

ORIGINAL RESEARCH

Fluorescein Guided High grade Glioma Resection: A Retrospective Analysis

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ABSTRACT

Background: High grade glioma resection under fluorescein guidance have shown improved visualization of tumor margin and has improved the extent of resection. **Methods:** This is a single centre retrospective analysis of 69 patients of high grade glioma operated under fluorescein guidance with operating microscope using yellow filter. The data was analyzed from December 2021 to December 2022 and was evaluated for surgical outcome in terms of residual tumor and post operative residual volume using T1 weighted contrast MRI (extent of excision), post operative complications with 6 month follow up. Intravenous fluorescein sodium (2mg/kg) was administered at the time of incision. **Results:** None of the patient had any adverse reaction to fluorescein. The mean preoperative tumor volume was 29.4cm³. Gross Total Resection (GTR) was achieved in 55 patients (79.76%) and STR in 14 patients (20.24%) with mean postoperative residual tumor volume 1.63cm³ (range 0.11 – 13.4cm³). 11 patients (15.9%) had Grade 3 and 58 (84.05%) patients had Grade 4 gliomas per WHO classification, 5th Edition. In post operative period 1 patient (1.14%) had multiple episodes of seizures, 3 patients (4.34%) had lower respiratory tract infection (LRTI), 5 patients (7.24%) developed wound infection and 3 patients died in post operative period during hospital stay, but it was not procedure related mortality. 59 patients (85.5%) had progression free survival at 6 month duration with average KPS of 82.5, 8 (11.59%) patients had recurrence at 6 month follow up, 2 (2.89%) patient died at 6 month follow up. **Conclusion:** FL guided excision of High grade glioma improves the extent of resection and helps in improving survival.

Keyword: Fluorescein Sodium, High Grade Glioma, Yellow Filter, Glioblastoma

Abbreviation:

WHO- World Health Organization MRI- Magnetic Resonance imaging GBM- Glioblastoma multiforme GTR- Gross Total Resection

STR- Sub Total Resection

CUSA- Cavitron Ultrasonic Surgical Aspirator FL – Fluorescein

HGG- High Grade Glioma

KPS- Karnofsky Performance Status LRTI- Lower Respiratory Tract Infection

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INTRODUCTION

Glioblastoma multiforme (GBM) is most common primary malignant brain tumor in adults; management policy includes maximal surgical resection followed by radiation and chemotherapy. Preserving vital neurological function is crucial when tumor involves area related to language, motor skills, sensory perception and cognition. Preoperative performance status, patient's age, the extent of surgical resection, radiotherapy and chemotherapy are the factors that influence patient prognosis^{1,2,3}, and the extent of resection is the only modifiable factor affecting post-operative survival^{4,5,6,7}. Infiltrative nature of Glioma makes complete resection difficult. Various adjuncts such as intraoperative MRI, intraoperative ultrasound,

navigation, use of fluorophores have been developed over time to improve the extent of resection but most of them have their own limitations. Sodium fluorescein is a fluorescent compound, used to enhance tumor visualization during surgery. It enhances the area of enhancement as in T1 Weighted contrast MRI image. Low dosage has been associated with minimal side effects. Initial studies used higher doses but advances like yellow filter integration into microscope reduced the required dosage and avoided the side effect. Studies have reported improved gross total resection (GTR) rates with fluorescein but its impact on patient survival was not found significant⁶.

Very few studies have been conducted for high grade glioma resection with low dosage of fluorescein under

microscope using yellow filter. This is a retrospective study of high grade glioma patients operated with use of fluorescein under microscopic yellow filter and analysis of the outcome with respect to post operative residual tumor volume, and postoperative complications, mortality and other morbidities.

PATIENTS AND METHODS

Approval for the study was taken by local ethical committee of the medical college, Jabalpur. All the patients who underwent FL guided glioma resection with microscopic yellow filter between December 2021 to December 2022 who have received radiation and chemotherapy and with a minimal follow up of 6 months were included in the study. However, patients who were lost to follow up within 6 months and who have not received radiation and chemotherapy were excluded from the study. Documents, preoperative and postoperative scans were reviewed. Patients with bilaterally located tumors, corpus callosal involvement, tumors in midline, basal ganglia, posterior fossa and brain stem on pre-operative MRI were excluded from the analysis. 76 patients underwent FL guided glioma resection with histopathological confirmation of Grade 3 and Grade 4. 3 patients did not receive radiation and chemotherapy and 4 patients could not be followed up till 6 months hence, excluded and total of 69 patients were taken for study. Histopathological diagnosis was confirmed according to WHO classification of CNS tumors, 5th edition, 2021 by neuropathologist.

RADIOLOGICAL EXAMINATION

Data was evaluated for tumor volume and tumor characteristics in T1 weighted, T2 weighted and contrast T1 weighted sequence of MRI. Post operative contrast MRI was obtained within 48 hours and was assessed for residual tumor volume. The tumor resection was graded as gross total resection or subtotal resection. Gross Total Resection (GTR) was defined as no residual enhancing tumor and Sub Total Resection (STR) was defined as any residual enhancing lesion on post operative gadolinium enhanced T1 weighted MRI. Late post operative MRI was obtained at the end of 6 weeks.

SURGICAL PROCEDURE

69 patients (n =69) were given fluorescein sodium 2mg per kg body weight through central venous line at the time of incision. Following the administration of fluorescein sodium parenchyma was found normal in color, tumor tissue was visualized only under microscope with yellow filter. Tumor resection was performed with the help of CUSA (Cavitron Ultrasonic Surgical Aspirator) in some cases. Usually resection of tumor was performed approximately 10 minutes after fluorescein administration and the resection of tumor was based on identifying yellow coloured tissue under yellow microscopic light.

POST OPERATIVE STAGE

All the patients were shifted to ICU in post operative period. Patients were given antiepileptics, antibiotics, anti- cerebral edema measures and steroids for 5 to 7 days and thereafter gradually tapered. All the patients were loaded with half dose of anti-epileptic drug before extubation and thereafter given antiepileptic in maintenance dosage. Antiepileptics were continued in maintenance dosage after discharge. Post operative MRI was done usually within 48 hours of surgery. All the patients underwent chemotherapy and radiotherapy with conventional radiation of a 6000-6500 cGy radiation after wound healing usually started within two weeks after surgery.

RESULTS

None of the patient had adverse reaction to fluorescein. There was scleral yellowing and yellowish urine in immediate postoperative period, which improved in 2-3 days.

EXTENT OF RESECTION

The mean preoperative volume of tumor was 29.4 cm³ (range: 10.4- 71.5 cm³). Gross total excision of tumor as per post op MRI was possible in 55 patients (79.76%) and subtotal was done in 14 patients (20.24%), with mean post operative Residual volume of 1.63 cm³ (With aRange of- 0.11- 13.4 cm³) **Table 2**

HISTOPATHOLOGY

11 patients (15.9%) had Grade 3 and 58 patients (84.05%) had Grade 4 histopathology according WHO CNS tumor classification, 5th edition, 2021. **Table 2**

POST OPERATIVE COMPLICATIONS

In post operative period, 3 patients (4.34%) had LRTI, 5 patients (7.24%) developed wound infection, 1 patient (1.14%) had 3 episodes of seizures despite on antiepileptic drugs which resolved with add-on antiepileptic treatment. (**Table 3**) 3 Patient died in early post operative period, but none of them were procedure related mortality, all 3 had lower respiratory tract infection became ventilator dependent. Wound infection was minor in 4 patients, improved with suturing and antibiotics, one patient required bone flap removal and debridement of wound due to persistent purulent discharge from wound and gram negative infection.

PROGRESSION FREE AND OVERALL SURVIVAL AT 6 MONTH

59 patients (85.5%) had progression free survival at 6 months with an average KPS of 82.5. (**Table 3**) 8 (11.59%) patients had recurrence at 6 month follow up period, 2 (2.89%) patients died at 6 months follow up, confirmed telephonically.

Table 1: Patient Characteristics

Characteristics		Number of Patients(n)
Total		69
Gender	Female	37 (53.63%)
	Male	32 (46.37%)
Age (Years)	Mean	56.7
	Range	44-69
Pre- operative(KPS Score)	Mean	76.5
	Range	70-100
Symptoms / Sign	Intermittent Headache	55
	Seizures	12
	Hemiparesis	10

KPS - KPS- Karnofsky Performance Status

Table 2: Tumor Characteristics

Features		Number of Patient (n)
Tumor Location	Fronto parietal	45 (65.22%)
	Temporo- occipital	24 (34.78%)
Tumor Volume (cm ³)	Mean	29.4
	Range	10.4 to 71.5
Histology (WHO 5 th Edition classification)	Grade 3	11 (15.91%)
	Grade 4	58(84.05%)
Extent of Resection	GTR	55 (79.76%)
	STR	14 (20.24%)
Post operativeResidual Volume (cm ³)	Mean	1.65
	Range	0.11- 13.4

GTR – Gross Total ReactionSTR – Sub Total Reaction

Table3: Post operative Complication and out come

Post operative Complication	Number of patients	
Seizures	1 (1.14%)	
Wound Infection	5 (7.24%)	
Chest Infection (LRTI)	3 (4.34%)	
Death	3 (4.34%)	
Follow up at 6 months	Recurrence	8 (11.59%)
	KPS (Average)#	82.5
	Death	2(2.89%)

KPS- Karnofsky Performance Status LRTI-Lower Respiratory Tract Infection

#. – KPS was calculated after excluding patient of recurrence

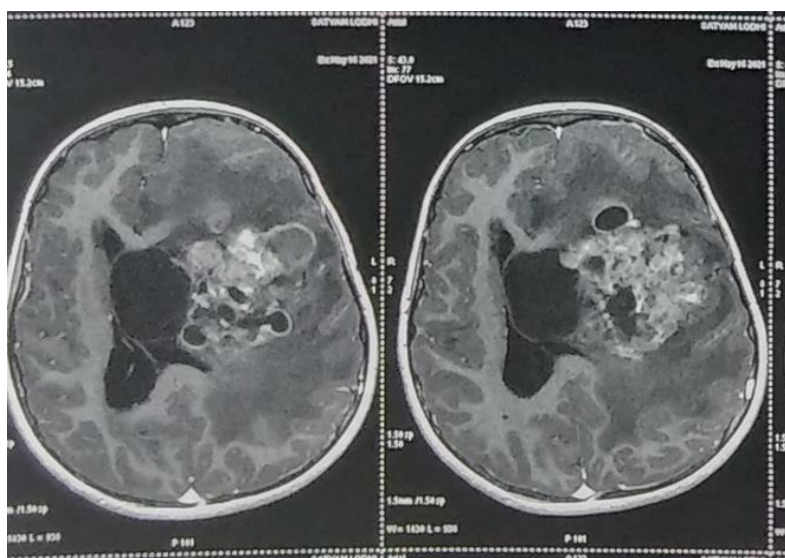


Fig.1: Preoperative MRI Scan

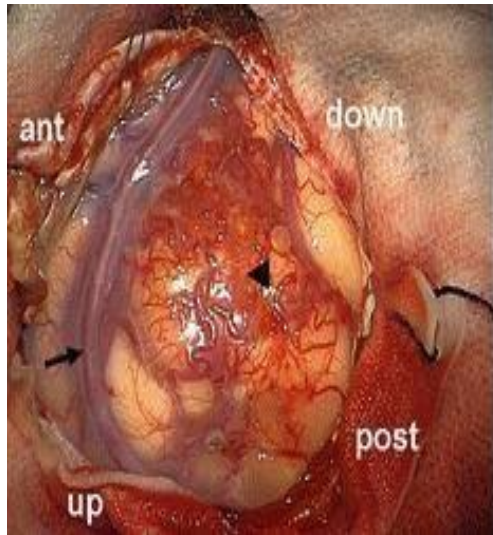


Fig 2: Intraoperative view of tumor under white light of microscope

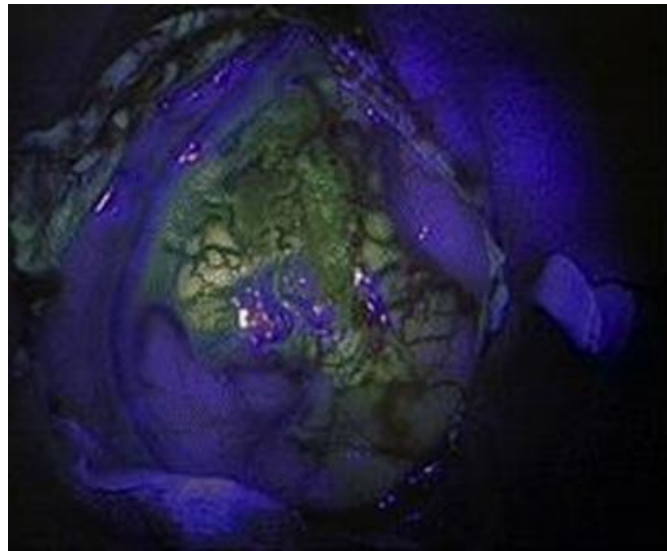


Fig 3: Intraoperative visualisation of tumor under microscope with Yellow filter

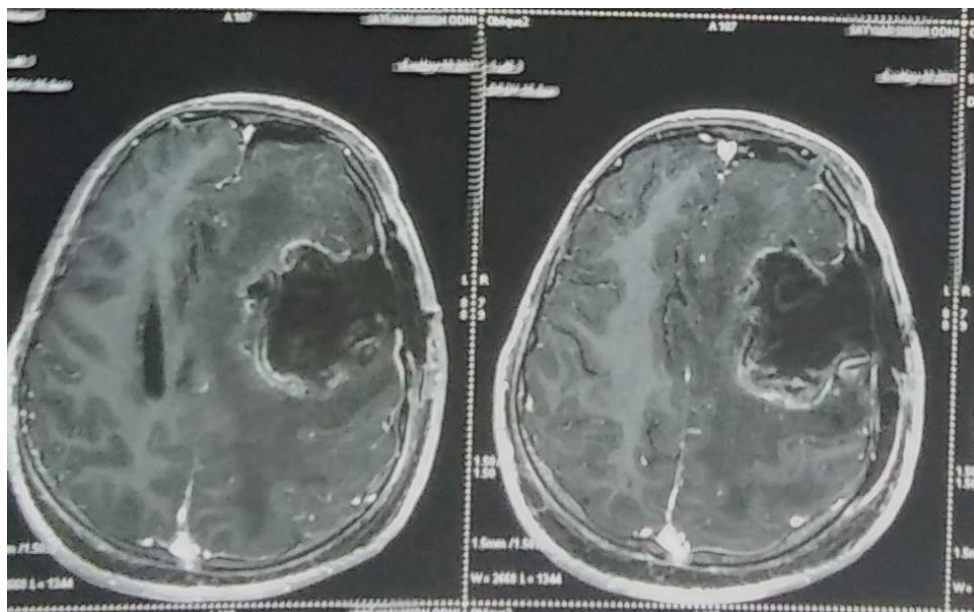


Fig 4 a

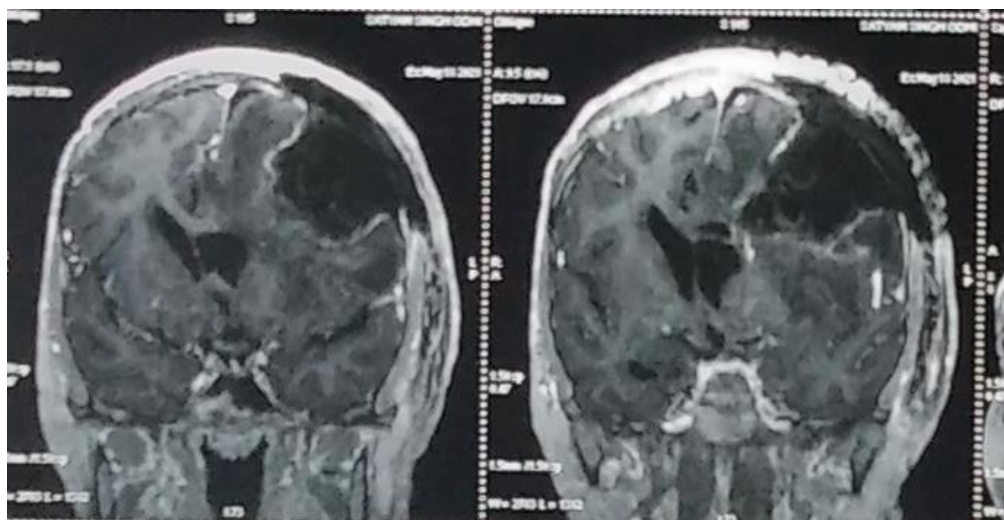


Fig 4b

Fig 4 a and b: Postoperative MRI scan of operated patient

DISCUSSION

High grade glioma is the most common malignant primary brain tumor in adults.⁷ Current practice of management includes maximal surgical resection of tumor followed by radiation and chemotherapy. For gliomas involving language, motor, sensory and cognitive areas removal of maximal tumor with preservation of vital neurological function is opted than resection of tumor based on neuro-imaging^{2,3}. Preoperative performance status, age of patient, extent of surgery, radiotherapy and chemotherapy are the factors affecting the prognosis.^{1,2,3} Extent of resection is the only modifiable factor in post operative survival of patients.^{4,7} Infiltrative nature of the tumor prevents the complete resection. (bochen) Various adjuncts such as intraoperative ultrasound, neuronavigation, intraoperative MRI, cortical stimulation and fluorophore guided resection have been developed over time^{8,9} to improve the extent of resection and therefore survival of patient but all the methods have their own limitations.

Sodium fluorescein is a fluorescent compound with peak excitation in 460 to 500 nm range and peak emission in yellow green part of spectrum between 540 to 690 nm¹⁰. Once administered fluorescein is metabolised by liver to fluorescein glucuronide and excreted by kidneys with a half life of 264 minutes.^{11,12} It accumulates in the areas of brain where blood brain barrier is compromised and collects in the extracellular space^{13,14}. Fluorescein has minimal side effects like skin reaction, syncope, respiratory adverse events, cardiac adverse events and Seizures^{15,11} however frequency rate reported is one in 1,900 and frequency of death is one in 222,000.¹⁷ Two reports in literature have mentioned serious anaphylactic intraoperative hypotension and mild bradycardia with high dose of fluorescein (20 mg/kg)^{16,17} None other study has reported such complication. Study has suggested more complication in ocular surgery as compared to neurosurgical procedures as drug is given

under the effect of general anaesthesia during neurosurgical procedures.¹¹

Hong et al and other authors have reported fluorescein stained tissue has histological sensitivity and specificity of 90.8% and 83.3% respectively.^{18,19} Neira et al have shown that fluorescein staining extends beyond the contrast enhancing area into the non enhancing infiltrative tumor margins and highlighted its ability to reliability predict glioma associated pathology in both contrast enhancing and non contrast enhancing areas and has a potential role in facilitating supramarginal resection even into non enhancing margins of HGG²⁰. Initial studies were done with high dose of fluorescein (20mg/kg) under white light of microscope but with the advent of yellow filter for microscope, dose of fluorescein has been significantly reduced from 20 mg/kg to 2-3 mg/kg, at same time side effect related to high dosage of fluorescein could be avoided. Various studies have been done for high grade glioma excision using fluorescein with yellow filter^{21,22,23}. Kuroiwa et al have performed microscopic resection following fluorescein injection and suggested that fluorescein makes surgery easier²⁴.

Shinoda et al have performed conventional microscopic excision with high dosage of fluorescein and found gross total resection was significantly more in fluorescein group but median survival time was not increased⁶. In 2008 Koc and co-worker performed prospective fluorescein guided resection with high dose FL under Xenon white light and have shown GTR in FL group but survival did not vary. In 2010 Okuda et al have shown FL guided resection with high dose under white light in brain metastasis and achieved local Control rate of 80%²⁵. Da silva et al have shown effective use of FL with skull base tumors²⁶. Schebesch and co-worker have performed low dose FL guided resection under yellow filter with microscope in 2013 and reported the use of FL for the resection of brain tumors is safe and feasible. Smith et

al in their meta analysis have reported 29.5% increase in GTR²⁷. Acerbi et al in their meta-analysis of 412 articles suggested FL guided surgery is safe, effective and convenient for achieving high GTR rates in high grade glioma but progression free survival and overall survival needs further prospective trials.¹⁸ Chen xi in their retrospective study with 5 year follow up have shown higher GTR rates in FL group specially for temporal and occipital lobes and postoperative residual tumor volume was also significantly smaller in FL group.²⁸ and suggested FL facilitates tumor visualization and tumor margin delineation and reducing surgical bleeding and duration of surgery.²⁸ Acerbi et al in their phase II prospective study have shown a total resection rate of 80% with a mean of 92.6% tumor resection rate with volumetric analysis. They have reported 6 months progression free survival rate of 71.4%.²⁹

M. K. Hamamcloglu et al in fluoroscein guided resection with yellow microscopic filter have reported 79% of complete removal and found sodium fluoroscein was helpful for tumor demarcation regardless of tumor grade³⁰. There was 79.8% GTR in our study which is similar to M.K. Hamamcloglu and Acerbi et al, our 6 month progression free survival was 85.5% which is higher as compared to Acerbi et al which may be related to lower number of cases in Acerbi study. Kuroiwa et al in 1998 have reported that fluorescein can leak out of damaged vessel obscuring the fluorescein positive regions of HGG if resection is performed too early²⁴ hence suggested optimal timing of resection as 10 minutes to over 90 minutes²⁴. We have not faced such issue as intravenous fluorescein was given at the time of incision, and resection was started usually after 15 to 20 minutes of drug infusion.

LIMITATION

Our study is retrospective, also follow up duration is limited to 6 months, we could not analyse the survival of patients.

CONCLUSION

Fluorescein guided surgery using yellow filter under microscope is a safe, effective and improves the extent of resection in high grade gliomas.

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