“What’s new in the genetics and treatment of brain tumours in children and adults?”

David D. Eisenstat, MD, MA, FRCPC
Director, Division of Pediatric Hematology, Oncology & Palliative Care
Professor, Departments of Pediatrics and Medical Genetics, University of Alberta
Muriel & Ada Hole Kids with Cancer Society Chair in Pediatric Oncology
Consultant, Neuro-Oncology, Cross Cancer Institute
Lecture Objectives

1) An overview of childhood and adult brain tumours

2) How has progress has been made “one child at a time”?  
   - the example of medulloblastoma and clinical trials

3) What’s new in diagnosis and therapy?  
   - the impact of cancer genetics and targeted therapies
Primary Brain Tumours - Epidemiology

- ~24,000 new cases (USA)
- approximately 2,400/year in Canada
- ~18,000 deaths/year due to primary CNS cancer
- incidence 11.5/100,000 (Central Brain Tumor Registry of the USA: CBTRUS)
- 1.5% of all cancers; 2.5% of cancer deaths
- more than 50% are malignant gliomas (adults)
Primary Brain Neoplasia in Adults*

- GBM, glioblastoma multiforme (40%)
- Infiltrative astrocytoma (42%)
- Meningioma (3%)
- Medulloblastoma (2%)
- Ependymoma (3%)
- Mixed oligoastrocytoma (2%)
- Oligodendroglioma (6%)
- Pilocytic astrocytoma (2%)

* Total is > 100% due to rounding.
GBM, glioblastoma multiforme.

adapted from Levin VA et al Cancer: Principles & Practice of Oncology (1997)
Pediatric Brain Neoplasia: Frequency

- GBM, glioblastoma multiforme.
- Low grade astrocytoma
- Anaplastic astrocytoma
- Medulloblastoma (15-20%; 30-40% PF)
- Ependymoma
- Pilocytic astrocytoma
- Meningioma
- Schwannoma
- Germ cell tumor
- Oligodendroglioma
- Brainstem glioma
- AT/RT

Adapted from Levin VA et al. Cancer: Principles & Practice of Oncology (1997)
Epidemiology of pediatric brain tumours – HSC

Pediatric Brain Tumours

- cancer is the most common cause of death in children, after accidents & trauma
- CNS tumours are the 2nd most common cancer in children (20-25%), after leukemia
- incidence may be increasing
- embryonal tumors and low grade astrocytomas are main diagnoses
- often infratentorial
Risk Factors

Ionizing radiation:
- meningioma risk $\uparrow$ 10X
- glioma risk $\uparrow$ 3-7 fold
- latency 10-20 years
WHO: Histological Classification of CNS Tumours

1. Tumours of neuroepithelial tissue
2. Tumours of cranial & spinal nerves
3. Tumours of the meninges
4. Hematopoietic neoplasms
5. Germ cell tumours
6. Cysts & tumour-like lesions
7. Tumours of the anterior pituitary
8. Local extensions of regional tumours
9. Metastatic tumours
Neuroepithelial Tumours

- **Astrocytic:** Astrocytoma, AA, GBM, JPA, PXA, SEGA
- **Oligodendroglial:** Oligodendroglioma, AO
- **Ependymal:** Ependymoma, AE, myxopapillary, subependymoma
- **Mixed gliomas:** Oligoastrocytoma
- **Choroid plexus:** CPP, CPC
- **Neuronal & Mixed:** DNET, ganglioglioma, gangliocytoma
- **Pineal tumors:** Pinealoma, pineoblastoma
- **Embryonal tumours:** Neuroblastoma, retinoblastoma, PNET (medulloblastoma, supratentorial & spinal PNET)
Astrocytomas: Histology

• 1. Cellularity
• 2. Nuclear & Cellular pleomorphism
• 3. Endothelial proliferation
• 4. Mitotic figures
• 5. Necrosis
Astrocytic Tumors: WHO Classification

• I/II  Well-differentiated astrocytoma (15-20%)
• III  Anaplastic astrocytoma (30-35%)
• IV  Glioblastoma multiforme (40-50%)

• I, II  “low grade”
• III, IV “high grade”
Glioblastoma Multiforme (GBM)

Preoperative FLAIR (left) and T1 gadolinium images (right)

Glioblastoma Multiforme (GBM)

Cellularity, vascular proliferation, Necrosis and a high mitotic rate (MIB1/Ki67 immunoreactivity)
Neuroimaging

• CT scan vs. MRI:
  - blood, calcium, bone (CT)
  - white matter, posterior fossa, brainstem, spinal cord (MRI)
  - allergy to contrast, renal toxicity
  - radiation vs. magnetic field

• MRS: tumour vs. normal

• PET scanning: recurrence vs. necrosis
MRI vs PET for Recurrent Glioma

Recurrence

Radiation Necrosis

Prados et al, 1998
Magnetic Resonance Spectroscopy

Bernstein & Berger, 2000
Role of Surgery

- Tissue diagnosis
- Tumor debulking ≠ “cancer surgery”
- Decompress CSF pathways & optic nerves
- Improved results of subsequent therapy
- Reduced drug resistance
- Potential for cure
- Palliation: Second resection alone may prolong survival for a median of 6 months [DeAngelis, 2001]
Radiotherapy

- Conventional radiotherapy
  - 3D conformal techniques/IMRT
  - Hyperfractionation strategies

- Interstitial Brachytherapy

- Radiosurgery:
  - SRS: stereotactic radiosurgery
    - “gamma knife”
  - SRT: stereotactic radiotherapy
Role of radiation

- Prolong survival
- Dose-response for high-grade glioma
  - 45 Gy (13 wks median survival)
  - 60 Gy (42 wks)
- Control local infiltration
- Palliation/symptom control
Chemotherapy

• **Neoadjuvant:** before surgery or radiation
  – tumor is present as a marker of response to therapy
  – end-point: response-rate
  – uncertainty regarding benefit to overall survival

• **Adjuvant:** follows surgery or radiation
  – usually no tumor is present as a biological marker
  – end-point: relapse-free survival
  – uncertainty regarding tumor cell sensitivity

• **Concurrent:** used with surgery or radiation
Chemotherapy: Drug Delivery

- Oral
- Intravenous
- Intra-arterial
- Interstitial (directly into tumor)
- Local therapy: [Haroun & Brem, 2000]
  - 3.85% Carmustine (BCNU) Gliadel-impregnated polymer wafers (FDA-approved); dose-escalation studies (up to 20%)
  - 5FU microspheres as a radiosensitizer
  - other radiosensitizers: IUdR, tirapazamine
Chemotherapy - Limitations

- **Myelosuppression** may limit effective dose (role for high dose chemotherapy and autologous peripheral blood stem cell rescue - HDCT/PSCR in chemosensitive tumors eg. PNET); nb. prior craniospinal XRT

- **Blood-brain barrier (BBB)**

- **Resistance** to alkylating agents (eg. nitrosoureas) by DNA repair proteins such as \( O^6\text{-MGMT} \) (\( O^6\text{-methylguanine-DNA methyltransferase} \))

- **Other mechanisms of resistance:**
  - MDR1, p-glycoprotein, MRP (multidrug resistance protein), mismatch-repair deficiency
Figure 4: Kaplan-Meier estimates of overall survival by MGMT status. Patients with methylated MGMT (A). Patients with unmethylated MGMT (B).
PEDIATRIC CANCER

Cancer is the leading cause of death in children after accidents & trauma

After leukemia, brain tumours as a group are the most frequent diagnosis

Medulloblastoma is the most common malignant brain tumour of childhood

from Prados Brain Cancer (2002)
Leading Causes of Death in Children Age 1-14

- Accidents: 39%
- Cancer: 11%
- Congenital: 8%
- Homicide: 6%
- Heart disease: 4%
- Suicide: 2%

National Center for Health Statistics, 2001
Rarity of childhood cancer has resulted in:

International network of children’s cancer programs which cooperatively studies and manages children’s cancer.

Children’s Oncology Group
Causes

- Less environmental contribution
- Predisposing syndromes:
  - disorders of growth or development
- Adult cancer-predisposing syndromes have cancer as phenotype
- Childhood cancer - predisposition usually part of a recognized syndrome
Difficulties with diagnosis

- Symptoms are common, cancer is not.
- Symptoms are not usually due to cancer.
- Usually diagnosis is not apparent (maybe not even suspected) at first visit.
Medulloblastoma - Prognostic factors

- Medulloblastoma is a treatment responsive disease
- Treatments are multimodality and include surgery, radiation and systemic chemotherapy
- Multi-institutional, cooperative group studies (COG: CCG/POG; SIOP; UKCCSG; HIT; PBTC; Head Start) have made significant contributions
Medulloblastoma - Risk stratification

- **Average risk** 3 yr OS 70-85%
  (> 3 yrs, <1.5 cm² residual tumour, M°)

- **High risk** 50-60%
  (bulky residual tumour, metastatic disease M+)

- **Infants** 30-50%
  (delay, limit or avoid radiation)

- **Recurrent disease** 10-20%
• **Average risk**
  
  - *Reduce dose* of craniospinal radiation (36 Gy → 23.4 Gy → 18 Gy age < 8 yr)
  - Implementation of *conformal 3D radiation treatment/planning*
  - Maintain total dose of 55.8 Gy to posterior fossa
  - Maintain adjuvant chemotherapy
  - Role of *pre-irradiation chemotherapy (neoadjuvant)* remains undefined
Medulloblastoma - Principles of therapy

• **Average risk**

  Goal is to *reduce* long-term neuro-endocrine, neuropsychological effects and *maintain* very good rates of EFS and OS without increasing the risk of neuroaxis failure.

  **EFS** = event-free survival  
  **OS** = overall survival
Medulloblastoma - Conformal radiation

Treating the tumour bed rather than the entire posterior fossa with a conformal boost allows for a significant sparing of critical structures with similar failure rates in the posterior fossa (ACNS0331 study).

Reducing craniospinal radiation for average risk patients

Standard (STD) dose 36 Gy vs. reduced (REF) dose 23.4 Gy craniospinal radiation (CSI) without adjuvant chemotherapy:


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<th>STD</th>
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<tr>
<td>5 yr EFS</td>
<td>67±7.4%</td>
<td>52±7.7%</td>
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<tr>
<td>8 yr EFS</td>
<td>67±8.8%</td>
<td>52±11%</td>
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</table>

*For reduced dose CSI without systemic chemotherapy:*
- ↑risk of early relapse
- early isolated neuraxis relapse
- lower 5 yr EFS and OS
Reducing craniospinal radiation for average risk patients

Standard (STD) dose 36 Gy vs. reduced (REF) dose 23.4 Gy craniospinal radiation (CSI) with adjuvant chemotherapy

Packer R et al JCO (1999) pilot study using reduced dose CSI, with adjuvant chemotherapy in 65 patients
5 yr EFS 79±7%

CCG/POG study A9961 built on this treatment strategy (Packer R et al JCO 2006)
5 yr EFS 81%
5 yr OS 86%
A9961 Event Free and Overall Survival – Standard Risk Medulloblastoma

Medulloblastoma – Principles of therapy

High risk


![Graph showing survival rates with different residual tumour sizes](image)

- Residual tumour > 1.5 cm²
Medulloblastoma - Principles of therapy

High risk
identified metastatic stage, residual tumour and age as independent prognostic factors

Age < 3 years
Medulloblastoma - Principles of therapy

High risk


Metastatic disease
Medulloblastoma - Principles of therapy

**Metastatic Disease (M)**

- **M0** no evidence of metastatic disease
- **M1** positive CSF (lumbar, > 2 weeks postop)
- **M2** intracranial dissemination
- **M3** intraspinal dissemination
- **M4** systemic (extraneural) metastases to bone, bone marrow, other
Medulloblastoma - Leptomeningeal disease

Linear contrast enhancement

Nodular enhancement

Meyers SP et al. AJNR 2000
Medulloblastoma - Principles of therapy

- **High risk**
  - **Intensify** systemic chemotherapy with **standard dose CSI**
  - Role of neoadjuvant chemotherapy remains undefined
  - High dose chemotherapy (HDCT) with autologous stem cell rescue (ASCR) is one current treatment strategy
    - feasibility study: Strother *et al* *J CO* (2001)
  - Identify **very high risk** groups prospectively
  - Concurrent **tumour biology** studies in patients treated in an identical manner
Medulloblastoma - Principles of therapy

- **Infants (< 36 mo.)**
  - Redefine role of **radiation**: age, involved field vs. CSI
  - Role of “**second look**” surgery to achieve MRD
  - High dose chemotherapy with autologous stem cell rescue
  - **“Tandem”** transplants
  - Exclude AT/RT (atypical teratoid/ rhabdoid tumour) from cohort
- **Geyer JR et al** /JCO (2005)
  CCG9921 for medulloblastoma: 5 yr EFS 32%
Medulloblastoma in young children has a poor prognosis.
Furthermore, cognitive function in survivors is often impaired owing to treatment with cranial radiotherapy.

This study obtained promising results in children undergoing intensive chemotherapy alone.

Phase II, 43 patients.

- 5 yr EFS 68% OS 77% for M0
- 33% 38% M+
Medulloblastoma – Principles of therapy

Recurrent disease

- HDCT/ ASCR
  - **best candidates** have isolated local relapse, chemosensitive disease and MRD at time of HDCT
  - several conditioning regimens for myeloablation are used
- Phase I (toxicity) and Phase II (response rate) studies
- Targeted therapies: growth factor receptors/ signalling pathways, biological response modifiers (eg. retinoids)
Medulloblastoma - Prognostic factors

All medulloblastomas are W.H.O. grade IV

Histological sub-types:

• Classic →
• Desmoplastic
• Large cell
• Anaplastic

http://www.neuropat.dote.hu/
Medulloblastoma - Histology

Desmoplastic medulloblastoma

photomicrographs courtesy of Dr. Roy Rhodes
Medulloblastoma – Histology

Anaplastic/large cell medulloblastoma

H&E

αSynaptophysin

Moderate or severe anaplasia is associated with aggressive clinical behaviour in patients with medulloblastoma. Eberhart CG et al Cancer (2002)


photomicrographs courtesy of Dr. Roy Rhodes
Microarray analysis can distinguish CNS embryonal tumours

Ramaswamy and Golub *J Clin Oncol* 2002
Microarray analysis can distinguish CNS embryonal tumours

Pomeroy S et al Nature 2002
Microarrays: Distinguishing “classic” from desmoplastic MB

Pomeroy S et al Nature 2002
Microarrays: Distinguishing survivors from treatment failures

Microarrays can distinguish metastatic from non-metastatic disease

MacDonald T et al Nature Genetics 2001
Combining gene expression profiles with clinical parameters

Gene expression Metastatic disease

Only patterns of gene expression was significant by univariate analysis (p=0.03)
Combining gene expression profiles with clinical parameters

Fernandes-Teijeiro et al J Clin Oncol 2004
1. maximal, safe resection to reduce tumour burden
2. reduction of craniospinal radiation (CSI) from 36 Gy to 23.4 Gy to reduce treatment related toxicities of radiation to the CNS
3. conformal radiation therapy/3D planning for boosts to the posterior fossa
4. adjuvant multiagent chemotherapy
Adolescents and Young Adults (AYA)

• Teenagers often present late with advanced signs and symptoms
• Fall “between the cracks” between Pediatrician, GP/Family Physician and Adult health care system
• Less commonly tolerate therapy – more toxicity
• Poor recruitment to clinical trials
• Pediatric vs. Medical Oncologists
Accrual to Cooperative Group Clinical Trials

10/97 to 9/98

Number Patients on Clinical Trials

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< 20 Year Olds = 22% of Total Cooperative Group Accrual
Medulloblastoma in 2nd Decade of Life

Canadian Pediatric Brain Tumor Consortium

72 patients, age > 10 years
11 different treatment protocols
52% standard risk

Favorable prognosis
5 yr OS 78%  PFS 70%

Toxicity significant when compared to younger children
- Ototoxicity 45% (Gr. II+)
- Neurotoxicity 71% (Gr. II+)
- Hematotoxicity 95% (Gr. III+)
- Weight loss >10% 73%
- Feeding intervention 45%

Dose modification 75%
- with protocol discontinuation in 25%

[Tabori U et al. Cancer 103:1874-80, 2005]
Medulloblastoma in 2\textsuperscript{nd} Decade of Life

Canadian Pediatric Brain Tumor Consortium

72 patients, age > 10 years

Patterns of relapse:

Late relapses – median 3.0 years (0.3 – 6.8 yrs)

Time to relapse increased with age

After relapse, patients fare poorly

[Tabori U et al. IJROBP 64:402-407, 2006]
Medulloblastoma – Principles of therapy in children

1. maximal, safe resection to reduce tumour burden

2. reduction of craniospinal radiation (CSI) from 36 Gy to 23.4 Gy to reduce treatment related toxicities of radiation to the CNS

3. conformal radiation therapy/3D planning for boosts to the posterior fossa

4. adjuvant multiagent chemotherapy
Given the heterogeneity of genetic changes within risk groups of children with medulloblastoma, can we personalize therapy?
Molecular predictive markers

A group led by Dr. Michael Taylor at the Hospital for Sick Children identified four molecular sub-groups

Distribution of the four molecular sub-groups by age

Using commercially available antibodies to identify the four molecular sub-groups

Using four antibodies in the Neuropathology laboratory accurately diagnoses the four molecular sub-groups.
Does assignment to a molecular sub-group correlate with patient outcomes?

## Medulloblastoma

<table>
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<th>Subtype</th>
<th>Kool Northcott</th>
<th>Expression characteristics</th>
<th>Genetic characteristics</th>
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<td>Children</td>
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Can we use this new molecular classification to assign treatment? Childhood MB

Potential stratification – childhood medulloblastoma (MB)

Pathological diagnosis = MB

- NO metastatic disease
- AND
- GTR / residual tumor ≤ 1.5cm² MRI
- AND
- Pathology = classic or desmoplastic
- AND
- NO MYC amplification

- Wnt MB
  - Low-risk protocol

- Non-Shh/Wnt MB
  - Standard-risk protocol

- Shh MB
  - Standard-risk protocol + Shh antagonist

- Metastatic disease
- OR
- Residual tumor >1.5cm² MRI
- OR
- Pathology = LC/A
- OR
- MYC amplification

- Shh MB
  - High-risk protocol + Shh antagonist

- Non-Shh/Wnt MB
  - High-risk protocol

- Wnt MB

Medulloblastoma – Prognostic factors

Future cooperative group studies will **stratify** individual patients on the basis of **clinical** and **molecular** markers and assign treatments on that basis.

As well, drugs that target specific growth factor/signalling pathways will be combined with cytotoxic therapies (radiation and chemotherapy) to:

1. **maximize** long-term survival
2. **minimize** short & long-term toxicities
3. **optimize** neurodevelopmental outcomes and quality of life
Late Effects of Therapy

No late effects if no cure

Many childhood cancer survivors look, feel and are normal

Many have, or develop, long term (permanent) or late onset side effects of the disease and treatment
Late Effects of Therapy

Neuropsychologic sequelae

– cranial radiation
– intrathecal chemotherapy
– high dose intravenous chemotherapy
– anatomic location of tumour and role of surgery
– ?10-30% of childhood leukemia survivors
– permanent, irreversible, BUT interventions are possible with appropriate support
IQ continues to fall many years after treatment

Effect of Treatment on Neurocognitive Functions in Infant Medulloblastoma

Late Effects of Therapy

Neuropsychologic sequelae

– prospective assessments by neuropsychologist with liaison to the school system
Late Effects of Therapy

Second malignancies

– genetic predisposition
– carcinogenic chemotherapy/radiation

– incidence depends on specifics of age, therapy, genetic predisposition
Sequential Genetic changes Observed in the Pathogenesis of GBM

Putative GBM cells of origin:
- Neural stem cell
- Transit amplifying cell
- Neural/Glial progenitor
- Astrocyte
- Oligodendrocyte

Primary GBM subtypes:
- Classical
  - EGFR mutation/amplification/overexpression
  - PTEN loss/mutation
  - CDKN2A loss
  - NES overexpression
  - Notch & Shh pathways activation
- Mesenchymal
  - NF1 loss/mutation
  - TP53 loss/mutation
  - PTEN loss/mutation
  - MET, CHI3L1, CD44, MERTK overexpression
  - TNF family & NFκB pathways activation
- Neural
  - EGFR amplification/overexpression
  - Gene signature of normal brain
  - Neuron marker expression
    - (NEFL, GABRA1, SYT1, SLC12A5)
  - Remains to be better defined
- Proneural
  - PDGFRA amplification
  - IDH1 mutation
  - PIK3A/PIK3R1 mutations
  - TP53, CDKN2A & PTEN loss/mutation
  - Proneural marker expression
    - (SOX, DCX, DLL3, ASCL1, TCF4)
  - Oligodendrocytic marker expression
    - (PDGFRA, OLIG2, TCF3 and NKK2-2)
  - HIF, PI3 kinase & PDGFRA pathways activation

Grade II/III Astrocytoma

Sequential genetic alterations & clonal evolution

Van Meir E et al. CA: A Cancer Journal for Clinicians 2010; 60:166-93
RT vs RT + PCV for newly diagnosed malignant glioma (MRC Trial, N = 674)
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jurgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., Rene O. Mirimanoff, M.D. and the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group

N Engl J Med
Volume 352;10:987-996
March 10, 2005
Study Overview

- The combined treatment was safe and reduced the risk of death by 37 percent.

- The results of this trial are encouraging, especially because no previous trial of radiotherapy plus chemotherapy has shown a survival benefit over radiotherapy alone.

- The results with temozolomide should serve as a stepping-stone to much better treatment for brain tumors.
Continuous Temozolomide (TMZ) in Combination With Radiotherapy: Study Schematic [CE.3]

TMZ 75 mg/m² qd x 6–7 weeks

TMZ 200 mg/m² qd x 5 days repeat every 28 days x 6 cycles

Weeks

▲ = Daily treatment

Kaplan-Meier Estimates of **Progression-free Survival** According to Treatment Group

![Graph showing Kaplan-Meier estimates for progression-free survival](image)

- **Radiotherapy**
- **Radiotherapy plus temozolomide**

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Kaplan-Meier Estimates of Overall Survival According to Treatment Group

Overall and Progression-free Survival According to Treatment Group

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<th>Variable</th>
<th>Radiotherapy (N=286)</th>
<th>Radiotherapy plus Temozolomide (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival (mo)</td>
<td>12.1 (11.2–13.0)</td>
<td>14.6 (13.2–16.8)</td>
</tr>
<tr>
<td>Overall survival (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>84.2 (80.0–88.5)</td>
<td>86.3 (82.3–90.3)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>50.6 (44.7–56.4)</td>
<td>61.1 (55.4–66.7)</td>
</tr>
<tr>
<td>At 18 months</td>
<td>20.9 (16.2–26.6)</td>
<td>39.4 (33.8–45.1)</td>
</tr>
<tr>
<td>At 24 months</td>
<td>10.4 (6.8–14.1)</td>
<td>26.5 (21.2–31.7)</td>
</tr>
<tr>
<td>Median progression-free survival (mo)</td>
<td>5.0 (4.2–5.5)</td>
<td>6.9 (5.8–8.2)</td>
</tr>
<tr>
<td>Progression-free survival (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>36.4 (30.8–41.9)</td>
<td>53.9 (48.1–59.6)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>9.1 (5.8–12.4)</td>
<td>26.9 (21.8–32.1)</td>
</tr>
<tr>
<td>At 18 months</td>
<td>3.9 (1.6–6.1)</td>
<td>18.4 (13.9–22.9)</td>
</tr>
<tr>
<td>At 24 months</td>
<td>1.5 (0.1–3.0)</td>
<td>10.7 (7.0–14.3)</td>
</tr>
</tbody>
</table>

* A total of 160 patients in the radiotherapy group and 60 patients in the radiotherapy-plus-temozolomide group received temozolomide as salvage therapy. CI denotes confidence interval.
5 year follow-up

9.8% OS at 5 yrs – TMZ + RT
1.9% RT alone

Stupp R et al, Lancet Oncology (2009)
Conclusion

• The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity.
Malignant Glioma: Salvage Protocols

• There is **no standard of care** for recurrent GBM

• Phase II - targeted therapies:
  – Monotherapy
  – Combined with chemotherapy
  – Targeting more than one pathway
Assessing Response

• **Pitfalls:**
  – “Pseudoprogression”
  – “Pseudoresponse”
45 yr. Woman Treated With 60Gy/30fx RT + Concurrent TMZ

• Is this true progression?
• What is the best management?
  – Reoperate?
  – Persist with Adjuvant TMZ (150 mg/m² 5/28-day regimen)?
  – Or change chemotherapy/clinical trial

Courtesy, Dr. James Perry, Odette Cancer Centre, Toronto
Improved Imaging Changes Over Time
(reduced dexamethasone, patient better)

Why?
- Resolution of treatment effect;
- delayed response;
- effect of adjuvant treatment?

Courtesy, Dr. James Perry, Odette Cancer Centre, Toronto
Two patients with GBM – RT/TMZ
A is progressing, B is responding

Case and images courtesy of Dr N Laperriere, PMH
In fact, the opposite is true!

A

Post-op pre-RT  1 month post-RT  5 months post-RT

B
Pseudoprogession

A

Post-op pre-RT

1 month post-RT

5 months post-RT

11 months post-RT

B

27 cc

47 cc

34 cc

0.4 cc
“Pseudoprogression”
– Limitations of Gd-MRI –

• Detection of increased enhancement/edema following completion of chemoradiation
  – Seen in the past, even with conventional RT alone, but especially with brachytherapy and intracavitary treatment

• MRI at 4 weeks post-RT/TMZ:
  – Up to 30–50% of patients have worse scans (and PD by conventional criteria)
  – Half of these are asymptomatic
  – Of these, up to half have resolution of these changes over several months

• This may be more common in MGMT +ve pts¹

MGMT promoter methylation status and pseudoprogression in GBM

OS by MGMT promoter methylation status

OS by progression status

Implications of pseudoprogression

• Impact upon clinical trials  
  – PFS  
  – Entry into trials for recurrent disease
• What is the significance of a 4-6 wk post-RT scan?
• Anticipate more requests to consider debulking in the post-radiotherapy period
• Translational research required: novel MRI sequences, biomarkers

Courtesy, Dr. James Perry, Odette Cancer Centre, Toronto
New criteria for response assessment

• The “Macdonald” criteria – 1990
  – Based upon CT, contrast enhancement
  – Not intended for evaluation of cytostatic or targeted therapies

• RANO (Response Assessment in Neuro-Oncology)

• cannot judge progressive disease within 12 weeks of END of radiotherapy unless:
  a) New enhancement outside of RT field, or
  b) Histopathological evidence of viable tumour

RANO Criteria Summary

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-Gd+</td>
<td>0</td>
<td>≥ 50% ↓</td>
<td>&lt; 50% ↓</td>
<td>≥ 25% ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 25% ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>=, ↓</td>
<td>=, ↓</td>
<td>=, ↓</td>
<td>=, ↑</td>
</tr>
<tr>
<td>New Lesion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Present</td>
</tr>
<tr>
<td>Steroids</td>
<td>0</td>
<td>=, ↓</td>
<td>=, ↓</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical</td>
<td>=, ↑</td>
<td>=, ↑</td>
<td>=, ↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>Any</td>
</tr>
</tbody>
</table>

Response Assessment in Neuro-Oncology Working Group

*aProgression occurs when this criteria is present.
RANO = Response Assessment in Neuro-Oncology; SD = stable disease; FLAIR = fluid-attenuated inversion recovery; NA = not applicable.
Wen et al, JCO 2010.
Targeted anti-VEGF therapy – bevacizumab
The problem of “pseudoresponse”

Dramatic imaging responses
• Steroid like effect on vasculature and edema
• 6mo PFS about 30-50%
• Recently approved by Health Canada for recurrent GBM
• Clear patient benefit in many cases

• No controlled data
• Response criteria controversial
• No definite evidence of an overall survival advantage
• Unique patterns of failure
• ‘rebound’ once stopped (?)
• Unique toxicities – wound healing, thrombosis, GI and intracranial bleeding

Partial response to bevacizumab for recurrent GBM: T1Gd and FLAIR

2 cycles (one month) of bevacizumab monotherapy on stable steroids

from Lancet Neurology December 2008
Infiltrative growth pattern after treatment with bevacizumab

56 yo man, recurrent multifocal GBM. pre- and post-9 mo of bevacizumab

from Lancet Neurology December 2008
Bevacizumab Therapy for GBM: Challenges

• Strategies to optimize therapeutic benefit

<table>
<thead>
<tr>
<th>Study</th>
<th>Median OS (mos)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAIN (BEV alone)</td>
<td>9.2</td>
<td>8.0–11.7</td>
</tr>
<tr>
<td>BRAIN (BEV + irinotecan)</td>
<td>8.7</td>
<td>7.8–10.9</td>
</tr>
<tr>
<td>NCI (BEV alone)</td>
<td>7.8</td>
<td>5.3–13.5</td>
</tr>
</tbody>
</table>

• Lack of effective therapy after BEV failure
• Resistance
  – More aggressive/infiltrative phenotype
• Biomarkers
Bevacizumab “Rebound”

Pre-Rx

PR: 1 Cycle BEV

PD on BEV

6 wks After Stopping BEV

Does Anti-VEGF Therapy Increase Invasion/Metastases?

Preclinical Data (GBM)
Challenges with VEGF-targeted therapy

- **Pseudoresponse**
  - Vascular permeability effect(s) make judging anti-tumour effect difficult by conventional imaging
  - Is PFS a useful measure of efficacy?
- **Alteration of the biology/natural history of GBM**
  - Differential effect on neo-angiogenesis vs infiltrative disease
  - Vascular co-option
  - Change to an infiltrative phenotype (?)
- **Duration of effectiveness may be modest**
  - Resistance, mechanisms of breakthrough unclear
  - Often robust ‘rebound’ enhancement on stopping, with little response to subsequent therapy

Courtesy, Dr. James Perry, Odette Cancer Centre, Toronto
Phase II Trial of Continuous Dose-Intense Temozolomide in Recurrent Malignant Glioma: RESCUE Study


Temozolomide Dose-Intense Rescue

GBM
Concomitant RT + TMZ

Disease progression

B1 (Early) (Adjuvant failure)
B2 (Extended) (Extend maintenance failure)
B3 (Rechallenge)

Months

Stop
Kaplan-Meier Estimate of Progression Free Survival in Patients With Recurrent Glioblastoma

Progression-Free Survival (%)

- Early: 3.6 months (1.4 – 5.9)
- Extended: 1.8 months (1.7 – 1.9)
- Rechallenge: 3.7 months (1.1 – 7.4)

Median
42-Year-Old Woman With GBM Treated With Continuous Dose-Intense Temozolomide After Failure on the NCIC-CTG/EORTC Trial

- PD: 9 months after RT + TMZ, 6 cycles adjuvant TMZ
- CR after 4 cycles continuous TMZ 50 mg/m²
- Response durable for 12 months
RESCUE results: 6-mo PFS, GBM groups

- Early: 27.3% (n=33)
- Extended: 7.1% (n=28)
- Rechallenge: 33.3% (n=27)
6 Month Progression-Free Survival (PFS) and 1-Year Survival in Patients With Recurrent Glioblastoma

<table>
<thead>
<tr>
<th>Groups</th>
<th>6-month PFS</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>27.3%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Extended</td>
<td>7.4%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Rechallenge</td>
<td>35.7%</td>
<td>28.6%</td>
</tr>
</tbody>
</table>
Conclusions

• Continuous dose-intense temozolomide is active in patients relapsing after standard therapy
• Patients who progress early during adjuvant therapy or after a treatment break obtained the most benefit
• 6-mo PFS and OS are comparable to bevacizumab
• Minimal toxicity compared with other options
• RESCUE showed differences in prognosis depending on the duration of adjuvant therapy and treatment-free interval at the time of relapse

Courtesy, Dr. James Perry, Odette Cancer Centre, Toronto
Malignant Glioma: Emerging Therapies

Convection enhanced delivery (CED) to the tumour

Drugs to overcome TMZ resistance
  MGMT and PARP inhibitors

Antiangiogenic therapies
  anti-integrins (cilengitide), anti-HGF, anti-VEGF, anti-VEGFR, other

Targeted molecular therapies vs:
  Akt, EGFR, FTI, HDAC, HSP90, Met, mTOR, PI3K, PKC, PDGFR
  Proteosome, Raf, Src. TGFβ

Immunotherapies – Dendritic cell, EGFRvIII peptide vaccines, Mabs

Gene therapy

Stem-cell directed
Canadian recommendations for the treatment of recurrent or progressive glioblastoma multiforme

J.C. Easaw MD PhD, W.P. Mason MD, J. Perry MD, N. Laperrière MD, D.D. Eisenstat MD MA, R. Del Maestro MD PhD, K. Bélanger MD, D. Fulton MD, and D. Macdonald MD for the Canadian Glioblastoma Recommendations Committee*

Easaw JC et al/ Current Oncology 2011; 18(3): e126-e136
Recommendation 1: Multidisciplinary Approach

To optimize treatment outcomes, the management of patients with recurrent glioblastoma should be individualized and should involve a multidisciplinary team approach, including neurosurgery, neuropathology, radiation oncology, neuro-oncology, and allied health professions.
Recommendation 2: Imaging

-The standard imaging modality for assessment of recurrent glioblastoma is Gd-enhanced magnetic resonance imaging (MRI).
-Tumour recurrence should be assessed according to the criteria set out by the Response Assessment in Neuro-Oncology Working Group (RANO).
-The optimal timing and frequency of MRI after chemoradiation and adjunctive therapy have not been established.
Recommendation 3: Pseudo-progression

-Progression observed by MRI after chemoradiation can be pseudo-progression. - Treated patients should not be classified as having progressive disease by Gd-enhancing MRI within the first 12 weeks after the end of radiotherapy unless new enhancement is observed outside the radiotherapy field or viable tumour is confirmed by pathology at the time of a required re-operation.
-Adjuvant temozolomide should be continued and follow-up imaging obtained.
Recommendation 4: Repeat Surgery

-Surgery can play a role in providing symptom relief and confirming tumour recurrence, pseudo-progression, or radiation necrosis.
-However, before surgical intervention, it is essential to clearly define treatment goals and the expected impact on prognosis and the patient’s quality of life.
-In the absence of level 1 evidence, the decision to re-operate should be made according to individual circumstances, in consultation with the multidisciplinary team and the patient.
Recommendation 5: Re-irradiation

Re-irradiation is seldom recommended, but can be considered in carefully selected cases of recurrent glioblastoma.
Recommendation 6: Systemic Therapy

- **Clinical trials**, when available, should be offered to all eligible patients.
- In the absence of a trial, systemic therapy, including temozolomide rechallenge or anti-angiogenic therapy, may be considered.
- Combination therapy is still experimental; optimal drug combinations and sequencing have not been established.
Conclusions

• Rapid advances in translational medicine have been made for glial tumours in children and adults

• Prospective tumour banking should be incorporated into clinical practice

• Molecular markers can be used for diagnosis (IDH1 mutation) and as prognostic factors (MGMT promoter methylation, 1p/19q co-deletions) in adult high grade gliomas

• The identification of chromatin remodelling protein mutations for pediatric GBM opens up new frontiers towards understanding the pathogenesis of these tumours
Lecture Objectives

1) An **overview** of childhood cancer, with an emphasis on brain tumours

2) How has progress has been made **“one child at a time”**?
   - the example of **medulloblastoma** and clinical trials

3) What’s new in diagnosis and therapy?
   - the impact of **cancer genetics** and **targeted therapies**
Acknowledgements

Dr. Paul Grundy for permission to use some of his medical student lecture slides

Dr. James Perry for permission to use some of his lecture slides on recurrent GBM

The Hole Family
Questions?

Dr. David Eisenstat
eisensta@ualberta.ca
Submitted Questions

- Advances in technology?
- Advances in medication?
- Best hospital for research?
- Options for clinical trials – 5 “W”s
- How do doctors learn about advances?
- Any options for meningioma?
- What to do about chronic headaches?
- Non-medicinal therapy of seizures such as extracts from *Cannabis sativa*?
- What factors are considered in deciding whether to operate or monitor a patient?
- When does a doctor choose to make the decision for the patient or present the options for the patient to decide?
Adapted from: Wigle JT and Eisenstat DD, The Developing Human, 2013
Clinical Trials

• **Preclinical**: cell lines, xenografts, animal models
  – “mouse ≠ man”

• **Phase I**: Toxicity is treatment endpoint
  – usually less than 20 patients
  – establish dose for later Phase II trials
  – most patients enter Phase I trials having failed standard therapies or prior clinical studies
  – treatment benefit is *not* the specific goal
  – challenge of using non-cytotoxic biological therapies in a traditional Phase I setting (“surrogate” end-points)
Clinical Trials

• Phase II: Measure anti-tumor response
  – may be monotherapy or unique combination of chemotherapeutic agents
  – 30-50 patients
  – goal: observed response rate of 20-30% (adult gliomas)
  – bias of patient selection factors: small numbers of patients, selection of younger, healthier patients with good KPS may over-estimate the “true” response rate
  – Phase II “windows” in Phase III studies
Clinical Trials

• Phase III: Therapeutic Efficacy
  – Comparison of new agent/combination with standard therapy in a randomized trial
  – If there is no standard therapy, other arm is placebo-controlled *double-blind* or *observational* if an adequate placebo does not exist (*open-label* study)
  – an *intent-to-treat* analysis should always be done
Clinical Trials

• **Phase III:** Therapeutic Efficacy
  – Phase III studies are necessary to determine the survival impact of adjuvant systemic therapy, especially in the setting of minimal residual disease (MRD) or stable/non-progressive disease (eg. LGG)

• **Phase IV:** Post-marketing studies
  – expand clinical indications
Assessing Response – Macdonald Criteria

• CR (Complete response)

• PR (Partial response) >25% reduction

• SD (Stable disease) ± 25%

• PD (Progressive disease) >25% increase
Assessing Response

• **Pitfalls I:**
  - Prior local therapy:
    - BCNU wafers, SRS, interstitial brachytherapy
  - **Gadolinium enhancement ≠ Tumor burden**
  - 2D vs. 3D volumetric analysis
  - bias of interval of MRI scanning
  - inter- & intra-observer variation
  - need for central radiology review
  - stable disease or overall survival may be important end-points for some CNS tumors
Assessing Response

• **Pitfalls II:**
  – Altered metabolism of chemotherapeutic agents due to: concurrent *corticosteroids* and *anticonvulsant drugs (ACDs)* in patients with brain tumors
Classification of Evidence

- **Class I**: randomized controlled clinical trials (RCTs);
  - includes meta-analyses of RCTs
- **Class II**: observational studies with concurrent controls (case-control & cohort studies)
  - IIa. Prospective, not randomized
  - IIb. Retrospective, case-controlled
Classification of Evidence

• Class III: other evidence
  (includes historical controls, expert opinion)

  – IIIa Uncontrolled observational series
    • IIIa1. Prospective or serial observations
    • IIIa2. Retrospective series
  – IIIb Case reports
  – IIIc Topic reviews