant brain tumors, improving the total resection rate and preserving the function according to the area in which the lesion was located.

Discussion:

Fluorescein is an easily available method for guided tumor resection but it is a contrast better than a tumor marker. Fluorescence can improve resection with minimal risk and margins they are clearly visualized.

Conclusion:

Fluorescein-guided resection is a safe method of tumor resection that allows keeping the functionality of the patient, is another tool in the armamentarium of the neurosurgeon to achieve maximum safe resections, which increases the progression-free time of disease in high-risk lesions grade.