Running Title: Seizure and Cognitive Outcomes after Resection of Glioneuronal Tumors in Children

Authors: Andrew M Faramand [1], Nicola Barnes [2], Sue Harrison [2], Roxanna Gunny [2], Tom Jacques [3], Zubair M Tahir [2], Sophia M Varadkar [2,3], Helen J Cross [2,3,4], William Harkness [2], Martin M Tisdall [2,3].

   1-University College London, London, UK.
   2- Great Ormond Street Hospital, London, UK.
   3- UCL Great Ormond Street Institute of Child Health, London, UK.
   4-National Centre for Young People with Epilepsy, Lingfield, UK)

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Corresponding Author:

Mr Martin Tisdall MBBS BA MA MD FRCS(SN)
Consultant Paediatric Neurosurgeon, Great Ormond Street Hospital
Honorary Senior Lecturer, UCL Great Ormond Street Institute of Child Health
Honorary Consultant Neurosurgeon, National Hospital for Neurology and Neurosurgery
Great Ormond Street

London WC1N 3JH, United Kingdom
Tel 020 7405 9200 Ext 8862
Fax 020 7813 8279
martin.tisdall@gosh.nhs.uk

Key points:

- The majority of children with epilepsy secondary to glioneuronal tumours will eventually require surgical resection (80.5%).
- Eighty percent of patients in this cohort where seizure free at final follow up.
- Complete tumour resection is associated with the highest chance of seizure freedom.
- A shorter duration of epilepsy and an older age at seizure onset are associated with higher cognitive functioning.

- **Summary:**

Objective: Glioneuronal tumors (GNT) are well recognized causes of chronic drug resistant focal epilepsy in children. Our practice involves an initial period of radiological surveillance and anti-epileptic medications with surgery being reserved for those with radiological progression or refractory seizures. We planned to analyze the group of patients with low grade GNT aiming to identify factors affecting seizure and cognitive outcomes.

Methods: We retrospectively reviewed the medical records of 150 children presenting to GOSH with seizures secondary to GNT. Analysis of clinical, neuroimaging, neuropsychological, and surgical factors was performed to determine predictors of outcome. Seizure outcome at final follow up was classified as either seizure free (group A), or not seizure free (group B) for

patients with at least 12 months follow up post-surgery. FSIQ was used as a measure of cognitive outcome.

Results: 86 males and 64 females were identified. Median pre-surgical FSIQ was 81. One hundred and twenty one patients (80.5%) underwent surgery. Median follow up after surgery was 2 years with 92 patients (76%) having at least 12 months follow up after surgery. Seventy four patients (80%) were seizure free, 18 (20%) continued to have seizures. Radiologically demonstrated complete tumour resection was associated with higher rates of seizure freedom (p= 0.026). Higher pre-surgical FSIQ was related to shorter epilepsy duration until surgery (p=0.012), and to older age at seizure onset (p=0.043).

Significance: A high proportion of children who present with epilepsy and GNT go on to have surgical tumor resection with excellent post-operative seizure control. Complete resection is associated with a higher chance of seizure freedom. Higher pre-surgical cognitive functioning is associated with shorter duration of epilepsy prior to surgery, and to older age at seizure onset. Given the high rate of eventual surgery, early surgical intervention should be considered in children with continuing seizures associated with GNT.

Key words: Epilepsy surgery, Paediatric Neurosurgery, bening tumours, dysembryoplastic neuroepithelial tumours, gangliogliomas.

- **Abbreviations**

AED- Antiepileptic Drugs

DNT- Dysembryoplastic Neuroepithelial Tumours

FCD- Focal Cortical Dysplasia

FSIQ- Full Scale Intelligence Quotient

GG- Ganglioglioma

GNT- Glioneuronal Tumours

GOSH- Great Ormond Street Hospital

- **Introduction**

    Glioneuronal tumours (GNT) consist of a mixture of glial and neuronal cells and are a common cause of chronic focal epilepsy in children[1]. The majority of GNT consist of gangliogliomas (GG) and dysembryoplastic neuroepithelial tumours (DNET) [2]. Epilepsy secondary to these tumours is often resistant to pharmacological treatment [3] and in this context, surgical tumour resection may provide effective seizure control[4, 5].

    The surgical management of GNT is typically influenced by oncological factors (i.e. tumour progression) and/or the treatment of the associated epilepsy [6]. The main goal of epilepsy surgery is resection of the epileptogenic zone whilst minimising post-operative deficits [7]. Effective seizure control rates can be achieved post-surgery when concordance exists between clinical, electrophysiological, and radiological data[8].

    Rates of complete seizure freedom postoperatively vary from 62% [9] to 100% [10]. The duration of epilepsy until surgery, degree of tumour resection, seizure type, and age at seizure onset have all been suggested to be factors relating to seizure outcome after surgery for GNT [3, 4, 11, 12].

    The focus of the current published literature is seizure outcome after surgery. There is limited understanding of the factors that predict seizure outcome after surgery and little data available on the pre

and post-operative cognitive functioning in children and adolescents with GNT [13-15]. Identifying the predictors of seizure, and cognitive, outcomes is paramount for patient selection and pre-surgical counselling.

The aim of this study is to describe the experience and outcomes of paediatric patients presenting to our institution with GNT associated epilepsy and to identify factors associated with postoperative seizure and cognitive outcomes: thereby improving patient selection and identifying the optimal time point for surgical intervention.

• **Methods:**

➢ **Patient Selection:**

A single institution retrospective analysis was approved by local review board. Patients presenting to Great Ormond Street Hospital (GOSH) with seizures associated with presumed GNT were identified by probing the electronic clinical document database using the search terms "glioneuronal tumours", "ganglioglioma", and "dysembryoplastic neuroepithelial tumour", "epilepsy". The search returned 3500 documents, which were carefully examined.

Clinical, neuroradiological and neuropathological data were collected. Requirements for inclusion in the study were:

1- Seizures as the presenting symptom.

2- Complete clinical data sets available.

3- Preoperative MRI available for review.

4- Presumed GNT identified on radiological imaging or

5- GNT confirmed on post-operative histopathology in those who underwent surgical resection.

> ➢ **Pre-Surgical Evaluation:**

All children underwent routine pre-surgical evaluation. This included full history and neurological examination, video EEG telemetry, and magnetic resonance imaging (MRI). In children with sufficient cognitive ability, the Wechsler Intelligence Scale for Children (WISC IV) was used to assess neuropsychological status and calculate full scale intelligence quotient (FSIQ).

Potential surgical candidates were discussed at a multi-disciplinary epilepsy surgery meeting to determine suitability for surgery. Current practice at GOSH consists of an initial period of radiological surveillance and medical management, with surgery being reserved for those with tumour progression on serial radiological evaluation or medically refractory seizures (defined as the failure of 2 or more appropriately selected anti-epileptic drugs (AED) to control seizures [16]). The decision to offer surgery is based around predicted seizure outcome from presurgical data and surgical risks related to tumour location.

> ➢ **Surgical Procedure:**

Surgical resection was performed at GOSH by one of two consultant paediatric neurosurgeons (MT and WH). The aim of surgery was removal of the lesion identified on MRI and in selected cases guided by intraoperative electrocorticography (Ecog). The tumour was resected and the adjacent tissue was removed up to the next pial border so long as presumed eloquent cortex was not involved in the resection. After surgery, the tissue was submitted for histopathological examination.

> ➢ **Follow up and Seizure Outcome:**

All patients who underwent surgery were seen in the outpatient clinic by the operating neurosurgeon 6 weeks after the operation for general examination. Further clinical review was carried out at 6 and 12 months postoperatively. A repeat MRI was performed to determine the presence of any

residual tumour 3-12 months after surgery. Post-surgical neuropsychological tests were performed 12 months after surgery to assess post-operative neuropsychological state.

Seizure outcome was recorded using the Engel classification [17]. Weaning of medication was usually initiated 6-24 months post- surgery depending on the degree of seizure control.

> ### Statistical Analysis:

To assess the relationship between seizure outcome and pre and post-operative factors, the patients were categorized into two groups (group A corresponding to Engel class I and group B corresponding to Engel class II, III, and IV). Statistical analysis was carried out using IBM SPSS statistics software version 22. Univariate Logistic regression was used to analyse the effects of age at seizure onset, degree of resection, tumour location, histopathology, duration of epilepsy until surgery, and age at surgery, on seizure outcome. Univariate linear regression analysis was used for the analysis of epilepsy duration, and age at seizure onset on cognitive outcomes. A P-value < 0.05 was considered statistically significant and correction for multiple comparisons was not performed.

• Results:

> ### Demographics and Clinical Characteristics

190 patients presented to GOSH with seizures secondary to GNT in the period between 1995 and 2015. Forty patients were excluded because of incomplete data; Out of the 40 patients, 21 had underwent resection, however no operative or follow up data was available. Six patients were controlled on medications, however they transitioned to adult neurosurgery and had no follow up information. In 13

patients, no documents were available for review. A total of 150 patients were included in the study. Eighty-six patients were males, and 64 were females (male to female ratio 1.4:1). The presenting symptom in all the cases was epilepsy. Seizure type was reported in 125 patients: focal seizures with impaired awareness were the seizure type in 70 patients (56 % of cases), 53 patients had focal seizures with unimpaired awareness (35% of cases), and 2 patients had infantile spasms. Evolution to a bilateral convulsive seizure was reported in 30 patients (20%).

The median age at seizure onset was 3 years (interquartile range (IQR) 1-7). Figure 1 shows age distribution at seizure onset. The median age at the time of presentation to GOSH was 7.3 years (IQR 4-13). The median duration from seizure onset until presentation to review at our institution was 2.8 years (IQR 1-5.4).

Figure 1

MRI scans revealed that the tumour was located in the temporal lobe in 66%, the frontal lobe in 16%, the parietal lobe in 11%, and the occipital lobe in 7%. Figure 2 illustrates tumour location frequency.

Figure 2

Some cases with GNT found on histopathological assessment of surgical specimens were previously given alternative radiological diagnoses at presentation. Initial radiological diagnosis consisted of 100 cases of DNT (66.2%), 20 GNT (13.2%), 17 FCD (11.3 %), 8 GG (5.3%), 3 hippocampal sclerosis (2%), and 1 case of hamartoma (0.7%).

➢ **Surgical Resection and Histopathology**

Of the 150 patients reviewed, 121 patients (80.5 %) underwent surgery, 18 patients (12%) had adequate seizure control on medication without surgery, and 11 (7.3%) were undergoing presurgical evaluation at the time of this data collection. Of the patients who did not undergo surgery, 2 of them were

deemed to be unsuitable candidates for surgery due to the proximity of the tumour to the eloquent cortex. Therefore of those who had completed evaluation 121/139 (87%) of those presenting with GNT associated epilepsy went on to surgery.

In those who underwent surgery, the indication for surgery was for seizure control in 111 patients (91.7% cases), whilst surgery was performed in 10 patients (8.3% of cases) for tumour progression. Patients who underwent surgery were resistant to a median of 4 AED before surgery, (range 2-5 drugs). The most commonly used AEDs were carbamazepine, lamotrigine, sodium valproate, and levetiracetam.

Median duration from seizure onset until the time of surgery was 4.2 years (IQR 2.2-8). The median age at time of surgery was 9.3 years (IQR 6-14). The median duration from first presentation to our institution until surgery was 1.5 years (IQR 0.5-2.5). Figure 3 shows patient distribution based on the time from seizure onset until surgery. Figure 4 shows the distribution of age at time of surgery.

Figure 3 and Figure 4

Histopathology confirmed the tumour as DNT in 47 patients (38.8%) and GG in 44 cases (36.3%), GNT not otherwise specified in 28 (23.1%), 1 desmoplastic ganglioglioma and 1 angiocentric glioma. Additional pathology was found in 9 cases (FCD in 5 (5.0%), and hippocampal sclerosis in 4 (3.3%) cases).

➢ **Post-Operative Complications**

6 patients (4.5% of cases) suffered post-operative complications. 3 patients had transient blurring of vision, 1 patient developed a subdural empyema, and 2 patients developed pseudomeningocoele which required drainage via needle aspiration. No patients suffered from permanent motor or visual deficits.

➢ **Post-operative MRI**

At 12m following surgery, MRI in 56 cases (45.8%) showed no tumour residuum, whereas in 50 (40.8%) patients residual tumour tissue was seen. 14 patients (11.7%) were yet to undergo imaging, or their MRI results were not available for review at the time of this data collection.

➢ **Follow up and Seizure Outcome**

Median follow up was 2 years (IQR 1-3.3) 92 patients (76% of cases) had at least 12 months of follow up after surgery. Seizure outcome was assessed for those with at least 1 year of follow up. Engel classification was as follows: Engel class I (group A) in 74 patients (80.4%), and Engel classes II-IV (group B) in 18 patients (19.6%).

At last documented follow up, AED were discontinued in 39 (42.9%) seizure free patients. The remaining 53 Engel class I patients (58.1%) continued taking 1 or 2 AED.

Twelve patients underwent reoperation at a median of 5.3 years after the first procedure. Eight patients underwent a second procedure due to seizure recurrence, and 4 patients had surgery because of growth of tumour residuum. Of the 8 patients who underwent a second operation for seizure recurrence, 4 achieved seizure freedom. The remaining 3 patients achieved seizure freedom after a third procedure (2 underwent further resection and 1 underwent gamma knife radiosurgery). In one patient seizures remain poorly controlled, and further evaluation is ongoing.

➢ **Relation of Pre-Operative Parameters to Seizure Outcome**

Eighty two patients with at least 12 months post-operative follow up had post-operative MRI reports available. Thirty eight patients had complete resection of the tumour, whereas 44 patients had some residual tumour. Of those with complete resection, 33 (86.8%) patients were classified in group A, and 5 patients (13.2% of cases) were classified in group B. Of those with residual tumour on post-operative MRI,

31 patients (70%) were classified as group A, and 13 patients (30%) were classified as group B. Patients with complete resection were more likely to be seizure free (P = 0.026).

The median duration from epilepsy onset until surgery was 5.4 years in patients who were in group A at last follow up (minimum 12 months follow up). Patients in group B had a median duration of 4 years from seizure onset to time of surgery. No relationship was identified between duration of epilepsy until surgery and seizure outcome (P= 0.46). The age at seizure onset (P=0.992), and the age at surgery (P=0.117) did not correlate with seizure outcome.

Seizure type was reported in 73 patients with at least 12 months of follow up after surgery. Thirteen patients had seizures that evolved to a bilateral convulsive seizure. Seizure outcome did not correlate with seizure type or evolution (P= 0.58, 0.69, respectively). Sixty patients with DNT and 32 patients with GG were followed up for a minimum of 12 months. No correlation was established between histopathology and seizure outcome (P= 0.89). Table 1 summarizes the pre-surgical factors and seizure outcome after surgery.

Table 1. Pre-surgical factors and seizure outcome after surgery in patients with at least 12 months of follow up

➢ **Neuro-Psychological Findings**

Pre-operative FSIQ was available for 90 patients. Median FSIQ was 81 (IQR 71-95). Distribution of FSIQ is shown in Figure 5. Higher pre-operative FSIQ was related to shorter duration of epilepsy until surgery (coefficient =-1.7, P=0.012). Higher pre-operative FSIQ was also related to an older age at seizure onset (coefficient= 1.4, P= 0.043). Tumour location and age at time of surgery did not correlate with FSIQ outcomes.

Figure 5

FSIQ 1 year post-operatively was available in 41 patients. Median post-op FSIQ was 86 (IQR 16). Post-operative FSIQ was significantly influenced by pre-operative FSIQ (P=0.008). As demonstrated in **supporting document 1**, 25 patients (61%) had a median gain of 8 points in FSIQ, 15 (36.5%) patients had a decline in FSIQ post-operatively, median of 6 points, and 1 (2.5%) patient had no change in FSIQ post-operatively.

Duration of epilepsy until surgery, age at seizure onset, and degree of resection did not significantly predict post-operative FSIQ.

The difference between pre and post-operative FSIQ (post-op FSIQ – pre-op FSIQ) did not correlate with the duration of epilepsy until surgery and the age at seizure onset (p>0.05).

- **Discussion**

In this study, the natural history and outcomes of children presenting to GOSH with epilepsy due to GNT are presented. Surgical resection of these tumours provides children with a high chance of seizure cure. Complete tumour resection is the main predictor for seizure freedom after surgery. Factors such as the duration of epilepsy until surgery, age at seizure onset, and tumour location are not found to influence seizure freedom rates after surgery. An older age at seizure onset, and a shorter epilepsy duration until surgery are associated with higher preoperative FSIQ.

❖ **Surgery and Post-Operative Complications**

The vast majority (>80%) of patients presenting with GNT associated epilepsy at our institution go on to have surgical treatment. Epilepsy control is the main therapeutic goal for surgical resection of GNT[3, 18, 19]. In our series, 91.7% of patients underwent surgery for seizure control. Additionally, the remaining 8.3% of patients underwent surgery because of tumour growth detected with serial neuroimaging. No malignant transformation was observed in this series. However, even though the biological nature of these tumours is usually benign, particularly when patients present with epilepsy, cases of tumour growth or malignant transformation have been reported[3, 4, 20]. Additionally we found that longer duration from onset of epilepsy to surgery was associated with lower preoperative FSIQ. These data suggest that resective surgery in this group should be offered sooner and should be discussed with patients and families at diagnosis rather than waiting until current definitions of drug resistance are met.

Forty six percent of patients had complete resection on postoperative imaging. This is low compared to some reports in the literature. Sandberg et al. 2005 report that gross total resection of the tumour was achieved in 100% of patients included in their analysis[10]. The surgical policy deployed avoids following the tumour into the potentially eloquent white matter tracts. In particular the majority of these cases involved the temporal lobe and these tumours often extend into the temporal stem. These portions of the tumours were not resected in order to reduce the risk of adverse events and with the understanding that the white matter prtion of the tumour is considered unlikely to be part of the epileptogenic zone. This strategy is supported by the high rates of seizure freedom presented in this study. Complications following surgery were recorded in 4.5% patients. Complication rates reported in the literature following resection of GNT range between 0% and 52%[13, 21]. The low complication rate reported in this series compares favourably with the literature. The most common post-operative complication reported was transient visual deficit. Visual deficits is the most commonly reported complication in the literature, particularly when the tumour is located in the temporal lobe[22].

❖ **Seizure Outcome**

In this study, seizure freedom rate at final follow up was 80.4%. This is consistent with the literature reported seizure free rates of 62% to 100%[9, 10].

In our series, 42.9% of seizure free patients were successfully weaned off medications at final follow up. Aronica et al. 2001 report that 20% of their patients were successfully weaned off medications [3] whereas Lee et al. 2009 reported 70%[21]. However, using the percentage of people off medications may not be an accurate representation of treatment success. This is because the decision to wean AED is influenced by many factors such as the preference of the treating physician, age of the patient and duration of follow up[23].

In our series, 8 patients underwent a second operation for seizure control, of which 4 patients achieved seizure freedom. The practice at GOSH is that patients with recurrent seizures after the first surgery and the presence of residual tumour on imaging, would undergo repeat evaluation to determine the appropriateness of revision surgery. Ramantani et al. 2013 report that patients who undergo a second operation due to seizure recurrence have a higher chance of achieving seizure freedom (3 patients required a second operation, the 3 patients became seizure free after surgery). They recommend that re-operation should occur at the youngest age possible, to profit from the high level of plasticity in the developing brain to compensate for any neurological deficits[24].

❖ **Prognostic Factors**

In our series, complete resection with no residual tumour on postoperative neuroimaging was the only factor associated with higher rates of seizure freedom. Higher rates of seizure freedom after complete tumour resection have been previously demonstrated in adult and paediatric populations with lesional epilepsy, including DNT and GG[9, 14, 25]. However, in contrast to our findings, Kirkpatrick et al. 1993 did not find the completeness of resection to be related to seizure outcome [13].

Blumcke et al. 2002 also found that seizure outcome was influenced by the resection of the epileptogenic lesion and not by complete resection of the tumour[18]. Nevertheless, Giulioni et al. 2005

report higher rates of seizure freedom compared to Blumcke et al. 2002 despite the resection of the tumour alone (86.6% and 72%, respectively) [26].

Some patients in this study who had complete tumour resection were not seizure free at final follow up. Conversely, another group of patients who were seizure free at final follow up showed residual tumour on postoperative MRI. The rate of complete tumour resection in this series reflects a surgical strategy in the earlier patients to restrict resection to the grey matter (presumed epileptogenic component) of the tumour rather than chasing tumour into the white matter. In some patients, such as those with extension into the temporal stem and basal ganglia, this strategy may reduce surgical risks. Pilcher et al. 1993 found that a group of patients were seizure free after lesionectomy despite the fact that the preoperatively identified epileptogenic lesion was not resected. They propose that whether the surrounding brain tissue needs resection depends on the degree of reorganization that this brain tissue has undergone over time, and its ability to independently produce seizures[27]. Hu et al. 2012 report seizure outcome in 55 patients who underwent surgery for the management of epileptogenic GG. They found no difference in seizure outcome between patients who underwent lesionectomy and patients who underwent resection of the tumour and the surrounding tissue[28].

Complete resection improves seizure outcomes in patients with many brain pathologies, including low grade gliomas, FCD, and cavernous malformations [29]. Aronica et al. 2001 report that residual GG is observed in tumours that undergo malignant transformation. Therefore, complete tumour resection should be pursued whenever possible to optimise seizure control and reduce the risk of future tumour growth or malignant transformation[3, 30]. However, complete resection may be challenging, particularly if the tumour involves or is in close proximity to eloquent brain regions[26].

There was no correlation between seizure outcome and duration of epilepsy. Notably 36 of 44 children with a long history of epilepsy (range 5 years-14 years), were seizure free post-operatively. This finding is in line with the reports by Giulioni et al. 2005, Lee et al. 2009, Ogiwara et al. 2010, and Ramantani et al. 2014 [15, 21, 26, 31]. Some authors report improved seizure outcomes in children who have a

shorter duration of epilepsy prior to surgery[3, 4, 32]. It is worth noting; however, that series containing adult patients are more likely to detect a correlation between epilepsy duration and postoperative seizure outcome. Adult series tend to have a longer epilepsy duration prior to surgery compared to paediatric series. For example, both Morris et al. 1998 and Luyken et al. 2003, who did report a correlation, had a mean epilepsy duration prior to surgery of 11.8 years and 12 years, respectively [4, 20]. In contrast, no correlation between epilepsy duration and seizure outcome was reported by Ramantani et al. 2014 or Fernandez-Garcia et al. 2011 with a mean duration of epilepsy of 3.8 years and 4.7 years, respectively [14, 15].

Age at seizure onset did not influence the rate of seizure cure in contrast to Aronica et al. 2001. However, in line with our results, Aronica et al. 2001 found that the age at operation also did not influence seizure outcome[3].

Seizure outcome did not differ according to location of the tumour. Of the reviewed literature, only Chang et al. 2010 found that tumours located in the temporal lobe were associated with better seizure outcome[12]. Patients with seizures that evolved to bilateral convulsive seizures did not have worse seizure outcome. This is in contrast to the findings by Morris et al. 1998, Aronica et al. 2001, and Minkin et al. 2008 [3, 4, 33].

There was no statistically significant difference in seizure outcome according to the subtype of GNT. Clusmann et al. 2002 found that patients with underlying GNT were more likely to be seizure free after surgery compared to patients with an underlying glioma (astrocytoma, oligoastrocytoma, and glioblastoma)[19].

❖ **Neuro-psychology**

In our series, the group of patients with a longer duration of epilepsy prior to surgery had a lower preoperative FSIQ. This is in line with published reports by Cormack et al. 2007, Garcia-Fernandez et al.

2011 and Ramantani et al. 2014 who report worse cognitive outcomes in patients with lower age at seizure onset [14, 15, 34]. Neuropsychological studies have demonstrated that an earlier age at seizure onset is associated with poorer cognitive functioning[35]. Vendrame et al. 2009 analysed cognitive outcomes in children younger than 3 years old who were diagnosed with epilepsy. They found that an earlier age at seizure onset and a longer duration of epilepsy are associated with worse cognitive outcomes. They also added that long term epilepsy may reduce brain plasticity, and as such a longer epilepsy duration may limit possible post-operative gains in cognitive function[36]. Skirrow et al. 2011 studied the long term cognitive outcomes (> 5 years) in children who underwent surgery for resistant temporal lobe epilepsy. They report gains in FSIQ in children who underwent resection. This was attributed to the cessation of AED in seizure free patients following surgery[37].

In addition to the lower FSIQ observed with longer epilepsy duration, Garcia-Fernandez et al. 2011 report better cognitive outcomes in patients who undergo surgery before seizures become medically intractable[14]. Surgical intervention early after the onset of seizures may protect against the known deleterious effects of chronic epilepsy on the developing brain [38].

In this study, the median duration between seizure onset and referral to the epilepsy surgery unit was 2.5 years. In 2012, The National Institute for Health and Care Excellence (NICE) published recommendations encouraging early referral for children with epilepsy, because of the profound developmental, behavioural, and psychological effects that may be associated with continuing seizures. Such recommendations can help shorten the interval between seizure onset and time of surgery, and so minimize the possible decline in neuro-cognitive functions.

Post-operative FSIQ was found to be significantly dependant on pre-operative FSIQ results. 1 year post-operative neuro-psychological evaluation revealed FSIQ improvement in 25 patients, a decline in 15 patients, and no change in 1 patient. However, a longer duration of follow up may be required to determine the eventual change in FSIQ. Skirrow et al. 2011 studied the long term intellectual outcomes after temporal lobe epilepsy surgery in children. They found that improvements in intellectual function

need at least 6 or more postoperative years to be observed[37]. Our data show that resection of brain tissue in this group of patients does not appear to have a short term deleterious effect on cognitive function.

- **Future Directions and Study Limitations**

This study is limited by its retrospective nature. Performing randomized controlled trials to compare outcomes across a homogenous group of patients can provide stronger conclusions and recommendations. The variable intervals between pre-surgical evaluation and follow up, reduce the ability to effectively compare seizure outcomes among patients.

It has also been reported that seizure freedom declines with time [9]. However, because seizure outcomes were reported at variable follow up points, this potential drop in seizure freedom over time is complex to study. Reporting seizure outcomes at specific follow up intervals for all patients might help overcome this limitation.

The proportion of seizure free patients is high, as such the ability to detect statistically significant difference between seizure free and not seizure free groups is reduced. Studying a larger patient population could provide further insights.

This study analyses seizure and cognitive outcomes in GNT patients who underwent surgery for drug resistant epilepsy. Reports suggesting better outcomes in patients undergoing surgery before seizure refractoriness is established are interesting. Trials should be considered to determine if better outcomes are achieved when surgery is performed earlier, before drug resistance is established.

FSIQ was used to measure cognitive outcomes in children. However, behavioural problems are commonly seen in patients with both epilepsy and brain tumours, particularly when the tumour is located in the frontal lobe [39]. As such, our neuro-psychological results are limited by the limitations of the measure (FSIQ) used to detect them. A study focusing on the different cognitive and behavioural aspects in children with GNT might provide more information on the short and long term effects of epilepsy on the developing brain. In addition, longer duration of follow up is expected to shed more light on the long

term cognitive outcome and the change after seizure control and cessation of AEDs, as the effect on FSIQ after surgery in other patient groups has been shown to become apparent only after some time > 5 years [37].

- ## Conclusion

The vast majority of children with GNT presenting with seizures are refractory to AED and go on to have surgical treatment .Our results support surgical intervention to treat epilepsy due to GNT in paediatric patients. This is supported by the high seizure freedom rate (80.4%), the low post-operative morbidity (4.5%), and the high rate of stopping AED in patients who are seizure free (42.9%). Early and complete tumour resection, when possible, should be performed to optimize seizure and more importantly cognitive outcomes. A shorter epilepsy duration prior to surgery is associated with better preoperative cognitive function.

STATEMENT: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Pre-surgical factors and seizure outcome after surgery in patients with at least 12 months of follow up

Variables	Total	Group A	Group B	P-value
Number (% of total)	92 (100%)	74 (80.4%)	18 (19.6%)	
Sex (M/F)	52/40	45/29	7/11	0.098
Median age at seizure onset (years)	3.25	3.25	3.25	0.992
Median age at first assessment (years)	7.5	7.5	7.5	0.861
Median age at surgery (years)	8.9	8.9	8.9	0.117
Median duration from epilepsy onset until surgery (years)	4.13	5.4	4	0.46
Tumour location (temporal/extra-temporal)	65/72	55/22	13/5	0.87
Side of tumour (right/left)	40/52	29/45	11/7	0.93
Secondary generalization	13	10 (76.9%)	3 (23.1%)	0.694
Degree of tumour resection (total/partial/unknown)	38/44/10	33/31/10	5/13/0	0.026