Pathological Brain Tumour Diagnosis: Then and Now

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Cure for Life Foundation Brain Cancer Research Visiting Academic
Pathological Analysis – Then and Now

• Classification - what kind of tumour is it?
• Grading - how bad is it?
• What is the molecular subtype?
• Is there a therapeutic target?
ca. 1865
RUSTY-CAPPED SPARROWS
sexes similar

winter

summer

juv.

CHIPPING SPARROW

for comparison with winter Chipping Sparrow, above

juv.

CLAY-COLORED SPARROW
(See p. 283)

imm.

FIELD SPARROW

SWAMP SPARROW

juv.

RUFIOUS-CROWNED SPARROW

AMERICAN TREE SPARROW
Classic Histopathological Analysis

• Classification - what kind of tumour is it?
• Grading - how bad is it?
Tumour Grading

- I
  Low grade
- II
- III
  High grade
- IV
Grade I  Grade II  Grade III
WHO “Blue Books”
Evolution of Diagnostic Techniques

• Histology
• Histology plus immunohistochemistry
  – e.g. meningioma with EMA
• Histology plus molecular, e.g.
  – Oligodendroglioma with 1p/19q
  – Astrocytoma with p53
  – Glioblastoma with $MGMT, IDH1$
• Molecular plus histology
• Molecular only
Evolution of Diagnostic Techniques

- Histology
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Meningioma – Immunohistochemistry for EMA
Immunohistochemical Profile of Diffuse Astrocytoma

ATRX  p53  Mutant IDH1

A TRX  p53  Mutant IDH1
Infiltrating Edge of Astrocytoma – Mutant IDH1
Histology/Immunohistochemistry

**Advantages**
- Assures presence of diagnostic tissue
- Distinguish tumour from nontumour
- Cheap (sort of)
- Fast (usually)
- Vast past experience
- A surrogate for molecular data in some cases
- Good starting point, context, for molecularly-based studies to subclassify tumor and identify therapeutic targets

**Disadvantages**
- Depends on specimen size and tissue sampling
- Subjective
- Experience dependent
- Broad categorizations (usually)
- No identification of specific treatment targets
Histology/Immunohistochemistry

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- Assures presence of diagnostic tissue
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Pathological Analysis – Now (and Future)

- Classification - what kind of tumour is it?
- Grading - how bad is it?
- What is the molecular subtype?
- Is there a therapeutic target?
1p-19q test
Proposed Mechanism For Derivative Chromosome In Oligodendroglialomas

Griffin et al.. J Neuropathol Exp Neurol 2006;65:988-994
Proposed Mechanism For Derivative Chromosome In Oligodendrogliomas

KRAS Exon 2 Point Mutation (p.G12D)
KRAS Exon 2 Point Mutation (p.G12D)
Molecular Analysis

- **Advantages**
  - Fast (potentially)
  - Identification of specific molecular changes
    - Ideally, identifies responsive (lastingly) therapeutic targets

- **Disadvantages**
  - Cost, but rapidly getting cheaper
  - Requires special equipment and experience not available in many laboratories
  - May tax laboratories trying to meet demands for multiple new tests for multiple organ systems
  - Potentially overwhelming amounts of data
  - Most abnormalities of no proven specific utility
Few CNS Tumours Have Therapeutically Exploitable Molecular Targets

- Pilocytic astrocytoma (*BRAFv600E* mutation: Dabrafenib, Vemurafenib)
- Ganglion cell tumours (*BRAFv600E* mutation: Dabrafenib, Vemurafenib)
- Pleomorphic xanthoastrocytoma (*BRAFv600E* mutation: Dabrafenib, Vemurafenib)
- Subependymal giant cell astrocytoma (*mTOR* inhibitors: Rapamycin, Everolimus)
- Medulloblastoma (*shh* inhibitor: LDE or Vismodegib)
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<th>TUMOUR TYPE</th>
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**Legend:**
- **POS**
- **NEG**
- **NOT DONE**
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<th>TUMOUR TYPE</th>
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- **IDH1/2**: MUT. (POS), MUT. (NEG), GAIN 7 (POS), CODELET. (POS), ATRX (POS), ALT (POS), T.B.N. (NOT DONE), T.B.N. (NOT DONE)
- **p53**: MUT. (POS), GAIN 7 (POS), CODELET. (POS), ATRX (POS), ALT (POS), T.B.N. (NOT DONE), T.B.N. (NOT DONE)

**Legend**:
- **POS**: Green
- **NEG**: Red
- **NOT DONE**: Grey
Requirements for Development and Implementation of Molecular Markers

- Innovation
- Acceptance
- Communication
- Coordination
- Prioritization

- Realism
  - Number of specific tests requested, and projected volume of each
  - Cost/benefit analysis
- Financial support for development and maintenance