Mixed Neuronal-glial Tumors
Common benign tumour types: Histological features and molecular characterisation
Nice 9th Sept, 2019
Maria Thom, UCL London
WHO (2016) classification: Neuronal and mixed neuronal-glial tumours

Dysembryoplastic neuroepithelial tumour
  Gangliocytoma
  Ganglioglioma

Anaplastic ganglioglioma
Dysplastic cerebellar gangliocytoma
Desmoplastic infantile astrocytoma and ganglioglioma
Papillary glioneuronal tumour
Diffuse leptomeningeal glioneuronal tumour
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma
Paraganglioma
General concepts of neuronal/glial tumours

- **Neuronal differentiation**
  - Demonstrated histologically
  - Supported by immunohistochemistry
    - Mature neuronal markers: NeuN, synaptophysin, neurofilament,
    - Immature neuronal markers: MAPs, Nestin, βIIIITubulin etc

- **Common clinical features**
  - Low grade (many WHO grade I)
  - Low incidence of anaplastic transformation
  - Present with epilepsy
  - Often in temporal lobe

- **Molecular profile**
  - Distinct from IDH1/2 wild type gliomas: e.g MAPK pathway mutations
CLINICAL PRESENTATIONS & PATHWAYS

LOW GRADE GLIONEURONAL TUMOURS

Ganglioglioma
DNT
Pilocytic astrocytoma
PXA, MNVT

Drug resistant
‘Long-term’ focal epilepsy
e.g. TLE
Epileptologist

OTHER PRIMARY CNS TUMOURS

Astrocytic tumours
Oligodendroglial tumours
Glioblastoma
Other gliomas

Neurological
signs/symptoms, short Hx
(± symptomatic seizures)
Neuro-oncologist

Therapy → Optimal seizure control
Tumours low grade / hamartoma-like
Molecular genetics: Not included in current
WHO classification

Therapy → Oncology management
Intermediate/high grade
Molecular genetics: WHO established
diagnostic and prognostic biomarkers
INTEGRATED DIAGNOSIS
e.g. IDH1-wt glioblastoma
Glio-neuronal/ neuronal tumours (GNT)  
WHO 1st → Revised 4th Editions

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<td>Rosette Forming Glioneuronal Tumour</td>
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<td>Multinodular Vacuolating Neuronal Tumour</td>
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<td>Diffuse Leptomeningeal Glioneuronal Tumour</td>
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2020 ?  
More entities to be added or consolidation of tumour types?
GNT: Controversies and challenges

1. Heterogenous appearance / mixed cell composition
   – Small samples, difficult to exclude other LGG
   – Many do not show typical histology (‘non-specific’)
   – Can show composite features of > 1 tumour type
2. New histological variants continue to be described
   – e.g. MNVT, PLNTY
3. When molecular analysis is required and what tests?
4. What makes them epileptogenic?
   – Is there neurodevelopmental abnormality / dysplasia
5. Identification of tumours at risk for progression/anaplastic transformation
Dysembryoplastic Neuroepithelial Tumor: A Surgically Curable Tumor of Young Patients with Intractable Partial Seizures

Report of Thirty-nine Cases

Catherine Daumas-Duport, M.D., Ph.D., Bernd W. Scheithauer, M.D., Jean-Paul Chodkiewicz, M.D., Edward R. Laws, Jr., M.D., and Claude Vedrenne, M.D.

Departments of Pathology (CD-D, CV) and Neurologic Surgery (J-PC), Hôpital Sainte Anne, Paris, France, and Departments of Pathology (BWS) and Neurosurgery (FRL), Mayo Graduate School of Medicine, Rochester, Minnesota

1 = ‘Glioneuronal element’

SIMPLE DNT

2 = Cortical dysplasia

3 = Multinodular architecture

COMPLEX DNT

1 = ‘Glioneuronal element’

1988

2000

‘NON-SPECIFIC’ DNT
DNT: Neuroimaging appearances

**Case 1 TEMPORAL**

- Lack of mass effect
- Cortical based
- Cystic / multicystic
- T2, FLAIR ↑signal
- T1 ↓signal
- Calcification ±
- Enhancement ±
- Lack of surrounding oedema

**Case 2 FRONTAL**

- Wedge shape / ‘transmantle sign’

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*Pathology–MRI Correlations in Diffuse Low-Grade Epilepsy Associated Tumors*

Aliya Al-Hajri, MD, Salim Al-Mughairi, MD, Alyma Somani, PhD, Shu An, PhD, Joan Liu, PhD, Anna Miserocchi, MD, Andrew W. McEvoy, FRCS, Tarek Yousry, FRCP, Chandrashekar Hoskote, FRCP, and Maria Thom, FRCPath
Dysembryoplastic Neuroepithelial tumour

Midline location of ‘DNT’ (46 cases reported)
- Lateral ventricle (3), 3rd Ventricle (10)
- Septum pellucidum (23)
- Caudate (8), Thalamus (2)
Dysembryoplastic Neuroepithelial tumour (syn. DNT DNET)

Macroscopic
Size: Few mm → several cm
Can be exophytic
Often cystic and ‘gelatinous’
Dysembryoplastic Neuroepithelial tumour (syn. DNT  DNET)
DNT: Different low power appearances and correlations with subtypes

- **Cortical expansion** → **SIMPLE TYPE**
- **Multinodular** → **COMPLEX TYPE**
- **Diffuse/ cortical growth ± rarefied white matter** → **NON SPECIFIC TYPE**
Dysembryoplastic Neuroepithelial tumour (syn. DNT  DNET)  
Typical COMPLEX DNT

40 F  
Seizure since age 5  
MRI - ? DNT  
Operated July 2019

NeuN
• Shows architecture of tumour /relationship with cortex
• For the analysis of cortical dysplasia
Histological Features of DNT

Oligodendroglial like cells

Pleomorphism +/-

Glioneuronal element (entrapped ‘floating’ neurones)

NeuN

Alveolar pattern

NeuN

Calcification

Rosettes
Other histological Features of DNT

EXOPHYTIC GROWTH

VENTRICULAR EXTENSIONS

PIGMENTATION

GRANULAR BODIES AND ROSENTHAL FIBRES
**DNT: IMMUNOHISTOCHEMISTRY PANELS**

### Immunohistochemistry used:
- To demonstrate glio/neuronal differentiation
  - Heterogeneity of labelling is often seen
  - No specific IHC markers for DNT
- To exclude other glioma types (e.g. IDH1 gliomas)

### Table: Immunohistochemistry Panels

<table>
<thead>
<tr>
<th>Group</th>
<th>ANTIBODY</th>
<th>Max % POSITIVITY reported in series</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuronal</td>
<td>MAP2 &gt; NeuN &gt; synapto &gt; Neurofilament</td>
<td>50% &gt; 44% &gt; 28% &gt; 5%</td>
<td>Thom 2011, Wolf 1997, Honovar 1999</td>
</tr>
<tr>
<td>Interneurones</td>
<td>Calbindin &gt; calretinin &gt; Pavalum &gt; GAD</td>
<td>57% &gt; 20% &gt; 18% &gt; 13%</td>
<td>Wolf 1997</td>
</tr>
<tr>
<td>Glial</td>
<td>Olig 2 &gt; GFAP</td>
<td>100% &gt; 21%</td>
<td>Azzarelli 2004, Marucci 2012</td>
</tr>
<tr>
<td>Stem cell</td>
<td>PDGFRβ/α &gt; Nestin &gt; CD34</td>
<td>100% &gt; 86% &gt; 25%</td>
<td>Thom 2011, Stone 2017</td>
</tr>
<tr>
<td>Proliferation</td>
<td>KI67&lt;1%</td>
<td>73%</td>
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</table>

**Immunohistochemistry used:**
- To demonstrate glio/neuronal differentiation
  - Heterogeneity of labelling is often seen
  - No specific IHC markers for DNT
- To exclude other glioma types (e.g. IDH1 gliomas)
DNT : SYNAPTOPHYSIN

↑EXPRESSION IN WHITE MATTER NODULES
↓EXPRESSION IN CORTICAL NODULES
DNT: NEURONAL MARKERS

Inconsistent expression in oligodendroglial like cells
DNT: GLIAL MARKERS

GFAP -

GFAP +/−

GFAP +

OLIG2 +
DNT: STEM CELL AND OTHER MARKERS

NESTIN+

PDGFRB+

CALBINDIN+

NESTIN+

CD34-

CD34+
1. Seizure outcomes
   - Seizure-free + off anti-epilepsy drugs: 86%
   - Seizure-free + on anti-epilepsy drugs
   - Not seizure-free: 14%

2. Residual tumour on MRI
   - Stable
   - Progressive growth
   - Haemorrhage, cystic change

3. Recurrence on MRI
   - Same location
   - Other location

4. True tumour Progression in confirmed DNT
   - Higher grade (WHO III/ IV)

Residual tumour
- Satellite lesions
- Presence of adjacent dysplasia
- Long pre-operative seizure period

Malignant transformation of DNT
- Rare event (8 reports in literature)
- Risk factors
  - Residual tumour
  - Older age
  - Adjuvant treatments

Bonney et al., 2016 (29 series / 756 cases)
Initial presentation at age 12 with focal epilepsy
Worsening of seizures control: Temporal lobectomy carried out at age 56 after MRI and EEG.

Seizure free 3 years
Then recurrence noted on MRI
Anaplastic glio-neuronal tumour
Rosette-like pattern
Focally high Ki67 index.

First surgery, age 56

DNT
Ki67 5% in areas
IDH1-ve
No LOH 1p/19q

2nd surgery, age 59

TUMOUR PROGRESSION IN DNT
Malignant Transformation of a Dysembryoplastic Neuroepithelial Tumor (DNET) Characterized by Genome-Wide Methylation Analysis

Dieter Henrik Heiland, MD, Ori Staszewski, MD, Martin Hirsch, MD, Waseem Masalha, MD, Pamela Franco, MD, Jürgen Grauvogel, MD, David Capper, MD, Daniel Schrimpf, Dr. sci. hum., Horst Urbach, MD, and Astrid Weyerbrock, MD
GANGLIOGLIOMA

FIRST DESCRIBED
Courville, 1930

WHO GRADE I

Macroscopic
Well delineated, cystic or solid

MRI
T1: solid component iso to hypointense variable contrast enhancement
T2: hyperintense, cystic component peritumoural oedema uncommon
T2* calcified areas

Intraoperative smear
Toludine Blue
GANGLIOGLIOMA: HISTOLOGICAL CRITERIA

**Neuronal component**
Dysmorphic, clustered, binucleate
Prominent aggregates or **focal**

**Glial component**
Oligodendroglial
Pilocytic like
Fibrillary astrocytic

**Growth pattern**
Nodules
Single mass
Diffuse pattern in cortex with satellite nodules

GANGLIOCYTOMA – NO GLIAL COMPONENT (RARER)
NEURONAL MARKERS

Highlight abnormal morphology, distribution

MAP2

SYNAPTOPHYSIN

NEUROFILAMENT

SMI32

NeuN +/-

Ki67

Calbindin ++
Value of CD34 immunolabelling in Ganglioglioma

- Sensitivity / specificity:
  - 70-80% of GG tumours
  - CD34 expressed in other CNS tumours: PXA, some (giant cell) glioblastoma and 20% of DNT
  - Also in Focal cortical dysplasia IIB

- Useful to demonstrate:
  - Patterns and extent of infiltration in hippocampus and cortex
  - Peri-lesional satellite nodules in cortex
  - Dysmorphic neurones often NEGATIVE
1. Seizure free: 63-100% 
Follow up 1 - 10 years 
(Boney et al., meta-analysis of 19 series)

Seizure freedom
Increased extent of resection
Shorter duration of epilepsy
Younger age at surgery

2. Recurrence / Progression to anaplastic Ganglioglioma GIII

Relatively uncommon (1-3% of cases)
- GG III May arise de-novo
- Increased anaplasia in glial component
- ↑ Ki67
Molecular prediction for progression?
Case: 21 Female

Onset of seizures age 18

Focal and generalised seizures

↑frequency recently

GANGLIOGLIOMA, WHO GRADE I, BRAF MUTANT SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)
Main histological differential diagnosis

- DNT
  - Oligodendroglioma
  - Pilocytic astrocytoma
  - Low grade diffuse glioma
  - Ganglioglioma
  - Oligodendroglial hyperplasia
  - Neurocytoma
  - RGNT

- Ganglioglioma
  - Cortical infiltration by
    - Oligodendroglioma
    - Astrocytoma
  - PXA
  - Focal cortical dysplasia

- Gangliocytoma
  - Focal malformation / focal cortical dysplasia
LOCAL MOLECULAR ALGORITHM FOR ADULT GLIOMAS (2019)

IDH (R132H) MUTANT → IDH1 NEGATIVE

IDH R132H mut ATRX loss → CDKN2A/B No loss
- No further testing
- MA
- CNV
  - Low
  - High
  - All
  - AllII

IDH R132H mut ATRX retained → CDKN2A/B No co-del
- No further testing
- A_IDH
- GBM_IDH
- Oligo
- A_IDH
- A_GBM
- Others

CDKN2A/B Hom loss → IDH1/2 mut; ATRX loss
- A_IDH
- No further testing
- MA
- CNV
  - Low
  - High
  - All
  - AllII

1p/19q → IDH1/2 mut; ATRX retained 1p/19q co-del
- CDKN2A/B
- No loss
- Hom-del
- MA
- CNV

GBM IDH wt → IDH1, IDH2; H3 K27 [H3.3 K27M IHC], H3 G34; BRAF V600 [BRAF V600E IHC]; TERT; EGFR amp, CDKN2A/B; [BRAF Fusion]
- No further testing

GBM IDH wt → BRAF V600E
- No further testing
- MA
- MA

No mutations; +/- ATRX (depending on demographics, location, clinical need)

Histology | IHC | Sequencing, CNA | Diagnosis | Methylation array | CNV | Methylation class | No further testing

National Hospital for Neurology London, Acta Neuropath Comms, Jaunmuktane et al., 2019
BRAF V600E mutations:
- More frequent in GG > classical DNT
- ↑ temporal lobe tumours
- No clear prediction of outcome
- Correlated with CD34+
- MTOR activation

BRAF IHC typically highlights dysmorphic neurones

IHC for BRAF V600E ↑ sensitive than sequencing
Other BRAF mutations/fusion/copy number alterations reported in GG and DNT

Published series GG and DNT (classical)
FGFR1 and other MUTATIONS: DNT and GG

FGFR1 (mutations, duplications, SNV, fusions)
41-62% of DNT (classical): 5% ganglioglioma

(Qaddoumi et al., 2016 et, Rivera et al., 2017, Fina et al., 2017)

Less frequent mutations/fusions reported in DNT:
FGFR2, PDGFRA, NAV1-NTRK2, MYB-MAML2, PIK3CA

TWO MOLECULAR GROUPS
Mutations
Methylation
Gene expressions

Mainly
GG
Mainly
DNT

Molecular Classification of Glioneuronal Tumours

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<th>Demographic</th>
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<th>Group 2</th>
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<td>FGFR1 mutation</td>
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<tr>
<td>Gene Expression</td>
<td>Astrocytic</td>
<td>Oligodendrogial</td>
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STONE et al., 2018
DNT and GG: Surrogate Immunohistochemistry markers for mutation

**Stone et al., 2018**
CCND1, CSPG4, PDGFRA
In DNT group

**Pekmezci et al., 2018**
phospho-ERK in MNVT with MAP kinase signalling pathway

**Thom et al., 2018**
PDGFRB ↑ in DNT not GG

**Fina et al., 2017**
FGFR1 mutated DNT
MOLECULAR TESTING IN SUSPECTED LOW GRADE GG AND DNT

When and What to test?

When?
1. Specific patient features (older age, odd location, atypical MRI, short clinical history)
2. Histological features...
   1. Atypical - suggesting transformation from GI/II
   2. Small sample – diagnosis not certain
   3. Mixed histological tumour types
   4. Non-specific/ diffuse growth pattern

What Molecular tests
IDH1 / ATRX, BRAF V600E IHC

- IDH1mut / ATRX loss
  - CDK2NA/B MA
    - All, AIII, GBM
- IDH1mut / ATRX ret
  - lp/19q LOH
    - Oligo II
- BRAF V600E mut
  - No further testing
    - GG or DNT
  - Prediction for Grade III?
    - CDKN2A/B Deletion
      - K27M H3F3A mutation
      - TERT mutation
- ALL negative
  - NGS: FGFR1, MYB1 and rarer mutations
  - Methylation array
The DNA methylation-based (Heidelberg) CNS tumor classifier (www.molecularneuropathology.org).

Recognises 82 distinct CNS tumour types including LGG/DNT, GG/HemPA, LGG/GG

Capper et al., Nature 2018
Application of methylation array (MA): Case 1

52 M
4/12 TLE
↑4 seizure / day
MRI - LGG

Illumina Infinium HumanMethylation450 (450 k) array assessing 482,421 CpG sites

Histological diagnosis:
LGG / glio-neuronal tumour

Classifier:
Glioblastoma IDH wild type

Low grade glioma
Diffuse
No mitosis
Ki67 <5%

No mutations
IDH1, BRAF, ATRX, H327K
No LOH 1p/19q
No TERT mutation, No EGFR amplification

No mutations

2 years later
Progressed to Histological GBM/ CD34+

OUTCOME MA: change tumour grade
Application of methylation array (MA): Case 2

30 M, Temporal lobe epilepsy

**Methylation profiling report**

**Supplier information**
- Sample identifier: NH19-544
- Sentrix ID: 203145740002_R01C01
- Material type: FFPE DNA
- Gender: NA
- Supplier diagnosis: -

**Automatic prediction**
- Array type: EPIC
- Material type: FFPE DNA
- Gender: male

**Brain tumor methylation classifier results (v11b4)**

**Methylation classes (MCs with score >= 0.3)**
- Calibrated score: 0.98
- Interpretation: match

**Class descriptions**
- Methylation class low grade glioma, ganglioglioma: The methylation class "low grade glioma, ganglioglioma" is primarily comprised of tumors with a histological diagnosis of ganglioglioma, but to a lesser extent also dysembryoplastic neuroepithelial tumors. Tumors are exclusively located supratentorially. Median age is 20 years (range 7 to 49). Alterations of the MAPK pathway are frequent in this class, and in particular BRAF V600E mutation is highly recurrent. Most cases show a flat profile in copy number analysis, with rare cases showing gain of chromosome 7 and/or X (both in around 20% of cases).

**Copy number variation profile**

**Methylation class low grade glioma, Ganglioglioma**

**Histology dx:**
- LGG / glioneuronal NEC
- CD34+
- No dysmorphic neurones
- No classical DNT features
- No mutations IDH1, BRAF, ATRX
NEW ENTITIES

40 year old Male
Seizure onset age 18, Operated 2019

VACUOLATED NEURONES

Immunoprofile
Neuronal +
Oligodendroglial +
Astroglial +
Stem cell markers +
Low Ki67

VACUOLATED NEURONES
Over 90 cases reported in the literature (2013-2018)
Average age at diagnosis = 41 years
Temporal lobe most common site
Indolent and no growth
Some asymptomatic / incidental findings on MRI

**TUMOUR OR MALFORMATION?**

**Molecular genetics**
No common mutations: *IDH1, BRAFV600E, mTOR, FGFR1, MYBL*

**Recent reports with NGS**

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<tr>
<th>Mutations</th>
<th>NUMBER OF CASES</th>
<th>STUDY</th>
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<td><em>SUFU</em>, Ex8, codon108 G→T</td>
<td>1/9 cases</td>
<td>Thom et al., 2018</td>
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<tr>
<td><em>FGFR2-ZMYND11</em> fusion</td>
<td>1/6 cases</td>
<td>Choi et al., 2019</td>
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<td><em>BRAF</em> p. L597R</td>
<td>8/8 cases</td>
<td>Pekmezci et al., 2018</td>
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<td><em>BRAF</em> p. G469S</td>
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<td><em>MAP2K1</em> pQ56P</td>
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<tr>
<td><em>FGFR2-INA</em> gene fusion</td>
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</table>

No methylation class
A neuroepithelial tumor showing combined histological features of dysembryoplastic neuroepithelial tumor and pleomorphic xanthoastrocytoma—a case report and review of the literature.

Ishihara K, Tone R, Kobayashi K, Yoshida K, Hino H.
Department of Pathology, Saitama Medical University, Saitama, Japan. ishihara@saitech-med.ac.jp

Composite ganglioglioma/dysembryoplastic neuroepithelial tumor: a clinicopathologic study of 8 cases
Richard A. Prayson MD*, Karl M. Napekoski MD

Pilocytic astrocytoma as a predominant component of a recurrent complex type DNT

Krzysztof Zakrzewski, Wojciech Biernat, Paweł P. Liberski, Lech Polis, Emilia Nowostawska

A peculiar histopathological form of dysembryoplastic neuroepithelial tumor with separated pilocytic astrocytoma and rosette-forming glioneuronal tumor components

Ewa Matyja, Wiesława Grajkońska, Przemysław Kumiec and Andrzej Marchel

Clinical Short Communication
PIK3CA mutation in a mixed dysembryoplastic neuroepithelial tumor and rosette forming glioneuronal tumor, a case report and literature review

PXA + GG
PXA + DNT
GG + DNT
PA + DNT
PA + DNT + RGNT
DNT + RGNT
PLEOMORPHIC XANTHOASTROCYTOMA: SHOULD IT BE CLASSED AS A NEURONAL/GLIAL TUMOUR?

Evidence:
- Frequent neuronal differentiation
- Hybrid forms with GG
- Young adults, temporal lobe, cystic
- CD34 expression patterns similar to GG
- BRAF V600E mutations (50-78%)

Homozygous deletion of CDKN2A (50% PXA III)
Methylation class for PXA (Heidelberg classifier)

BRAF V600E confirmed on seq
Methylation analysis report:
Class: Pleomorphic Xanthoastrocytoma
BRAF mutation negative

Tumors without classic histological features of PXA → PXA methylation class
- Monomorphic diffuse gliomas
- Ganglionic tumors
- Astroblastoma-like
- Glioblastoma-like
- ATRT-like features

‘Molecular PXA’
SUMMARY AND FUTURE DIRECTIONS

- In many cases the histology diagnosis of Ganglioglioma and DNT is typical and these tumours are low grade and nonprogressive.
- Increasing application of molecular biology will:
  - Improve classification of glio-neuronal tumours, particularly in contentious cases (Integrated diagnosis)
  - Identify tumours at risk of progression
  - Influence management including identification of alternative treatments (e.g., BRAF, FGFR, mTOR inhibitors)
  - Better understanding of tumourigenic/epileptogenic pathways/mechanisms

<table>
<thead>
<tr>
<th>Histology Group</th>
<th>Classical DNT</th>
<th>Ganglioglioma</th>
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<tbody>
<tr>
<td>Grade</td>
<td>Grade I</td>
<td>Grade I</td>
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<tr>
<td>Molecular</td>
<td>FRGFR1 mutation</td>
<td>BRAF mutation</td>
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<td>Methylation group</td>
<td>DNT</td>
<td>Ganglioglioma</td>
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<td>Ganglioglioma, BRAF mutant, Grade 1</td>
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Acknowledgements