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The Role of Intraoperative Sodium Fluorescein-Guidance in Maximizing The Resection of Contrast-Enhancing Brain Gliomas

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ABSTRACT
Background: Glioma is the most common primary brain neoplasm. Surgical excision is the primary management modality for high-grade glioma. The aim of surgery is maximum safe resection for improving survival.
Objective: The aim of the current study was to evaluate the value of intra-operative sodium fluorescein in detecting boundaries and maximizing surgical resection of glioma.
Patients and methods: The study included 40 patients with pre-operative MRI showing contrast-enhanced lesions suspected to be high-grade glioma. Patients were operated on after IV injection of sodium fluorescein (5-8mg/kg) after induction of anesthesia. With the help of FL560 filters integrated into the Leica Provido microscope, all fluorescent areas could be resected. Volumetric assessment of the resected tumor tissue was calculated from pre-operative and early post-operative MRI with contrast.
Results: Gross total resection was achieved in most patients (95%), while in 5% of patients we just did near-total resection. The extent of resection ranged from 96 to 99% with a mean of 98.08%. The sensitivity and specificity of fluorescein for the high-grade glioma (contrast-enhanced areas) is 95% and 100% respectively.
Conclusion: The integration of intra-operative IV sodium fluorescein provided a safe, easy, and effective utility for differentiating tumorous from normal tissue thus maximizing the extent of resection of high-grade gliomas.
Keywords: Fluorescein, Intra-operative dyes, Glioma, Maximum resection, Glioblastoma.

INTRODUCTION

High-grade gliomas are malignant tumors of the central nervous system (CNS) that have a poor prognosis regardless of treatment plan (either chemotherapy, radiotherapy, or surgery) [(1)]. For patients with high-grade glioma, the degree of resection is a good predictor of increased survival [(2)]. Therefore, the first step in treatment should be maximal safe resection [(3)]. Only few lesions could be completely resected [(4)] as a result of glioma expansion into eloquent cortical and subcortical areas [(2)].

And even in non-eloquent areas, there is difficulty in differentiating the tumor tissue from the adjacent edematous brain at the margins of the resection area [(5)]. Therefore, many techniques were used for improving intra-operative glioma visualization and maximizing the extent of resection, such as neuronavigation [(6)], intra-operative Magnetic Resonance Imaging (iMRI) [(7)], and intra-operative ultrasound [(8)].

The most recent facility for eliciting brain region functions and defining and personalizing safe bounds of tumor removal is intra-operative electrophysiological monitoring and cortical and subcortical mapping conducted in awake-craniotomy operations[(9)]. Complete resection rates and 6-month progression-free survival rates (PFS) for patients with high-grade gliomas have been demonstrated to improve with the use of photodynamic detection, in which a dye or photosensitive drug is used to improve tumor localization and delineation by fluorescence. For example, the biological precursor of hemoglobin known as 5-aminolevulinic acid (5-ALA) causes the formation and accumulation of fluorescent porphyrins in different lesions [(10)].

As a replacement for 5-ALA, we can use sodium fluorescein (FL). FL, when given intravenously, can selectively concentrate in regions of the brain where the blood-brain barrier (BBB) has been compromised; these regions match to those that show contrast enhancement on pre-operative MRI scans[(11)]. FL has been found to enhance tumor visibility under either standard white light or a surgical microscope equipped with a specialized filter [(12)]. The primary emission wavelength of FL is in the green spectrum, between 540 and 690 nm, and it is triggered by a blue excitation wavelength peak between 460 and 500 nm. Using excitation and emission filters, it is straightforward to identify tumor parts [(11)].

In this study, we assessed the value and accuracy of using intra-operative sodium fluorescein injection in maximizing the resection of glioma, aiming to improve the surgical excision and make more benefit from surgery.

PATIENTS AND METHODS

Study population: Our study included patients in which pre-operative brain MRI with contrast showed enhanced lesions, which were suspected to be glioma, either for the first time or recurrent lesions. All patients were candidates for surgery.

We excluded patients with lesions starting from basal ganglion or brain stem, patients with reasons preventing the use of IV sodium fluorescein as previous hypersensitivity or renal insufficiency, patients with

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medical reasons precluding MRI examination (e.g., patients with a pacemaker).

The aim of surgery was total excision of fluorescent parts and taking a biopsy from the adjacent non-fluorescent non-eloquent parts for histopathological analysis. Forty patients fulfilled the criteria for selection and were operated upon in the period from June 2018 till June 2020.

Methods: This is a clinical trial, and the data were collected prospectively.

A detailed history was taken, with a general examination and pre-operative laboratory evaluation done for all patients to detect previous anaphylaxis to fluorescein, renal insufficiency, and for pre-operative evaluation. Every patient or his 1st-degree relatives were informed of the procedure in full detail and written consent was obtained. Every patient was investigated by a recent brain MRI with contrast. In the process of planning for surgery, the lesion was evaluated for its relation to the eloquent brain e.g., motor and speech centers, basal ganglion, thalamus, hypothalamus, and brain stem to assess the capability of gross total excision. Also, pre-operative assessment of neurological functions and GCS were recorded.

Procedure steps for every patient:

- We injected Sodium Fluorescein 10% directly intra-venous, in a peripheral line with the dose of 5mg/kg, immediately after induction of anesthesia.
- Ultra-sound was used in some cases to detect the best trajectory for subcortical lesions.
- Using a surgical microscope (Lecia Provido with integrated FL560 filters) we could identify the fluorescent glowing lemon-green parts. And at the same time could see normal brain tissue in yellow color and vessels in red color, and so FL560 filter could be used along the whole resection process safely.
- All fluorescent areas were resected and sent for histological examination. A second small biopsy from adjacent non-fluorescent non-eloquent tissue was obtained and sent separately for histological analysis.

After full recovery, postoperative assessment of neurological function and GCS were recorded. We performed early postoperative (within 72 hours) brain MRI with contrast to assess resection extent.

To calculate the percentage of resected tumorous tissue, volumetric assessment of the contrast-enhanced lesion in the preoperative and postoperative T1-contrast images was done.

The actual residual tumor volume was calculated by subtracting the volume of hyperintense areas in the post-operative T1 and T1-contrast images (to avoid including hyperintense signal of blood and blood products in the tumor bed). Then we calculated the extent of resection as following:

$$\text{Extent of resection} = \frac{(\text{pre-op volume} - \text{residual volume})}{\text{pre-op volume}} \ \%.$$

Studied variables: we measured the extent of resection to assess the value of using intra-operative fluorescein and compared the histological examination of both fluorescent and non-fluorescent samples to assess the sensitivity and specificity of sodium fluorescein in recognizing tumorous parts.

Ethical Consideration:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (ZU-IRB # 4843 / 30-9-2018). Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test and the Levene test (homogeneity of variances). Normal distribution of variables was described as mean and standard deviation (SD). When the data followed a normal distribution, an independent sample t test was utilized to make comparisons of means. When comparing more than two groups on a continuous parametric variable, a one-way ANOVA was utilized. The variation of a continuous parametric variable was analyzed between two time points for the same group using the paired sample t test. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

Descriptive data including patients' age and sex, presenting symptoms, tumor localization and its proximity to the eloquent brain, extent of resection, and histopathological analysis, are presented in Table 1.

Table (1): Summary of descriptive data of studied patients

No	Age/Sex	Presenting symptom	Location	Proximity to eloquent areas	EOR %	Post-operative new deficit	HPE of Fluorescent/ non-fluorescent specimen
1	70/m	headache	right parito-occipital	No	98%	none	GBM/normal
2	44/m	headache	right frontal	Yes	97%	none	GBM/invaded
3	48/f	confused	left parito-occipital	Yes	98%	none	GBM/normal
4	48/f	headache	left occipital	No	99%	none	GBM/normal
5	30/f	weakness	left frontal	Yes	97%	weakness	GBM/normal
6	56/m	confused	right temporal	No	98%	none	GBM/normal
7	55/f	headache	right temporal	No	97%	none	GBM/normal
8	58/m	headache	left frontal	Yes	97%	none	GBM/normal
9	38/f	weakness	left temporal	No	99%	none	GBM/normal
10	50/f	headache	left temporal	No	99%	none	GBM/normal
11	70/m	headache	left frontal	No	99%	none	GBM/normal
12	50/f	confused	left parito-occipital	Yes	98%	none	GBM/invaded
13	42/f	headache	right frontal	No	99%	none	GBM/normal
14	55/m	headache	right temporal	No	99%	none	GBM/normal
15	45/m	headache	left occipital	No	99%	none	GBM/normal
16	40/f	weakness	left frontal	Yes	97%	weakness	GBM/normal
17	65/m	headache	right parito-occipital	No	98%	none	GBM/normal
18	56/f	headache	left occipital	No	99%	none	GBM/normal
19	49/m	headache	right frontal	No	97%	none	GBM/normal
20	68/m	headache	left frontal	No	99%	none	GBM/normal
21	50/f	headache	left frontal	Yes	99%	none	GBM/normal
22	57/m	fits	right temporal	No	98%	none	GBM/normal
23	55/m	headache	right temporal	No	99%	none	GBM/normal
24	56/m	confused	right temporal	No	98%	none	GBM/normal
25	48/m	headache	right temporal	No	97%	none	GBM/normal
26	62/f	confused	left frontal	No	98%	none	GBM/normal
27	40/m	weakness	right frontal	Yes	99%	none	GBM/normal
28	52/m	headache	left frontal	Yes	96%	none	GBM/normal
29	42/f	headache	right frontal	No	99%	none	GBM/normal
30	50/m	headache	left frontal	Yes	97%	none	GBM/normal
31	48/f	headache	left temporal	No	99%	none	GBM/normal
32	50/f	confused	right temporal	No	97%	none	GBM/normal
33	50/f	headache	left frontal	Yes	99%	none	GBM/normal
34	57/m	fits	right temporal	No	98%	none	GBM/normal
35	56/m	headache	right temporal	No	97%	none	GBM/normal
36	45/m	headache	left occipital	No	99%	none	GBM/normal
37	56/f	headache	left frontal	Yes	96%	none	GBM/normal
38	40/f	weakness	left temporal	No	99%	none	GBM/normal
39	62/f	confused	left frontal	No	98%	none	GBM/normal
40	30/f	weakness	right frontal	Yes	99%	none	GBM/normal

Both sexes were represented in our study (19 Females and 21 Male). Age ranged from 30 to 70 years old with a mean age of 50.5 years. Regarding presenting symptom, headache was the most common presenting symptom (62.5%), 15% of cases presented with motor weakness, and 17.5% of cases were confused. On assessing preoperative neurologic deficits, 75% of the cases had no deficits, 25 % had motor weakness with motor power grade III and IV. Thirty-two patients (80%) operated for the first time, while 8 patients (20%) had previous surgeries and presented with recurrence, one of them had previous two surgeries and 7 operated once. Regarding the site of tumors in our cases, frontal, temporal, occipital and parieto-occipital lobes were represented by 45%, 35%, 10% and 10%, respectively. 55% of patients had the lesion in the left side of the brain, and 32.5% of patients had their lesion proximal to eloquent brain.

Intra-operative findings:

Fluorescence could be detected in all patients with variable degrees of homogeneity, being more intense and homogenous in the periphery of the lesion, and less homogenous in recurrent cases.

Postoperative:

We could achieve gross total resection in most patients (95%), while in 5% of patients, we just did near-total resection. Extent of resection ranged from 96 to 99% with a mean extent of resection of 98.08%. There was no statistically significant difference (P=0.776) in extent of resection between recurrent (Mean extent of resection 98%) and non-recurrent cases (Mean extent of resection 98.01%). The extent of resection in relation to the site of the tumor was (97.83%±1.15), (99%), (98%), and (98.14%±0.864) in frontal, occipital, parieto-occipital and temporal lobes respectively, with no statistically significant difference (P=0.185). Regarding the side of the lesion, mean extent of resection was 98% in right-sided lesions and 98.14% in left-sided lesions, with no statistically significant difference (P=0.664).

Regarding the proximity of lesions to eloquent brain, mean extent of resection was 98.3% in far lesions, while 97.62% in lesions near eloquent brain areas, with statistically significant difference (P=0.036*). Regarding results of histopathological examination, all fluorescent specimens (100%) were GBM. 95% of the non-fluorescent specimens showed the absence of tumor cells, while only 5% (2 cases) showed invasion by tumor cells, with 95.2% sensitivity and 100% specificity. GCS of all patients was 15/15 on post-operative day one, including the seven patients who were confused pre-operatively. Two patients (5%) developed a new deficit post-operatively in the form of motor weakness.

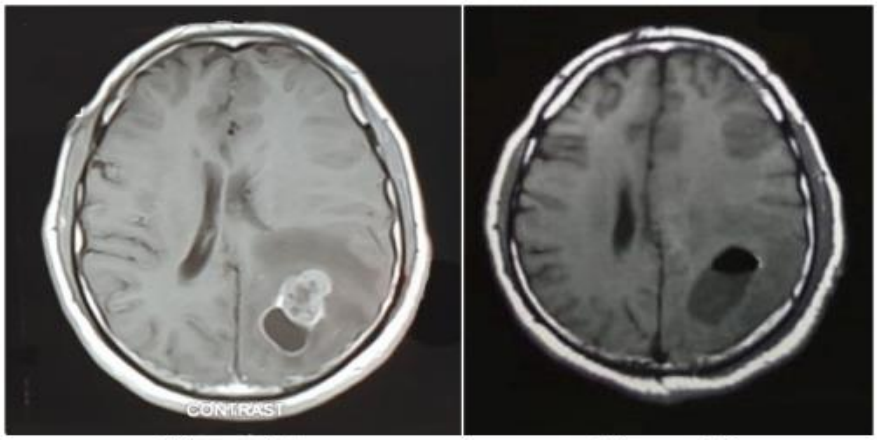

Figure 1A Figure 1B

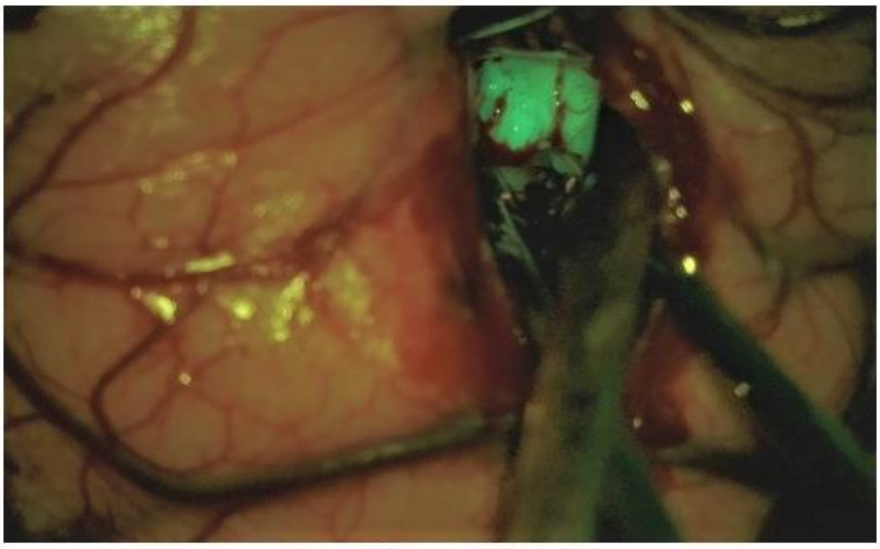

Figure 1C

Figure 1: (A) Pre-operative MRI brain with contrast, showing left occipital ring-enhanced lesion with central heterogeneous enhancement. (B) Early postoperative MRI brain with contrast, showing complete resection with extent of resection of 99%. (C) Intra-operative view under fluorescence mode, showing lemon-green, fluorescent part with normal visualization of the brain.

DISCUSSION

The use of intra-operative fluorescent dyes is a great facility in maximizing the resection of gliomas. A Phase III study showed that 5-ALA, which is more specific for glioma cells, significantly increase the extent of resection when compared to the regular microsurgery with white light, providing a progression-free survival benefit in this group [(13)].

However, the use of 5-ALA has some limitations precluding wide application, including cost (about 900 Euro per patient), the requirement of early administration pre-operatively, and loss of clear visualization of normal brain and vessels color under blue light. These drawbacks made a room for sodium fluorescein, as a beneficial alternative for 5-ALA. Sodium fluorescein has the advantages of significantly lower cost (5-8 Euro per patient), administration in the operation room just before surgery, very limited adverse effects, and the great benefit of visualizing the brain and vessels in their natural colors making demarcation of the tumor side-by-side with protecting normal brain and hemostasis easier with the whole resection procedure done under fluorescein mode. But sodium fluorescein induces nonspecific fluorescence of locations where there is a disruption of the blood-brain barrier, in contrast to 5-ALA, which causes the buildup of fluorescent porphyrins in malignant glioma cells [(14)].

Regarding the time of FL injection, although some surgeons injected it just before glioma resection [(15)], we used a low dose of sodium fluorescein (5mg/kg) and injected it in a peripheral line just after induction of anesthesia, making interval of about 50-60 minutes between injection and starting resection of the tumor. This timing also was stated by **Acerbi and co-workers** allowing a good diffusion of the dye in tumor tissue and preventing fluorescence of surrounding tissue [(16)].

We found that intravenous fluorescein is safe to utilize during excision of high-grade gliomas, and that doing so is linked to a higher rate of full resection of contrast-enhanced tumor at the early postoperative MRI. We could achieve growth total resection (GTR) of all fluorescent parts in 95% of cases with a mean extent of resection of 98.1%. Similar results were reported in previous studies. **Schebesch's research team** reported their first experience with 35 heterogeneous patients with a gross total resection of 95% of the contrast-enhancing tumor [(17)].

However, some studies showed lower GTR rates. In 2013, **Acerbi and co-workers** published the results of 12 patients with high-grade glioma who have been operated on using intra-operative FL, the rate of complete resection was 75% [(18)]. In a study by the same authors (2014), they achieved GTR in 80% of cases [(19)]. **Toshihiko Kuroiwa and co-workers** were the pioneers who integrated special filters into the regular surgical microscope they could achieve an 80% GTR rate [(20)].

Some reports stated a higher GTR rate. In 2013, **Diez Valle and co-workers** reported a prospective study on 12 patients with high-grade glioma. All patients were operated on using the FL-guided technique under the Y560 filter. The rate of complete resection was 100%, proven by early postoperative MRI. The authors used and found intraoperative neuro-navigation (contrast-enhanced T1 weighted images) corresponds well to the fluorescent areas. According to the authors, this finding strongly supports that FL fluorescence in high-grade glioma is equivalent to Gd-enhanced areas in MRI [(21)].

The differences in GTR rates could be attributed to the difference in site and size of lesions and its proximity to eloquent areas, as we found a statistically significant difference in extent of resection between groups concerning the proximity of the lesion to eloquent brain areas.

Although some surgeons prefer to resect the tumor in an inside-out fashion [(19)], we used the outside-in fashion, especially in cases with ring-enhanced lesions. This is because FL stains the contrast-enhanced areas, and so following fluorescent parts from outside is easier for achieving complete resection.

Developing a new postoperative neurological deficit after resecting GBM results in a decrease in overall survival. A careful balance between maximum extent of resection and saving neurological function needs to be highly considered to reduce the likelihood of neurological deficits from surgery [(22)]. And so, we aimed not to harm and to avoid causing new deficits to our patients. Only two patients from 40 developed new deficits in the form of contralateral hemiparesis. These results are accepted compared to the result of **Francaviglia and co-workers** on 47 patients, in which fifteen patients developed new neurological deficits, nine of which were transient [(15)].

To calculate the accuracy of sodium fluorescein, we sent 80 specimens for histopathological examination, 2 specimens from each patient (one from each fluorescent and non-fluorescent areas), and the results showed 95.2% sensitivity and 100% specificity. The high sensitivity is one of the advantages of sodium fluorescein over 5-ALA, the calculated sensitivity of 5-ALA is 85% [(15)]. Regarding the 100% specificity, it's not true specificity of fluorescein to high-grade glioma tissue, but the gadolinium contrast-enhanced areas. Complete resection of the high-grade glioma is defined as the complete resection of the contrast-enhanced areas [(23)]. So, the specificity of fluorescein to contrast-enhanced areas is roughly considered a relative specificity to GBM tissue. For that reason,

there are variations in specificity rates in different studies. **Acerbi and co-workers** published their results with sensitivity and specificity calculated 91% and 100% respectively [(18)]. **Zhang and co-workers** reported their results with the sensitivity and specificity of FL were 94.4% and 88.6% [(24)]. In the results of a study published in 2018, histopathological analysis of 110 tissue specimens demonstrated a sensitivity of 91%–94% and specificity of 90%–100% [(25)].

It worth mentioning that the two specimens from non-fluorescent parts, which showed tumorous cell invasion were from patients with recurrent lesions. This may be due to the heterogeneous fluorescence observed in surgery for recurrent cases. The issue of evaluating the specificity and sensitivity for recurrent tumor tissue and scar tissue needs to be investigated in future studies [(26-28)].

We didn't encounter any anaphylactic reactions to fluorescein in our cases, and the same was in most studies. To the best of our knowledge, the occurrence of adverse reactions to FL in the literature is very limited. Two cases showed anaphylactic reactions after the injection of FL for neurosurgical surgeries [(27,28)]. Both patients underwent surgery for high-grade glioma after the injection of FL in high doses (20mg/kg). Both patients developed severe hypotension during general anesthesia, and surgery had to be discontinued in one patient. Both patients transferred and managed in the intensive care unit and both patients fully recovered. The risk factors for adverse events in surgeries with FL include previous anaphylaxis and the injection of a high dose (20mg/kg) [(28)].

Limitations of the study: We had a relatively small number of patients, and we did not include a control group in our study. This should be considered in future studies. Data from our study can be used to design larger confirmatory studies to quantify the efficacy of fluorescein-guided surgery in maximizing the extent of resection of gliomas as well as improving the progression-free and overall patient survival.

CONCLUSION

Based on the results of this study on 40 patients, the integration of intra-operative IV sodium fluorescein provided a safe, easy, and effective utility for differentiating tumorous from normal tissue and maximizing the extent of resection in surgery for high-grade glioma. The high sensitivity and specificity to the contrast-enhanced areas made it accurate and dependable.

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