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• I have consulting/advisory board agreements with:
  • VBL, Bayer, Amgen, Del Mar

• I have pre-clinical laboratory and/or clinical trial support from the following companies:
  • Novartis, VBL, Bayer, BMS, Medicenna, Ipsen, Deciphera, Epicentrix, Orbus, Amgen, Istari, Oncoceutics,
‘Brain Tumor’ is not a diagnosis
Your team >>>> tumor

• Interactive session to help with questions you may have.

THE TEAM:
• Neurosurgeon
• Radiation oncologist
• Medical or Neuro-oncologist
• Neuropathologist
• Neuro-radiologist
• QOL, palliative care team
• Hospice care
• Survivorship clinic
• Neuropsychology/Psychology
• Caregiver programs
Glioma introduction

- Astrocytoma
- Oligodendroglioma
- Ependymoma
- *Malignant* Gliomas:
  - Grade III:
    - anaplastic astrocytoma
    - anaplastic oligodendroglioma
    - anaplastic ependymomas
  - Grade IV:
    - glioblastoma (GB)
• Male:female = 1.6
• More common in whites than blacks or Asians

About 17,000/year
Epidemiology:

- only known risk: exposure to ionizing radiation
- no other environmental exposures including cell phone use, infection or trauma has been shown to have an impact
- genomic variants that confer increased glioma risk:
  - telomerase reverse transcriptase (TERT, rs2736100),
  - epidermal growth factor receptor (EGFR, rs2252586, and rs11979158)
  - coiled-coil domain containing 26 (CCDC26, rs55705857)
  - cyclin-dependent kinase inhibitor 2B (CDKN2B, rs1412829)
  - tumor protein p53 (TP53, rs78378222)
  - regulator of telomere elongation helicase (RTEL1, rs6010620)
  - Pleckstrin Homology-Like Domain, Family B, Member 1 (PHLDB1, rs498872)
Primary CNS tumours – genetic predisposition

The majority of tumours are sporadic

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Nervous system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis type 1</td>
<td>NF1</td>
<td>17q11</td>
<td>Neurofibromas, malignant nerve sheet tumour, optic nerve gliomas, astrocytoma</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2</td>
<td>22q12</td>
<td>Bilateral acoustic schwannomas, multiple meningiomas, astrocytomas, glial hamartoma</td>
</tr>
<tr>
<td>von Hippel–Lindau Syndrome</td>
<td>VHL</td>
<td>3p25</td>
<td>Haemangioblastomas</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1</td>
<td>9q34</td>
<td>Subependymal giant cell astrocytoma, cortical tubers</td>
</tr>
<tr>
<td></td>
<td>TSC 2</td>
<td>16p13</td>
<td></td>
</tr>
<tr>
<td>Li–Fraumeni</td>
<td>p53</td>
<td>17p13</td>
<td>Astrocytomas/primitive neuroectodermal tumour</td>
</tr>
<tr>
<td>Cowden’s disease</td>
<td>PTEN</td>
<td>10q23</td>
<td>Dysplastic gangliocytoma of the cerebellum</td>
</tr>
<tr>
<td>Turcot’s syndrome</td>
<td>APC</td>
<td>5q21</td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td></td>
<td>HMLH1</td>
<td>3p21</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td></td>
<td>HPSM2</td>
<td>7p22</td>
<td></td>
</tr>
<tr>
<td>Naevoid basal cell carcinoma syndrome (Gorlin syndrome)</td>
<td>PTCH</td>
<td>9q22</td>
<td>Medulloblastoma</td>
</tr>
</tbody>
</table>
Diagnosis: Imaging in Neuro-oncology

- Present with any number of symptoms (focal v diffuse)
- Imaging
  - CT
  - MRI with and without contrast
  - DWI/ADC
  - Perfusion Imaging
  - Magnetic resonance spectroscopy imaging (MRSI)
  - PET
  - DTI
  - MEG
- Many more experimental imaging techniques
New 2016 WHO Classification “phenotype/genotype”

Diffuse astrocytic and oligodendrogial tumours – Introduction

This 2016 update of the 2007 WHO classification incorporates well-established molecular parameters into the classification of diffuse gliomas, and this nosological shift has impacted the classification in several ways. Most notably, whereas all astrocytic tumours were previously grouped together, now all diffuse gliomas (whether astrocytic or not) are grouped together, on the basis of not only their growth pattern and behaviours, but more pointedly of their shared IDH1 and IDH2 genetic status. From a pathogenetic point of view, this provides a dynamic classification based on both phenotype and genotype; from a prognostic point of view, it groups tumours that share similar prognostic markers; and from the eventual therapeutic point of view, it will presumably guide the treatment of biologically similar entities.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Astrocytoma</th>
<th>Oligoastrocytoma</th>
<th>Oligodendroglioma</th>
<th>Glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH status</td>
<td>IDH mutant</td>
<td>IDH wild-type</td>
<td>IDH mutant</td>
<td>IDH wild-type</td>
</tr>
<tr>
<td>1p/19q and other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>genetic</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>parameters</td>
<td></td>
<td></td>
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<tr>
<td>ATRX loss*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mutation*</td>
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</tr>
<tr>
<td>1p/19q codeletion</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Diffuse astrocytoma, IDH mutant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma, IDH mutant and 1p/19q codeleted</td>
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<td></td>
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</tr>
</tbody>
</table>

* = characteristic but not required for diagnosis

Fig. 1.01 Diffuse gliomas: from histology, IDH status, and other genetic parameters to WHO diagnosis.
H&E staining of HGG

Normal brain

Grade III oligo

Grade III astrocytoma

Grade IV/GBM
Histopathology, Glioblastoma

- Infiltrative
- Pleomorphic, hypercellular
- Visible mitotic figures
- Microvascular hyperplasia
- Pseudopalisading Necrosis
Prognostic Factors for HGG

• Age
• Performance status
• Extent of resection
• Molecular and cytogenetic markers
  – Methylation of $MGMT$ promoter
  – IDH-1 (or IDH-2) mutation
  – H3k27
What is *MGMT* promoter methylation?

- *MGMT* is the gene encoding MGMT, a.k.a. O\(^6\)-methyl-guanine-DNA methyltransferase
- MGMT is a DNA repair protein: transfers a methyl group from guanine to itself
- Methylation of the *MGMT* promoter prevents expression of MGMT, limiting DNA repair ability of cell
Treatment Milestones in Neuro-Oncology

Approvals

1970
- Lomustine
- First US Commercial CT
- Levin Criteria: CT scans

1980
- Carmustine
- First US Commercial MRI

1990
- Gliadel Wafer
- Macdonald Criteria: MRI + steroids; WHO Pathology Criteria

2000
- TMZ Relapsed AA Accelerated Approval
- TMZ 1L GBM
- RANO

2010
- Avastin rGBM
- Novo TTF

Technology Advances

AA = Anaplastic Astrocytoma.; 1L=first-line; RANO=Response Assessment in Neuro-oncology.
Treatment Paradigm
Goals of Surgery

- To provide a diagnosis, and to allow for molecular/cytogenetic analyses
- To relieve increased intracranial pressure
- To improve symptoms and increase survival, but this is tricky to prove…
  - No randomized trials completed or planned, and size of such a trial would be substantial
  - Nonrandomized trials all suffer from selection bias
  - No clear standard for evaluating extent of resection: Surgeon’s impression? Post-op MRI?
Rapid Tumor Progression?  
Or Pseudo-progression\textsuperscript{1,2,3} ...?

- Up to half of GBM patients have increased enhancement on first post-RT MRI
- Of those patients, $\frac{1}{3}$ to $\frac{1}{2}$ will stabilize or improve if continued on TMZ
- Physiologic/Metabolic imaging not always helpful

\begin{itemize}
  \item MRI + contrast
  \item MR perfusion
  \item $^{[18}F\text{FDG PET}$
\end{itemize}

\textsuperscript{1}Brandes, \textit{JCO} 2008  
\textsuperscript{2}Taal, \textit{Cancer} 2008  
\textsuperscript{3}Chamberlain, \textit{J Neurooncol} 2007
Imaging Challenge: Pseudoprogression

Treatment choices at progression

- Repeat resection
  - +/- Carmustine wafers (Gliadel)
  - +/- Follow with change in chemotherapy
- Bevacizumab single agent
- Novo-TTF/Optune
- Re-challenge with chemo
- Re-irradiation
- Radiosurgery
- Next generation sequencing
- Clinical trials
Metastatic Disease

- Leptomeningeal Metastases
- Brain Metastases
- Spinal Cord [& cauda equina] compromise
- 100,000+ cases per year
Leptomeningeal Disease

- PRIMARY TUMOURS OF CNS
  - PNETs, GCTs, Ependymoma, Oligodendroglioma, GBM

- SECONDARY INVOLVEMENT
  - Leukaemia / Lymphoma
  - Melanoma
  - Lung Cancer [esp small cell]
  - Breast Cancer*
  - Prostate Cancer*
Leptomeningeal Disease

• Symptoms can be non-specific and variable
• Mainly due to effects of tumour on nerve roots, direct infiltration of cord & brain or hydrocephalus
• Most have symptoms/signs at more than one site
  - Headache
  - Cranial or spinal nerve pain/dysfunction
  - Nausea/Vomiting
  - Weakness
• Early recognition important
CSF Cytology

LP not always safe [or appropriate]
Only ~50% pickup with 1 sample [high false negative]
Complementary to MR imaging
Leptomeningeal Disease

- Treatment depends on patient & tumour factors
- Traditionally a terminal event in solid tumours
- Can still be cured in some chemo/radiosensitive tumours
- Will be seen increasingly in younger patients without evidence of systemic disease as newer agents control disease outside of the blood brain barrier i.e. sanctuary site disease
Brain Metastases
Brain Metastases

• ~ 10X more common than primary CNS tumours
• Most common in terminal phase of disease
• Historically steroids +/- whole brain RT
• Can be presenting feature [5%+] of cancer – 50% of time primary found [usually lung]
• Again changing natural history – are we starting to see a new group of patients?
Brain Metastases: Epidemiology

**Primary Tumor** | **Relative Prevalence of Brain Metastases***
---|---
Colon: 5% | Annual U.S. incidence: > 170K  
Ratio Mets/Primary: 10:1  
All Cancer Patients: 15 - 30%  
Autopsy incidence: 10 - 30%  
Mean age: 60 years  
Median survival: 4-6 months
Melanoma: 9% | 
Unknown primary: 11% | 
Other known primary: 13% | 
Breast: 15% | 
Lung: 48% | 

*Incidence increasing with better systemic Rx and improved survival*

2001:2656-2670
Brain Metastases

Symptoms

- About 2/3 symptomatic at some point
- Typically slow, but can be acute e.g. bleed
- Seizures uncommon < 20%
- Raised ICP – headache, confusion, vomiting, lethargy
- Focal features – hemiparesis, visual field defects, ataxia
Imaging and Treatment
Brain Metastases

Investigations

• CT
• MR [20% solitary lesions on CT are multiple]
• Systemic investigations [if unknown primary]
• Biopsy if indicated

Treatment

• Patient factors
• Tumour factors
• Usually palliative
Brain Metastases

Treatment

• Resection
• Radiosurgery
• Adjuvant whole brain RT [prophylactic in SCLC]
• Whole Brain RT
• Best Supportive Care
• ? Chemotherapy, immunotherapy, clinical trials
Factors Used to Assess Therapy

- Number of metastases
- Size of lesion(s)
- Location
- Neurological deficits
- Age / KPS
- Primary tumor / stage
- Extracranial disease
- Patient’s input
Neuro-Oncology
Brain Metastases

Treatment

• Resection of solitary [1 – 3] metastasis
  • Large symptomatic metastasis/metastases causing mass effect or hydrocephalus
  • May improve survival – studies show +ve benefit, overview no overall advantage over WBRT, but fewer neurological deaths, increased time patient remains independent, no significant additional toxicity
  • Risk of bleeding/bleeding e.g. melanoma
  • Radio resistant tumours e.g. melanoma, renal cell & colorectal
  • Selected patients only
  • Beware post fossa mets – some strong suggestions of increased leptomeningeal mets – up to 35%
Neuro-Oncology
Brain Metastases

Treatment

• Radiosurgery
  • Single metastasis [1 – 8]
  • Never tested head to head with surgery, but considered same efficacy
  • Care with post-treatment oedema
Different linear accelerator/radiosurgery units
Neuro-Oncology
Brain Metastases

Conclusions
• Likely increasing numbers of patients with metastatic CNS disease
• Younger & fitter [& more demanding] than before
• Need better strategies for treatment i.e. optimise therapeutic ratio [max control v min effect on QOL]
Questions?
What brings you meaning and significance?
Insight, compassion, Wisdom
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