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Original Research Article

Radiological Low-Grade Glioma; Preoperative DTI and Functional MRI as an Aid in Preoperative Surgical Planning

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Abstract

Advances in the understanding of Low-Grade Glioma (LGG) biology have driven new paradigms in management. However, debate continues pushing the envelope toward improved quality of life and survival with safe gross total resection. In this article, we are trying to focus on the impact of the preoperative radiological data on the plan of management and intraoperative resection scenario. We applied a management protocol in our institute, in which we used functional magnetic resonance image (fMRI) and magnetic resonance tractography (MRt) data, in a prospective cohort of 56 patients with radiological diagnosis of LGG in the period from 2009 to 2016. Patients were divided depending on the management strategy into 3 groups: (1) gross total resection (GTR), (2) biopsy, (3) Don't touch. Our primary outcome was quality of life using Karnofsky scale (KPS). Secondary outcomes included: Focal neurological function and extent of resection. Distribution of the cases between the groups was 34, 18 and 4 cases in the GTR, Biopsy and don't touch groups respectively. We adopted radiological and clinical follow up every 6 months for a mean follow up period of 41.5 months. KPS < 70 (dependable) was found in 17/56 patients at presentation however at 18 months follow up 9/56 cases had KPS < 70 (dependable). Permanent morbidity (more than 6 months) was reported in 6/56 cases. Functional radiological preoperative data would be implemented in surgical decision making for patients with radiological LGG.

Keywords: Low grade glioma, LGG, DTI, Tractography, Functional MRI

INTRODUCTION:

Recently several considerations are involved in the management of patients with low-grade gliomas (LGGs). Advances in tumor biology, neuroimaging, and treatment paradigms have enabled the neurosurgeon to approach these patients with a better understanding of the disease entity and its natural history. However, still a lot of controversies need to be answered. Diagnostic strategies, which were previously considered reliable, have more recently been shown to vary per different subtypes. Surgical management algorithms are also shifted with more evidence to the role of greater extent of resection in reducing transformation rates and the importance of eloquence in defining surgical strategy (Barbone *et al.,* 1994; Afra and Osztie, 1997; Sanai, Chang and Berger, 2011).

Prognosis in LGG depends on several clinical factors. Chief among those is age over 40 years; Age at the time of LGG diagnosis was inversely correlated with time to progression. (Karim *et al.,* 1996, 2002) Clinical presentation with seizure only has a good prognostic factor. (Chang *et al.,* 2008) Interestingly most patients initially present with relatively good neurological function,

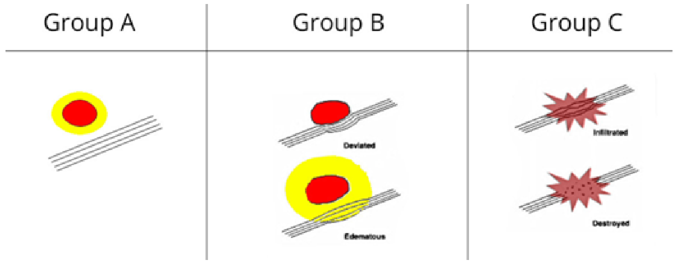

Figure 1. Types of effects of neoplasm on the DTI tracts

and seizures are the most common symptom at presentation (80%) (Bondy *et al.,* 2008; Sanai, Chang and Berger, 2011)

Advances in neuroimaging techniques are always add on to the surgical planning strategy. Knowledge of the plasticity of different brain function pathways in patients with low-grade glioma is important for neurosurgeons to achieve maximum resection while preserving neurological function (Zheng *et al.,* 2013). Functional MRI was accurate for identifying areas of neurologic function before surgical resection of LGG.(Hall, Liu and Truwit, 2005) Diffusion imaging tensor have been studied to differentiate between high and low grade glioma and to help in preoperative planning (Piyapittayanan *et al.,* 2013) with defining eligible cases for gross total resection (GTR).

Different management strategy have been suggested for patients with low grade gliomas including GTR, Radiation therapy, biopsy and adjuvant therapy or just observation especially that most of the patients can be asymptomatic however most of recent literature incline towards GTR as a plan of management whenever it safe, however most of low grade glioma delineate the eloquent brain areas, making achieving such job safely sometimes impossible. (Whittle, 2004; Pouratian and Schiff, 2010; Sanai, Chang and Berger, 2011)

Still with all the advances in technology and surgical technique there is still no evidence base treatment algorithm for patients with low-grade glioma defining when to do GTR, biopsy or just observation. In this study, we would like to share our experience to augment an evidence for such an algorithm.

METHODS

This is a Prospective cohort study including all adult patients presented to Ainshams university hospital in between July 2009 to August 2016 with symptomatic non-enhancing intra axial supratentorial brain tumors on MRI (Which, we called radiological low grade glioma). Patients with MRI images of enhancing intraaxial brain tumors or asymptomatic patients accidentally discovered to have intraaxial brain tumors or children (under age of 18 years) or biopsy proven high-grade glioma (WHO grade III or IV) (Louis *et al.,* 2007) were excluded from the study population. Informed consent was obtained from all individual participants included in this study.

Our primary outcome was Karnofsky performance status (KPS) as an indicator of the quality of life.
Secondary outcomes included Focal neurological function, Postoperative complications and extent of resection.

Clinical assessment

All patients had history, full neurological examination and assessment by an experienced neurosurgeon with documentation of baseline KPS and neurological status.

Radiological assessment

1) MRI brain T1 with and without contrast, T2 and flair were evaluated in all patients. Accordingly, patients were classified either as diffuse non-enhancing with ill-defined borders or focal non-enhancing with well-defined borders.
2) Functional MRI (fMRI) and DTI tractography were obtained to help in the decision making for all patients to identify eloquent and non-eloquent tumors, Effect on tract by the tumor was classified on tractography into 3 degrees as an update to Jellison et al classification: A) more than 1mm thickness of normal brain parenchyma between tract and tumor with no shift of the tracts, B) Tracts are shifted or edematous, C) Tracts are traversed by the tumor or totally destroyed. (Jellison *et al.,* 2004) *Figure 1*

Decision-making

- GTR was decided for patient with LGG in-group A and B tractography characteristic.
- Biopsy was decided for patients harboring tumors with the following criteria:
  - Group C tractography.
- Do not touch (follow up):
  - Group C tractography and the tumor involve eloquent fMRI spot.

Table 1. Histopathology classification of patients. PD: persistent deficit, TD: Transient deficit, ND: No deficit

Histopathology	Diffuse astrocytoma, NOS	Gemistocytic astrocytoma, NOS	Oligoastrocytoma, NOS	Oligodendroglioma, NOS
No. Of cases	27	14	5	10
Group A tractography	16	4	1	2
Group B tractography	6	6	4	6
Group C tractography	5	4	0	2
PD outcome	3	4	0	1
TD outcome	6	4	4	1
ND out come	18	6	1	8

Operative technique

Cases in which surgery or biopsy was decided preoperative MRI images including functional and DTI tractography was uploaded to the neuronavigation system. Patient head and landmarks were registered after head fixed on 3-pin fixator to the operating table. Maximum safe microsurgical resection was the goal in patients of group A and B tractography.
All biopsy specimens were formalin fixed and analyzed after staining with H & E, and immunostains by an experienced neuropathologist.

Follow up

When Surgery was indicated immediate postoperative MRI brain with gadolinium contrast was obtained postoperative day one to assets extent of resection. Postoperative base line neurological exam was recorded in all patients.

All cases where followed up clinically and radio logicallyin 3, 6, 12 months postoperatively then annually after that for 5 years. Patients were classified to have permanent neurological deficit if they have it for more than 6 months in the follow up. Chemo and radiotherapy was done per our institute protocol, which is out of our focus in this manuscript.

Statistical data analysis

All patients' data identifiers were coded and the linkage code was kept securely in locked folders with access to the approved investigators by the IRB at our institute. Extent of resection was calculated to all the cases where surgery was decided. Patients were classified either to develop temporary or permanent focal neurological deficit, incidence of postoperative neurological deficit was calculated in the cohort. A follow up curve was generated to illustrate the KPS of patient's cohort through the follow up.

RESULTS

This study included 56 patients (30 females and 26 males) with a mean age of 40.1 years. Surgery, biopsy or don't touch techniques were decided in 34, 18 and 4Patients respectively. Mean follow up was 41.5 months. Minimum follow up period for cases included in the study was 2 years. The most common pathological diagnosis in our cohort was diffuse astrocytoma, NOS in 27/56 patients and followed by gemistocytic astrocytoma, NOS in 14/56 patients. Table 1 describes histopathology, radiological characteristic for our study population.

Seizure was the most common presenting symptom, 52 (93%) of patients presented with seizures. All patients reported symptoms of increased intracranial pressure such as headache, nausea and vomiting, on presentation. Mental status changes were present in 4 cases of patients at the time of presentation. On examination, most of the patient had normal neurological exam with 6 patients having focal neurological deficit.

Functional and DTI information with patient outcomes: In our cohort, we had 11/56 cases having traversed or destroyed tracts (Group C), 2/11 of these patients had persistent neurological deficit. We had 13/27 patients in (group B) tractography with shifting of the tracts of these 12/13 had No or transient deficit. No persistent deficit was recorded in (group A) patients where the tracts were away from the tumor with our proposed treatment algorithm. *Figure 2*

In this series 14/56 cases presented with focal neurological deficit only 5/56 had persistent neurological deficit at the end of the follow up. KPS was recorded as baseline and followed up in our patient series, KPS < 70 (dependable) was found in 17/56 patients at presentation

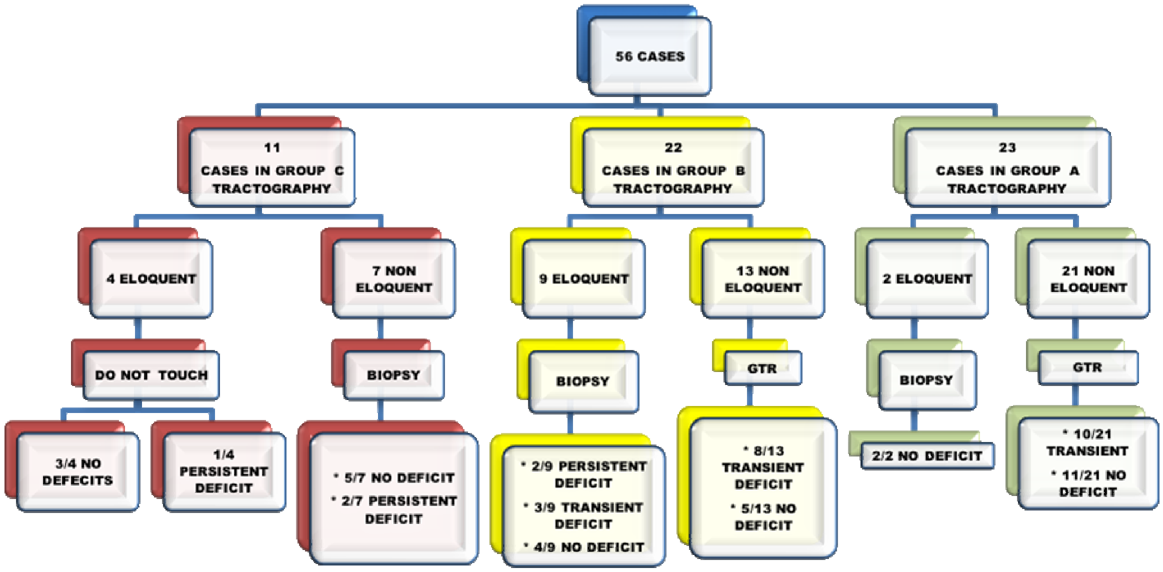

Figure 2. Decision tree algorithm and Focal neurological deficit results

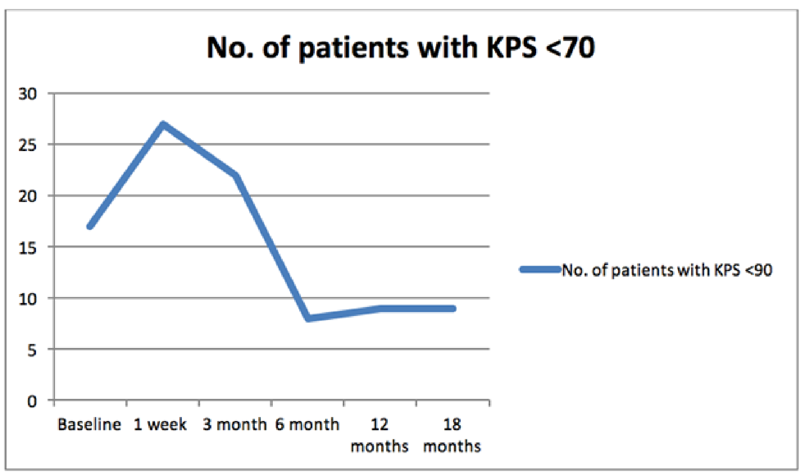

Figure 3. KPS follow up for patient cohort.

however at 18 months follow up 9/56 cases had KPS < 70 (dependable). *Figure 3*

Gross total resection was decided in 34/56 cases. No patients in this group had persistent deficit after 6 months follow up with 18/34 patients having transient deficit, gross total resection was achieved in 100% of cases when decided with the confirmation of intraoperative ultrasound and neuronavigation. On the other side in the biopsy group 4/18 (25%) patients had persistent deficit. Of note 1/4 patients in the do not touch group had persistent deficit in the follow up period.

DISCUSSION

Low-grade gliomas are not uncommon, representing 15% of all primary brain tumors.(Nitta *et al.,* 2015) They are typically affecting patients at a younger age than high-grade gliomas (4th vs 6th decade of life).(Grier and Batchelor, 2006) While LGGs are diffusely distributed along a variety of supratentorial regions,(Gutmann, 2008; Dudley *et al.,* 2015) they have a particular predilection for the insula and supplementary motor area.(Sanai, Chang and Berger, 2011) In our series we had 15/56 (27%) cases in eloquent areas of the brain, with all cases in the supra tectorial region of the brain.

Most patients initially present with relatively good neurological function, and seizures are the most common symptom at presentation (80%) (Bondy *et al.,* 2008; Sanai, Chang and Berger, 2011; Youland *et al.,* 2013). Seizures were the most common presentation in our cohort in which 93% of the patients presented with seizures.

For the past century, The 2016 World Health Organization Classification of Tumors of the Central Nervous System is both a conceptual and practical advance over its 2007 predecessor, the 2016 WHO classification of CNS tumors uses molecular parameters in addition to histology to define many tumor entities, thus formulating a concept for how CNS tumor diagnoses should be structured in the molecular era (Louis *et al.,* 2016).

As such, the 2016 CNS WHO presents major restructuring of the diffuse gliomas, consequently; a diagnosis of fibrillary astrocytoma is no more of use and a standalone nomenclature of gemistocytic astrocytoma is no more accepted, that might explain the constant use of the ", NOS = not otherwise specified" in all our cases. The 2016 edition has added newly recognized neoplasms, and has deleted some entities, variants and patterns that no longer have diagnostic and/or biological relevance (Louis *et al.,* 2016). Glioblastoma, IDH-wild type and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M–mutant; RELA fusion–positive ependymoma; medulloblastoma, WNT-activated and medulloblastoma, SHH-activated; and embryonal tumor with multilayered rosettes, C19MC-altered (Louis *et al.,* 2016).

Molecular based pathological diagnosis was not available at the time of conduction our study. In our study the most common histological subtype was the diffuse astrocytoma NOS followed by the gemistocytic, NOS type. Histological upgrading of LGGs is a special consideration for these patients, as it carries a dramatically worse prognosis. Of note, the documented incidence of LGG transformation ranges from 17% to 73% in recent clinical published studies suggesting a high level of variability, however there is inclination in the management decision towards radical excision (Dirks *et al.,* 1994; Piepmeier *et al.,* 1996; Afra and Osztie, 1997; Lote *et al.,* 1997; van Veelen *et al.,* 1998; McGirt *et al.,* 2008; Smith *et al.,* 2008; Chaichana *et al.,* 2010).

It is generally believed that successful surgical resection of these tumors has a significant effect on the rate of overall survival (OS) progression free survival and seizure control (Claus *et al.,* 2005; Suneja *et al.,* 2012; Bai *et al.,* 2015), however these kind of tumor have a preference to evolve in eloquent brain areas making the gross total resection not amenable in all cases (Claus *et al.,* 2005; Suneja *et al.,* 2012; Bai *et al.,* 2015). Recent advances in neurosurgical techniques with intraoperative MRI allowed for real time imaging of the surgical resection procedure and maximizing the safe extent of resection (Claus *et al.,* 2005; Suneja *et al.,* 2012; Bai *et al.,* 2015). Different techniques have been used to assets the degree of resection and provide intraoperative data, which help to guide the navigation during surgical resection, DTI tractography have been also applied to the intraoperative neuronavigation systems (Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, 2001; Nimsky *et al.,* 2004, 2011; Reinges *et al.,* 2004; Englot *et al.,* 2011, 2012; Bai *et al.,* 2015). We upload DTI tractography and functional images into our neuronavigation system, allowing us to navigate through surgical resection and detect eloquent nearby tract and functional brain areas more precisely.

To date no available evidence base management algorithm appears to be present in literature. (Berger MS, Deliganis AV, Dobbins J, 1994; Berger, 1996; Schulder and Biswal, 2003; Bauman *et al.,* 2009; De-Benedictis, Moritz-Gasser and Duffau, 2010; Hosoda *et al.,* 2011) we tried to classify LGG patients into three categories for management purposes; GTR, Biopsy and adjuvant therapy or Do not touch (observational). We applied preoperative functional MRI images and DTI tractography both to help in decision-making and intraoperative guidance when decided. We achieved GTR in all our cases when decided, in a mean follow up of 41.5 months we had improvement in baseline KPS score in 15% of cases, with no cases having any deterioration of KPS than base line. There was persistent focal deficit in 5/56(9%) cases.

In review of literature (LeRoux *et al.,* 1989; McGirt *et al.,* 2008; Sanai N, 2008; Souna *et al.,* 2010; Kuhnt *et al.,* 2011; Sanai, Chang and Berger, 2011) most authors inclined towards radical treatment of the LGG even if incidentally discovered. In our series we included only symptomatic cases,however outcomes observed in our study for patients with permanent deficit is 9%falling in the range 6.5-17 % of permanent deficit reported in literature.(Duffau *et al.,* 2005)

We found that DTI tractography and Functional images data does affect patient outcomes in which all permanent deficit were reported in patients of Group C tractography (which we describe as transected DTI tract images)(Angelini *et al.,* 2012) however in the group A and B there was no reported cases of permanent deficit. Still implementation of more LGG assessment advanced techniques would encourage development of more mature treatment paradigms.

CONCLUSION

Still with the relatively few number of cases in our study and the lack of randomization we cannot conclude an evidence based treatment algorithm but our results highlight the importance of patient selection in management of radiological LGG by different surgical techniques or even just observation tailoring the strategy depending on the preoperative functional radiological data. A lot of controversy still in management of asymptomatic incidentally discovered LGG, which needs further research.

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