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Intraoperative fluorescence-guidance in gross total resection of intra-axial brain tumors

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Abstract

To review the usage of fluorescein sodium in fluorescein guided surgery and the efficacy of this surgical technique on achieving gross total resection and its impaction of the patients suffering from intra-axial brain tumor as a safe and cheap way. Intra-axial brain tumors have some unique characteristics due to its nature and the fact that they develop from the brain parenchyma, in many cases they cause disruption in the blood brain barrier which lead to brain edema and facilitate the tumor uptake of enhancing fluorescent tracers. Fluorescence-guided surgery has been used over the years to achieve the goal of gross total resection of brain tumors due to the special properties of sodium fluorescein. Achieving total resection in these cases using cheap techniques are challenging due to lack of resources. Fluorescein guided surgery was done on 30 patients diagnosed with intra-axial brain tumors, all the patients underwent fluorescein sodium-guided surgical excision with different approaches according to the tumor's size and location and then evaluated for the extent of resection and the post operative unfortunate complications due to the gross resection. Total removal of the tumor was done in twenty-nine cases and in the remaining case subtotal resection was achieved with a small residual left. Postoperative hemorrhage was found in 2 cases which needed surgical evacuation. Postoperative hydrocephalus happened in also 2 cases and CSF diversion was done. Superficial wound infection in 1 case which received topical antibiotics and follow up with no need of surgical debridement. Death in 1 case. Using fluorescein sodium has a significant impact on the extent of resection of intra-axial brain tumors and simply made the surgery easier. This procedure is safe, simple, useful and available for gross total resection of intra-axial brain tumors.

Keywords: Intra axial brain tumors, fluorescein sodium, gross total resection, fluorescein guided surgery.

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1. Introduction

The human brain has a specific unique barrier that separates it from the blood which called the Blood Brain Barrier, it acts as a restrictive guard and demand control over substances that allowed to cross it.[1] Many tracers used to diagnose tumors can easily pass through the BBB if only the tumor caused disruption in that barrier [1]. Cytoreductive surgery aimed toward gross total resection plays an important role in prolonging the survival of patients, at least with patients with GBMs. [2]. 3.2 months longer in survival time of patients with more than 98% of excision and [3]. 4.9 months longer with total excision which is a longer survival time offered by Temozolamide.[4]. Fluorescein has been used in arteriovenous malformation surgeries [5]. vascular anastomosis [6], neck clipping in cerebral aneurysms [7] malignant gliomas and other brain tumors [5,8,9]. fluorescein sodium can be used for instant enhancement of the tumor. It has been widely used in eye surgeries [10] and it is free of any side effects and very cheap [11]. Shinoda et al [12] reported that using the white light of normal microscope with no special filters is effective under intravenous injection of high dose of fluorescein sodium (20 mg/kg) during GBM surgery. It has been reported that fluorescein can pass through the area of damaged BBB easily [13]. Many intraoperative events may affect the effectiveness of this approach as the possible contamination of the surgical field with blood containing fluorescent dye and also the accuracy of tumor detection because the intravenous markers may spread from edema producing mass with surrounding edema to non-tumor tissue [14,15]. In this study the fluorescein guided surgery was used without using any special microscope filters in all cases. The clinical, radiological and surgical results are analyzed.

2. Patients and methods

This study was done prospectively in the Neurosurgery department, Cairo University hospitals, was conducted on 30 patients diagnosed with intra axial brain tumors. Data

were collected over the period of time starting from Feb 2016 till Oct 2018. Cases had a follow up period of at least 18 months after discharge from hospital. All cases were assessed clinically and radiologically by magnetic resonance imaging (MRI) and computed tomography (CT) and clinically on admission to the hospital.

2.1 Operative technique

2.1.1 Surgical strategy and planning

Every individual case was treated as a separate entity according to the size and location of the tumor and the strategy of the operation was planned to attack the tumor putting in mind the main goal of achieving gross total resection.

2.1.2 Fluorescein sodium administration

Allergy test was performed before induction of anesthesia. Fluorescein sodium dosage was 15-20 mg/kg, it was given after the induction of anesthesia and before the incision of the dura mater. With administration of fluorescein sodium there was yellow coloring of the skin, mucous membranes, urine, and elsewhere, but it disappeared within 24 hours. There were no lasting side effects. Illustrative cases are presented in the following.

2.2 Surgical procedure

All the patients (n=30 patients) were assigned to fluorescence-guided surgery using fluorescein sodium (20-15 mg/kg bodyweight) before the dura mater incision, FS was administered into the central venous line as described by Shinoda et al. Following the administration of fluorescein, the whole tumor tissue was stained deep yellow with faint coloration of the adjacent brain tissue parenchyma and edematous brain but later on it fixes on location of broken blood-brain barrier by the infiltration of the tumor. The resection of the tumor was performed approximately 10-15 minutes after administration of FS. In most of the cases, the tumor tissue was removed en bloc after fine sharp dissection of the tumor boundaries from the normal brain tissue and blood vessels. But in some cases, it was removed piece by piece. In some cases, ultrasound aspiration was used. Resection of the tumor was based on identifying the fluorescein-stained tissue; which indicates the neoplastic tissue causing disruption in the blood-brain barrier. Resection was continued until the stained tissue was removed totally and normal brain parenchyma was seen.
A standard neurosurgical microscope with xenon white light illumination was used with no additional instruments or filters for the microscope.

2.3 Follow up and outcome

All patients were admitted to the ICU after the operation and since our goal in this study is to evaluate GTR and prognostic value of fluorescein usage during fluorescence-guided surgery, patients with postoperative MRI and survival follow-up were evaluated. Postoperative MRI was obtained within 24 hours, for the assessment of residual tumor volume. Gross total resection (GTR) or subtotal resection (STR) were performed in all patients. Gross total resection of the tumor was defined as no residual enhanced tumor on the postoperative Gadolinium-enhanced T1-weighted MRI.
Neurological examination was performed to all patients including GCS till the patients are discharged from the hospital. Follow-up of all patients after discharge in the outpatient clinic was performed to observe the neurological status, the wound and any other complications. According to the pathology identification of the tumor collected some patients with high-grade tumors were referred to the oncology department for radiation therapy and chemotherapy.

3. Results

Thirty cases with intra axial brain tumors were included in this study in the period from Feb 2016 to Oct 2018. There were 21 male patients (70%) and 9 female patients (30%). The age ranged from 3 to 65 years old. Location of the lesions in the brain were Frontal lobe lesions in 9 cases, Temporal lobe in 7 cases, Parietal lobe in 6 cases, Occipital lobe in 2 cases, Infratentorial neoplasm in 6 cases.

3.1 Tumor size at the greatest diameter (AGD)

More than 5 cm in 27 cases, less than 5 cm in only 3 cases. Extent of surgery achieved in the cases was gross total resection was achieved in 29 cases and sub-total resection in 1 case. Histological Findings: GBM in 19 cases, Low-grade glioma in 4 cases, Primary CNS lymphoma in 1 case, Metastasis in 4 cases, Others as Medulloblastoma in 2 cases. All patients diagnosed with high-grade gliomas and metastasis were sent to the Oncology department to receive adjuvant therapy.

3.2 Post-operative complications

Tumor residual in 1 case. Hemorrhage inside the tumor bed in 2 cases and needed surgical intervention. Hydrocephalus and needed surgical intervention of CSF diversion in 2 cases. Wound infection in 1 case, received medical treatment and follow up with no need of surgical debridement Death in 1 case.

4. Discussion

Different surgical techniques have been developed over the years to achieve total resection such as; intraoperative ultrasound, frameless stereotaxis and intraoperative MRI, they can help in the surgical planning to locate the borders of the tumors which are hard to differentiate from the adjacent normal brain tissue. Fluorescence-guided surgery is a procedure that can be easily performed and doesn't need additional time and instruments. [16]. Contrast enhancement of gliomas by intravenous administration of fluorescent markers in the surgical excision of brain tumors was attempted as early as 1948. [8]. Many previous publications stated that the use of fluorescein sodium made the surgery easier [12,17]. Stummer et al. 2006 [18] offered the results of a randomized multicentric phase III trial of surgical treatment of MGs with the use of 5-ALA. The results showed that fluorescence-guided resection allowed for complete tumor removal in 65% of cases. This percentage is almost twice that obtained with standard resection. In the study made by Shinoda, et al. 2003 [12]. they indicated that all the patients who underwent gross total resection showed significantly better survival in comparison with those who underwent subtotal resection.

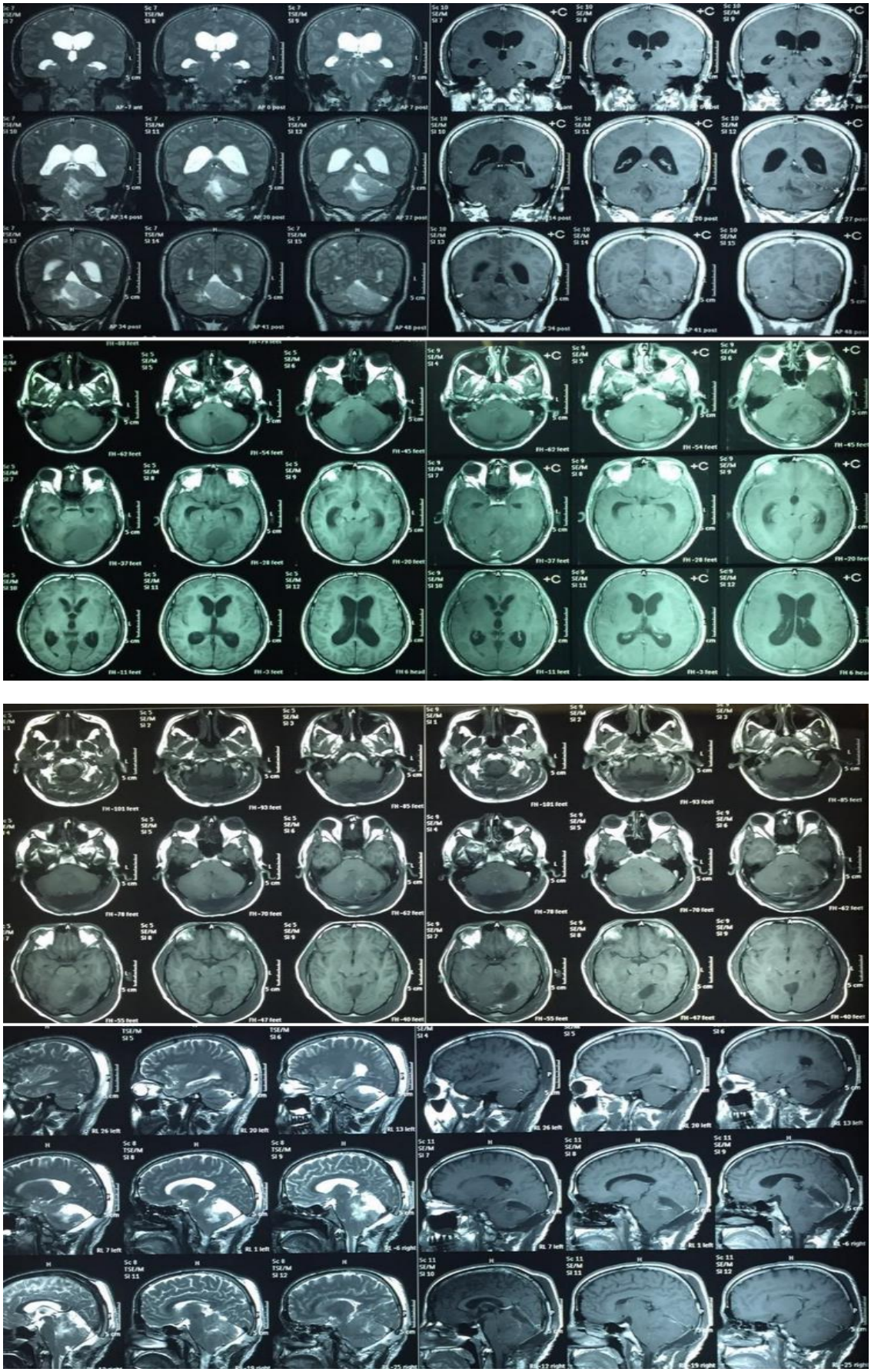

Figure 1: Pre and postoperative MRI shows complete removal of left cerebellar space occupying lesion.

Figure 2: yellow stained tumor.

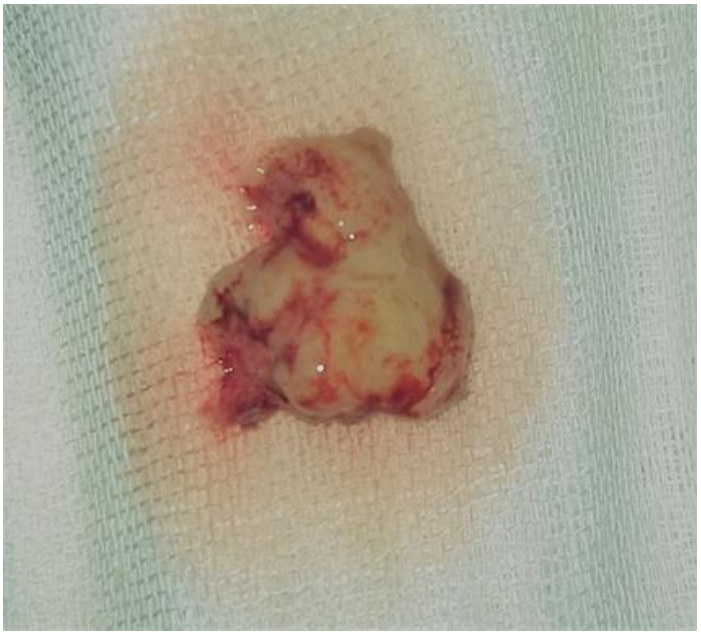

Figure 3: yellow stained resected tumor.

Table 1: Literature review

Author and year	Study design	Number of patients	Extent of resection	Surgical technique	Use of special instruments	notes
Shinoda et al., 2003	Controlled non-randomized retro-spective	105 divided into group A 32patients and group B 73 patients	GTR 49 STR 56	Group A (FS-guided surgery) and group B (without FS)	No	GTR in patients who underwent FS-guidance was significantly higher than patient who didn't
Okuda et al., 2012	Retro-spective	10	GTR 5 STR 5	FS-guided surgery	Using special microscope filter	Using barrier filter improves the reliability of resection during GBM surgery
Tykocki et al., 2012	Pro-spective	6	GTR 6 STR 1	5ALA-guided surgery	Using neuro-navigation	Neuro-navigation in highly suggested
Schebesch et al., 2015	Pro-spective	30	GTR 25 STR 5	FS-guided surgery	Using YELLOW 560nm filter	Fluorescein and using microscope filter are safe and practical tool for resection of cerebral metastasis
This study	Pro-spective	30	GTR 29 STR 1	FS-guided surgery	No	The lack of special instruments didn't affect the GTR rates

Although survival in the group that received fluorescein sodium was better than that in the group that did not, this difference was not significant, because fluorescein sodium itself is not a therapeutic. Okuda et al. 2012 [19]. reported in his study that, the use of FS resulted in transient yellowing of the skin, mucosa, and urine, but these side effects are spontaneously resolved within 24 hours in all patients with urinary excretion of the dye. No permanent side effects due to FS occurred.

5. Conclusions

Although fluorescein sodium has a zero specificity toward tumors but it has a 100% selectivity which puts it as the perfect choice in fluorescence-guided surgery. Maybe it has some disadvantages regarding its subjective color discrimination but the stained tissue could be seen sufficiently for resection without any need for special equipment only using the standard neurosurgical microscope with white light illumination. Fluorescein sodium used over the years as a fluorescence marker and it has been proven effective as an aiding tool in achieving gross total resection of brain tumors. This procedure is simple, safe, useful and universally available for resection of intra-axial brain tumors and over that fluorescein sodium is cheap and affordable in comparison to other tracers or even neuronavigational tools.

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