Medulloblastoma

Torunn I. Yock, MD, Massachusetts General Hospital, Harvard Medical School
Medulloblastoma

- 2nd most common pediatric brain tumor, but most common *malignant* brain tumor.
- Approximately 400 pediatric patients per year in US
- It can disseminate through the CSF and therefore necessitates CSI as part of treatment (in non infants).
- ~1/3 have dissemination at diagnosis
- Primitive cerebellar tumor of neuroectodermal origin, with gene expression distinct from other PNET *(primitive neuroectodermal tumor)*. (WHO 2016 changes this...)
- Mode and Median age is 5 and 7 years, but 20% present under the age of two.
- M staging from Chang Staging is prognostic and determines treatment.
# M Staging: Chang

<table>
<thead>
<tr>
<th>M Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No evidence of gross subarachnoid or hematogenous metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Microscopic tumors cells found in CSF</td>
</tr>
<tr>
<td>M2</td>
<td>Gross nodular seeding intracranially beyond the primary site (in cerebellar/cerebral subarachnoid space or in third or lateral ventricle)</td>
</tr>
<tr>
<td>M3</td>
<td>Gross nodular seeding in spinal subarachnoid space</td>
</tr>
<tr>
<td>M4</td>
<td>Metastasis outside cerebrospinal axis</td>
</tr>
</tbody>
</table>
Medulloblastoma: Work up

- **Brain MRI** pre-operative and within 24-72 hours after surgery
- **Spine MRI** pre-operatively if possible. *Note inferior border of thecal sac on lumbar MRI to ensure full field coverage. (We typically just go to S4 now).*
- **CSF cytology** 10-14 days after surgery
- Labs: CBC, LFTs, RFTs, endocrine if symptoms
- **Baseline endocrine labs** helpful with bone age x-ray
- **Baseline Audiology**
- **Baseline Neurocognitive Evaluation** (within 6 months of starting radiation therapy)
- **Pathology:** diffuse anaplasia or large cell variant?
3 Groups of Medullos

- Standard risk
- High risk
- Infant medullo

For the very NUANCED provider: intermediate risk (next slide explains)
“Intermediate Risk”

• M0, GTR patients with anaplasia or large cell variant—they are not high risk, but not average risk either) (See Packer data, JCO, 2006 in subsequent slide)

• Note: in molecular era, these patients are usually group C or group D

• Note: “Intermediate Risk” isn’t formally recognized. St. Jude has a “intermediate risk category” in their protocol and we (MGH) also do in our Lancet Oncology medulloblastoma paper. (see following slides)
Medulloblastoma: If not SUB Grouped: Treatment Overview (children ~3+)

• **Standard risk:** children with M0 disease and GTR or less than 1.5 cm$^2$ of residual disease, classic or desmoplastic histology.
  - Standard therapy: CSI to 23.4 Gy with PF/IF boost to 54 Gy +/- weekly vincristine (vcr) followed by chemotherapy. (usually cisplatin, vcr, cyclophosphamide or CCNU)
  - 5 year EFS/OS = 81%, 86% (Packer, 2006, JCO, 24:4204)

• **High-risk:** M+ disease or STR with >1.5 cm$^2$ of residual in primary site.
  - Standard therapy: CSI to 36 Gy with PF(IF) boost to 54 Gy, usually with concurrent CT (vcr and/or carboplatin) and followed by cisplatin based regimen.
  - 5 year EFS = 60-70% (or less depending on the study)
Infant Medulloblastoma

• Adverse effects of XRT most profound in very young children
• Usually HD CT employed, plus or minus RT usually local for the M0 group. (Use of RT controversial).
• Cure rates suffer due to 2 things:
  – 1. lack of RT employment
  – 2. biology of disease
### Molecular Subgroups of Medulloblastoma

<table>
<thead>
<tr>
<th>CONSENSUS</th>
<th>WNT</th>
<th>SHH</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho (2010)</td>
<td>C6</td>
<td>C3</td>
<td>C1/C5</td>
<td>C2/C4</td>
</tr>
<tr>
<td>Northcott (2010)</td>
<td>WNT</td>
<td>SHH</td>
<td>Group C</td>
<td>Group D</td>
</tr>
<tr>
<td>Thompson (2006)</td>
<td>B</td>
<td>C', D</td>
<td>E, A</td>
<td>A, C</td>
</tr>
</tbody>
</table>

#### DEMOGRAPHICS
- **Age Group:** Infant, Child, Adult
- **Gender:** Male, Female

#### CLINICAL FEATURES
- **Histology:**
  - **Classic, rarely LCA**
  - **Rarely M+**
  - **Very good**
- **Metastasis:**
- **Prognosis:**

#### GENETICS
- **CTNNB1 mutation**
- **3q+**
- **11p+**
- **PTCH1/SMO/SUFU mutation**
- **GLI2 amplification**
- **MYCN amplification**

#### GENE EXPRESSION
- **WNT signaling**
- **MYC+**
- **SHH signaling**
- **MYCN+**
- **Neuronal/Glutamatergic**
- **Minimal MYC/MYCN**

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Taylor, Acta Neuropath 2012
Practical Molecular Sub Grouping

- WNT pathway (very good prognosis)
- SHH pathway (good prognosis)
- Group C and D (often mixed together)
  - BUT, if myc amplified and anaplastic, we worry much more.
  - Group D is somewhat better than C prognostically
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**Average Risk Medulloblastoma**

ACNS0331 Schema *(closed to accrual-2015-presented at ISPNO, Liverpool, 2016)*

- **Age 3-7 years**
  - CSRT 23.4Gy
  - PF boost 54Gy
  - IF boost 54Gy

- **Age 8-21 years**
  - CSRT 23.4Gy
  - PF boost 54Gy
  - IF boost 54Gy

Weekly vincristine during XRT

PF: Posterior fossa and IF: Involved field, tumor bed

~10% decrement in DFS
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Average Risk Medulloblastoma


• NOTE: No difference in the IF vs WPF

• *Involved field* *(Tumor bed boost)* should be the standard at this point…

![Diagram](https://via.placeholder.com/150)
IF(TB) vs PF: DVH of the Brain

- Tumor bed (involved field) spares more brain than whole posterior fossa boost.
- No decrements in disease control.
- Essentially, should be standard now for localized MB
- We use for SR and HR when no mets in the PF
- Note: seems equivalent on the RCT, but data not formally presented. Phase II data reassuring (3 studies)

Mulhern et al, 2004, Lancet Oncology 5:399
COG RT Guidelines for IF Boost
(with TY modifications, ANCS 0331)

• GTV: includes any residual enhancing or non-enhancing tumor and the wall of the resection cavity. *(FUSE both post op and pre-op T1 post gad and T2 sequences)*

• CTV: is defined as the GTV plus a 1.5-cm margin *(we use 8-10 mm mostly)* except at bone or tentorial interface *(Buzz words: anatomically confined to posterior fossa, trim inside tentorium/boney PF)*

• PTV (photons only!!): an additional 0.3 to 0.5 cm around the CTV. *(Proton PTV is different—rotate with us. No time to explain in this talk)*

• HR protocol patients used whole PF boost (we only use this at MGH when on protocol or when we think it is better due to disease diffuseness—leptomeningeal spread)
# Children’s Oncology Group

## Average Risk Medulloblastoma

**ACNS0331 Chemotherapy Details**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Chemoradiotherapy</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 Days</td>
<td>Radiation Therapy (XRT)</td>
<td>4 wks</td>
</tr>
<tr>
<td>Cycle</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Week</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Day</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

### Chemotherapy

- **V**: Vincristine
- **A**: Cisplatin
- **B**: Lomustine

### Maintenance Chemotherapy

- **A**: Cisplatin (75 mg/m²) IV over 6 hours on Day 1
- **B**: Lomustine (CCNU) (75 mg/m²) orally on Day 1
- **A**: Vincristine (1.5 mg/m², maximum dose 2.0 mg) IV push or infusion Days 1, 8, and 15

### Cycle A (42 Days)

- **A**: Cisplatin (75 mg/m²) IV over 6 hours on Day 1
- **B**: Lomustine (CCNU) (75 mg/m²) orally on Day 1
- **A**: Vincristine (1.5 mg/m², maximum dose 2.0 mg) IV push or infusion Days 1, 8, and 15

### Cycle B (28 Days)

- **A**: Cyclophosphamide (1000 mg/m²) IV over 1 hour on Days 1 and 2
- **B**: Vincristine (1.5 mg/m², maximum dose 2.0 mg) IV push or infusion on Days 1 and 8
- **A**: MESNA (360 mg/m²/dose) IV infusion over 15-30 minutes starting 15 minutes prior to or at the same time as cyclophosphamide and repeated at 4 and 8 hours.

### Cumulative cisplatin dose 450 mg/m²
Histology:  
(Eberhart, *Cancer* 2002, 94:552)

- Patients with tumors with moderate or severe anaplasia fared worse than those without.
SR Medulloblastoma, CCG A9961

15% with diffuse or focal anaplasia

P = .89

But for no anaplasia vs any,
EFS$_5$ 83% vs 73% (p = .087)
OS$_5$ 89% vs 75% (p = .005)

Packer, JCO 2006
Prognosis by histologic subtype

EFS among 134 children treated on St Jude protocol (intensified adjuvant Rx) by histological subtypes

Gajaar, Lanc Onc, 2006
History: Average Risk Study Amended

- Based on Eberhart’s findings and the CCG A9951 and St Jude study (SJMB-96) findings, patients with diffuse anaplasia/large cell variant were excluded on the SR COG protocol. (2008)
- The High Risk Protocol was amended to allow enrollment, but because the M0 otherwise SR patients didn’t do quite as badly as the other HR patients, the new High risk protocol was named...
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Other Than Average Risk (High) Medulloblastoma

ACNS0332 Schema (was closed for futility analysis, now open enrolling)

Note: 18% of pts enrolled are M0, GTR, anaplastic!

Age 3-21 years

Concurrent vcr with RT

Concurrent vcr & carboplatin with RT

CT alone

CT + isotretinoin

Isotretinoin arms closed: Futility analysis showed no benefit (2015)

Based on preliminary data from the Reg A pilot showing 5 year EFS = 71%

Outcome of Children With Metastatic Medulloblastoma Treated With Carboplatin During Craniospinal Radiotherapy: A Children’s Oncology Group Phase I/II Study

Regina I. Jakacki, Peter C. Burger, Tianzi Zhou, Emiko J. Holmes, Mehmet Kocak, Arzu Onar, Joel Goldwein, Minesh Mehta, Roger J. Packer, Nancy Tarbell, Charles Fitz, Gilberti Vezina, Joanne Hilden, and Ian F. Pollack
This paper is why we treat pts with high risk, with carboplatin daily. Opinions vary as to when it is truly necessary as it is more toxic...

Aim: to report outcome of carboplatin as radiosensitizer in M+ medulloblastoma:

- Pts received 36 Gy CSI and boost to primary and gross mets.
- Daily Carbo dose was found to be 35 mg/m2: (given with weekly VCR)
- Regimen A: 6 months of maintenance chemotherapy (MC) with cyclophosphamide and VCR. No cisplatin!!!
- Regimen B: cisplatin added once max tolerated carbo dose found.
Jackaki et al. JCO 2012; M+ Medullo (FYI)

- 161 patients (median age, 8.7 years; range, 3.1 to 21.6 years) (including STPNET, reported later)
- 29(36%) of 81 patients with M+ MB had diffuse anaplasia.

**5 year PFS of 60-70%**
- *Regimen A No cisplatin: 5 yr OS and PFS: 82% and 71%.*
- *Regimen B: 5 yr OS and PFS: 68% and 59%* (NS difference, p=0.36)
- Anaplasia was a negative predictor of outcome.
Notice: a significant number of pts fail AFTER 5 years.

**Fig 1.** Kaplan-Meier curves showing the overall survival (OS) and progression-free survival (PFS) of patients with centrally reviewed metastatic medulloblastoma treated on regimen A, excluding four patients who were felt to have had pseudoprogression. The numbers below the survival curves reflect the number of patients at risk at any given time point.

**Fig 2.** Kaplan-Meier curves showing the overall survival (OS) and progression-free survival (PFS) of patients with centrally reviewed metastatic medulloblastoma treated at the recommended phase II dose of carboplatin on regimen A and regimen B. The numbers below the survival curves reflect the number of patients at risk at any given time point.

**Fig 3.** Kaplan-Meier curves showing no significant difference in the overall survival of patients with centrally reviewed metastatic medulloblastoma based on M stage. The numbers below the survival curves reflect the number of patients at risk at any given time point.

**Fig 4.** Kaplan-Meier curves showing the overall survival (OS) and progression-free survival (PFS) of patients with centrally reviewed metastatic medulloblastoma with and without anaplasia. The numbers below the survival curves reflect the number of patients at risk at any given time point.
How do we incorporate Molecular Grouping into treatment?

1. For Risk Stratification in new diagnoses:
   - Next COG average risk study… *(WNT pathway only, and getting 18 Gy CSI, rapid central path review)*
   - St Jude led medulloblastoma study… (all 4 sub groups and all risks, open at 20+ sites) [ClinicalTrials.gov Identifier: NCT01878617](https://clinicaltrials.gov/ct2/show/NCT01878617)

2. For better targeting in recurrent disease:
   - SHH pathway by selective inhibition of Smoothened receptor
     - Vismodegib (GDC-0449) (Genentech)
     - Sonidegib (LDE-225) (Novartis)
During Treatment

• Weekly CBCs, If ANC <500, consider CSI break and move to boost field. BUT, **NO OVERALL TREATMENT BREAK!**

• If platelets <30 consider platelet transfusion and CSI break with boost field.

• Try to avoid treatment breaks as prolonged overall treatment time is associated with poorer outcome (delCharco et al IJROBP 42(1):147; Paulino, IJROBP, 1998)
  – <45 days is optimal
Timing of Radiotherapy and Chemotherapy
Short Radiation Treatment Time

- Medulloblastoma is a tumor with a rapid doubling time
- Long breaks *during* radiotherapy can lead to worse disease control
- Older studies broke patients for hematologic toxicity, the newer studies do not… (switch from CSI to boost field)

<table>
<thead>
<tr>
<th>Study</th>
<th>Rx Time</th>
<th>5 yr DFS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paulino¹</td>
<td>&lt;50 days</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50 days</td>
<td>42%</td>
<td>0.003</td>
</tr>
<tr>
<td>DelCharco²</td>
<td>&lt;45 days</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;45 days</td>
<td>45%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Medulloblastoma Dogma: Radiation must come before Chemotherapy….

• Is this still true?
• Let’s look at why this came about….
Sequencing of CT/RT

- **Earlier trials of CT and RT sequencing show the CT1 (chemo first) arm to be inferior for disease control**
  - SIOP II Medulloblastoma study demonstrated diminished EFS in pts with CT1 (Bailley, Med Ped Onc, 1993)
    - RT breaks given for WBC <2.0 and platelets <50
    - RT treatment time not reported
  - German HIT 91 found inferior EFS in patients treated CT 1st compared with RT1st (Kortmann, IJROBP, 2000)
    - RT therapy in CT1st arm prolonged due to hematologic toxicity (difference found in children 6-18 years, 64% vs 84%, p=0.03),
  - For years, dogma has been RT1 in older children...
Sequencing of RT and CT

- More recent studies try not to break patients for heme toxicity during the radiotherapy unless sick or febrile.

- **POG 9031 (Tarbell, JCO 2013)** There was no significant difference in 5 yr EFS in RT1 or CT1.

- Average RT treatment times:
  - CT1: 46.3 days; 22 pts >50 days
  - RT1: 44.8 days; 11 pts >50 days

- **Gajjar (Lanc Onc, 2006)** found HR patients treated with induction chemotherapy (topotecan) had equivalent EFS to those who had immediate RT after surgery (70 vs 71%, p=0.8)

- **MGH data (Jimenez, IJROBP, 2013; and Yock et al, Proton phase II, 2016, Lanc Onc, also show no detriment to CT1)**

- **In summary, if we don’t break patients during the radiation, induction chemotherapy may be a safe and viable option for future studies and likely has a role in the youngest patients.**
Follow Up Studies

• H and P with neurologic exam
• MRI (Brain/Spine) q 3 months in year 1, q 4-6 months years in year 2 and 3, and annually thereafter.
• **Annual audiogram** until 5 years out or longer until stable. (and prior to each cycle of chemotherapy)
• **Neurocognitive evaluation** q 1-2 years after baseline until stable. *(ALL children with brain tumors should have this, early intervention allows for the best outcomes).*
• **Endocrine evaluation** q 6 months (bone age every year or every other year as GH deficiency can be a challenge to diagnose in pts with spinal RT)
Cerebellar Mutism/Posterior Fossa Syndrome

- Cerebellar mutism syndrome (CMS) is a postoperative syndrome typically arising 1 to 2 days after resection of a midline posterior fossa tumor (usually in medullo and super rare in adults)

- Characterized by:
  - diminished speech progressing to mutism,
  - emotional lability
  - hypotonia
  - ataxia.

- Large COG series (Robertson, J Neurosurg, 2006**) should 25% of kids affected and 92% were moderate to severely affected.
Posterior Fossa Syndrome/ Cerebellar Mutism

• Unclear etiology, **typically seen in 15-40% of children with medulloblastoma.** (Rare in adults, uncommon with other histologies)
• Risk factors include, (studies vary) large tumors, medulloblastoma (as opposed to other posterior fossa tumors), midline location, cerebellar-vermal surgical incision, brainstem invasion/pressure, extent of resection, younger age
• Symptoms may be mild and transient or severe and slow to recover
• Recovery can be complete or incomplete (average, 4-12 weeks, but as little as 1 week to many years may be required)
• **Radiation need not be delayed,** but vincristine may slow recovery of motor coordination (and we omit in moderate-severe cases).

PF Syndrome/Cerebellar Mutism: a continuum

- Classic Signs:
  - Hypotonia
  - Ataxia
  - Mutism, difficulty speaking (often able to speak immediately post op but lose ability over next 1-4 days).
  - Emotional lability/irritability
  - Difficulty/inability to perform voluntary movements

- Other manifestations:
  - Hemiparesis
  - Dysphagia
  - Cranial nerve deficits
  - Cortical blindness (reactive to light, but not able to fix or track)

- Note: even in severe cases, the children understand what is going on around them.
PF Syndrome (Korah, 2010, IJROBP, 77:106)

- Retrospective study medulloblastoma from Emory, n=63, 1990-2007
- Median f/u 7 years
- All had moderate to severe PF syndrome (Robertson 2006, J Neurosurg 105:444)
- Incidence: 29%
  - 1990-2000, incidence 17%, (GTR 77%)
  - 2001-2007, incidence 39%, (GTR 94%)
- RCT results published in 1999 (Zeltzer, JCO) showing decreased DFS in pts with M0 and STR (>1.5 cm2) 54% compared with NTR/GTR 78% changed pattern of care and surgeons are now more aggressive with resections
- Vermis splitting approach documented in 78% of patients with PF syndrome
- ONLY 22% had complete recovery
  - residual sequelae included dysarthric speech and ataxia
Ototoxicity

• Combined conventional radiotherapy and cisplatin chemotherapy can result in severe/unacceptable (grade 3 or 4) hearing loss in 50-60% of children.
• IMRT or Proton RT can reduce dose to cochlea.
• Sparing is greater still with the involved field boost (additional 40-50%).
• 25% POG Grade 3 or 4 hearing loss with IMRT (Paulino, IJROBP, 2010)
• 15% POG Grade 3 or 4 with protons (MGH data, Lancet Oncology, 2016)
• NOTE: cisplatin dose of 450 mg/m2 is a MAJOR contributor to hearing loss. (Happens early—after each cycle, RT effects typically happen late, 3 years plus)

Ototoxicity

• Note: total cisplatin dose for both SR and HR COG protocols is 450 mg/m2.

• Cisplatin alone can cause substantial high frequency hearing loss: (>50 dB hearing threshold in the 4000-8000 Hz frequencies) (Schell et al. 1989; Grewel, Pediatrics 2010, excellent review updated and on line ahead of print, Bass, Ped Blood and Cancer, 2016)
  – 15-40% treated with 270 mg/m2
  – 20-60% treated with 360 mg/m2

• Note: No matter how fancy we get with RT, there will still be hearing loss unless we change our chemotherapy practices.

• New WNT pathway SR protocol has 300 mg/m2. Rao (Mayo) has paper showing no decrement in DFS in pts with dose reductions on COG protocols.
Protons in Medulloblastoma
59 patients enrolled from 2003-2009 on prospective phase II protocol for proton radiotherapy

**Purpose:** to report the late effects and disease outcome of these patients

**Population:** 39 standard-risk, 6 intermediate-risk (M0, no residual and anaplastic/large cell), and 14 high-risk disease.

**Median age:** 6.6 years

**Median follow-up:** 7.0 years
# Medulloblastoma: Patient Characteristics

(Yock et al. Lanc Onc, 2016)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data (n=59)</th>
<th>(Continued from previous column)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (56%)</td>
<td>Boost field</td>
</tr>
<tr>
<td>Female</td>
<td>26 (44%)</td>
<td>Tumour bed involved field</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior fossa</td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (non-Hispanic)</td>
<td>53 (90%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (10%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>6-6 years (5-1-9-9)</td>
<td></td>
</tr>
<tr>
<td>&lt; 8 years</td>
<td>37 (63%)</td>
<td></td>
</tr>
<tr>
<td>≥8 years</td>
<td>22 (37%)</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New England</td>
<td>25 (42%)</td>
<td></td>
</tr>
<tr>
<td>Outside New England</td>
<td>34 (58%)</td>
<td></td>
</tr>
<tr>
<td><strong>Histological subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic</td>
<td>45 (76%)</td>
<td></td>
</tr>
<tr>
<td>Desmoplastic or nodular variant</td>
<td>6 (10%)</td>
<td></td>
</tr>
<tr>
<td>Anaplastic or large cell variant</td>
<td>8 (14%)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>39 (66%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate†</td>
<td>6 (10%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>14 (24%)</td>
<td></td>
</tr>
<tr>
<td><strong>Posterior fossa syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (24%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45 (76%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ventriculoperitoneal shunt?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (20%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>47 (80%)</td>
<td></td>
</tr>
<tr>
<td><strong>Children’s Oncology Group protocol enrolment?</strong></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 (20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>47 (80%)</td>
</tr>
</tbody>
</table>

*One patient aged 22-1 years was 21 at the time of diagnosis and thus eligible for the study but turned 22 years before starting radiation treatment. †Defined as MD patients with <1.5 cm³ of residual disease but with anaplastic or large cell variant. IACNS0331, eight patients; ACNS0332, two patients; ACNS0334, one patient; A9961, one patient. RBE—radiobiological equivalent. §Cranial radiation doses were 18 Gy for one patient, 23.4 Gy for 41 patients, and 27 Gy for one patient. ‡Data missing for eight patients.

Table 1: Patient and treatment characteristics
Medulloblastoma: Disease Control
(Yock et al. Lanc Onc, 2016)

- **Disease control is equivalent to other cooperative groups.**

- SR: 5 yr PFS/OS 85%/86% compared with 81-83%/85-86%

- HR: 5 yr PFS/OS 70%/75% compared with 59-71%/68-82%

<table>
<thead>
<tr>
<th></th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 years (95% CI)</td>
<td>7 years (95% CI)</td>
</tr>
<tr>
<td>All patients</td>
<td>80% (67-88)</td>
<td>75% (61-84)</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>85% (69-93)</td>
<td>81% (64-91)</td>
</tr>
<tr>
<td>Intermediate*</td>
<td>67% (19-90)</td>
<td>67% (19-90)</td>
</tr>
<tr>
<td>High</td>
<td>71% (41-88)</td>
<td>63% (32-83)</td>
</tr>
<tr>
<td>Risk (2008 revision)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>85% (69-93)</td>
<td>81% (64-91)</td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>70% (45-85)</td>
<td>63% (37-81)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic or desmoplastic</td>
<td>80% (67-89)</td>
<td>75% (61-85)</td>
</tr>
<tr>
<td>Anaplastic or large cell</td>
<td>75% (31-93)</td>
<td>75% (31-93)</td>
</tr>
</tbody>
</table>

*Defined as M0 patients with <1.5 cm² of residual disease but with anaplastic or large cell variant (n=6). p values are for the comparison between patient subgroups across the entire follow-up period.

COG/St Jude studies: Packer, JCO 2006; Gajjar, Lanc Onc 2006; Jackacki, JCO 2012; Tarbell, JCO 2013;
Clinical Outcomes Among Children With Standard-Risk Medulloblastoma Treated With Proton and Photon Radiation Therapy: A Comparison of Disease Control and Overall Survival

Bree R. Eaton, MD,* Natia Esiashvili, MD,* Sungjin Kim, MS,† Elizabeth A. Weyman, B.A.,‡ Lauren T. Thornton, B.S.,‡ Claire Mazewski, MD,§ Tobey MacDonald, MD,§ David Ebb, MD,‖ Shannon M. MacDonald, MD,‡ Nancy J. Tarbell, MD,‡ and Torunn I. Yock, MD‡

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Proton vs Photon Medulloblastoma: Equivalent Disease Control (Eaton, IJROBP, 2015)

- **Conclusion:** for Standard Risk Medulloblastoma, proton and photon DFS and OS was equivalent.
- Only clinical difference between groups is that the proton group was younger, and the photon cohort treated in a slightly earlier era.

**Fig. 1.** Kaplan-Meier curves of overall survival for medulloblastoma patients treated with photon and proton radiation therapy.

**Fig. 2.** Kaplan-Meier curves of relapse-free survival for medulloblastoma patients treated with photon and proton radiation therapy.
Medulloblastoma: Hearing Outcomes
(Yock et al. Lanc Onc, 2016)

- **Median audiogram fu: 5 years** (key for comparison)
- CI in patients of POG** grade 3 or 4 hearing loss at 5 years:
  - 16% by patient (determined by grade of worst ear)
  - 11% by ear
- Rates appear less than IMRT/amifostine cohort of 25% by patient and 24% in the CCG/POG A9961 standard risk study.
- No disease characteristic correlated significantly with hearing loss.

<table>
<thead>
<tr>
<th>Cumulative incidence (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>5 years</td>
</tr>
<tr>
<td>All patients</td>
<td>12% (4-25)</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>15% (4-31)</td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>7% (0-29)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4% (0-19)</td>
</tr>
<tr>
<td>Female</td>
<td>20% (6-40)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>15% (5-32)</td>
</tr>
<tr>
<td>≥8</td>
<td>6% (0-25)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>12% (2-33)</td>
</tr>
<tr>
<td>≥6</td>
<td>12% (3-29)</td>
</tr>
<tr>
<td>Vetriculoperitoneal shunt?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22% (3-53)</td>
</tr>
<tr>
<td>No</td>
<td>10% (2-24)</td>
</tr>
<tr>
<td>Cisplatin total dose</td>
<td></td>
</tr>
<tr>
<td>≤300 mg/m²</td>
<td>18% (2-46)</td>
</tr>
<tr>
<td>&gt;300 mg/m²</td>
<td>12% (3-28)</td>
</tr>
<tr>
<td>Cochlear mean dose (D50)</td>
<td></td>
</tr>
<tr>
<td>&lt;30 GyRBE</td>
<td>14% (2-37)</td>
</tr>
<tr>
<td>≥30 GyRBE</td>
<td>11% (3-27)</td>
</tr>
</tbody>
</table>

Only patients with both baseline and follow-up audiograms were included. We excluded patients with POG grade 3-4 hearing loss at baseline in one or both ears were excluded. Risk is for the 2008 revision.*For the comparison between subgroups across the entire follow-up period.

Table 2: Ototoxicity outcomes

Nageswara Rao, PBC, 2014; Paulino, IJROBP, 2010
Medulloblastoma: Neurocognitive
(Yock et al. Lanc Onc, 2016)

- **Median neurocognitive fu:** 5.2 years
- **Average FSIQ points loss per year:** 1.5 points
- **Age (<8 years) was the key determinant** (-2.0 points per year vs. -0.2)
- **WPF appeared better than IF, but the WPF group was older.**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Baseline mean score (95% CI)</th>
<th>Mean change per year (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ</td>
<td>54</td>
<td>104.5 (101.3 to 107.7)</td>
<td>-1.5 (-2.1 to -0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td>0.525</td>
</tr>
<tr>
<td>Standard</td>
<td>36</td>
<td>104.5 (100.6 to 108.5)</td>
<td>-1.4 (-2.1 to -0.7)</td>
<td></td>
</tr>
<tr>
<td>Intermediate-high</td>
<td>18</td>
<td>104.4 (98.7 to 110.1)</td>
<td>-1.8 (-2.8 to -0.7)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.586</td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>104.1 (99.6 to 108.5)</td>
<td>-1.4 (-2.1 to -0.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>105.0 (100.1 to 109.8)</td>
<td>-1.7 (-2.5 to -0.8)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>&lt;8 years</td>
<td>34</td>
<td>105.7 (101.6 to 109.7)</td>
<td>-2.0 (-2.7 to -1.3)</td>
<td></td>
</tr>
<tr>
<td>≥8 years</td>
<td>20</td>
<td>102.1 (96.7 to 107.5)</td>
<td>-0.2 (-1.3 to 0.9)</td>
<td></td>
</tr>
<tr>
<td>Craniospinal irradiation dose</td>
<td></td>
<td></td>
<td></td>
<td>0.949</td>
</tr>
<tr>
<td>18–27 GyRBE</td>
<td>42</td>
<td>105.1 (101.5 to 108.8)</td>
<td>-1.5 (-2.2 to -0.8)</td>
<td></td>
</tr>
<tr>
<td>36 GyRBE</td>
<td>12</td>
<td>102.1 (95.1 to 109.1)</td>
<td>-1.5 (-2.8 to -0.3)</td>
<td></td>
</tr>
<tr>
<td>Boost field</td>
<td></td>
<td></td>
<td></td>
<td>0.049</td>
</tr>
<tr>
<td>Involved field</td>
<td>34</td>
<td>105.6 (101.5 to 109.7)</td>
<td>-2.1 (-2.9 to -1.3)</td>
<td></td>
</tr>
<tr>
<td>Whole posterior fossa</td>
<td>20</td>
<td>103.0 (97.7 to 108.3)</td>
<td>-1.0 (-1.7 to -0.2)</td>
<td></td>
</tr>
</tbody>
</table>
Medulloblastoma: Neurocognitive
(Yock et al. Lanc Onc, 2016)

- FSIQ is comprised of 4 index components:
  - VCI (Verbal)
  - PRI Perceptive Reasoning
  - WM Working Memory
  - PS Processing Speed

- Average score 100, Standard Deviation 15

- The significant FSIQ loss is driven by processing speed and verbal comprehension index

- CSI in developing kids has an neurocognitive effect. Period. Protons or photons.
Medulloblastoma: Endocrine outcomes
(Yock et al. Lanc Onc, 2016)

- 5 year incidence of any endocrine deficit is 55% (63% at 7 years) (Median f/u 7 years)
- Photon reports 41-67%
- Endocrine deficits are variably present depending on how hard you look for them. We recommended screening at least yearly.
- Growth and thyroid hormone deficits were most common.
- Dose to hypothalamus was only correlate (next slide).

![Table 4: Neuroendocrine outcomes](image)
Medulloblastoma: Endocrine outcomes (Yock et al. Lanc Onc, 2016)

<table>
<thead>
<tr>
<th></th>
<th>3 years</th>
<th>5 years</th>
<th>7 years</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.592</td>
</tr>
<tr>
<td>Male</td>
<td>33% (18–50)</td>
<td>58% (38–73)</td>
<td>64% (41–79)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19% (7–36)</td>
<td>52% (30–69)</td>
<td>62% (38–79)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.499</td>
</tr>
<tr>
<td>&lt;8</td>
<td>27% (14–42)</td>
<td>59% (41–74)</td>
<td>69% (48–83)</td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>27% (11–47)</td>
<td>47% (24–67)</td>
<td>54% (28–74)</td>
<td></td>
</tr>
<tr>
<td><strong>Craniospinal irradiation dose</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.471</td>
</tr>
<tr>
<td>18–27 GyRBE</td>
<td>24% (13–38)</td>
<td>52% (36–66)</td>
<td>62% (44–76)</td>
<td></td>
</tr>
<tr>
<td>36 GyRBE</td>
<td>36% (12–61)</td>
<td>64% (31–84)</td>
<td>64% (31–84)</td>
<td></td>
</tr>
<tr>
<td><strong>Boost field</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.292</td>
</tr>
<tr>
<td>Involved field</td>
<td>22% (10–37)</td>
<td>48% (31–64)</td>
<td>58% (37–75)</td>
<td></td>
</tr>
<tr>
<td>Whole posterior fossa</td>
<td>35% (16–54)</td>
<td>65% (41–81)</td>
<td>70% (45–85)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypothalamus mean dose (D50)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.054</td>
</tr>
<tr>
<td>&lt;40 GyRBE</td>
<td>19% (8–33)</td>
<td>44% (27–60)</td>
<td>58% (37–74)</td>
<td></td>
</tr>
<tr>
<td>≥40 GyRBE</td>
<td>41% (20–61)</td>
<td>73% (47–88)</td>
<td>73% (47–88)</td>
<td></td>
</tr>
</tbody>
</table>

Data are cumulative incidence (95% CI) unless stated otherwise. p values are for the comparison between patient subgroups across the entire follow-up period. GyRBE=Gray radiobiological equivalents.

Table 5: Cumulative incidence of any neuroendocrine outcomes by subgroup
Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma

Bree R. Eaton, Natia Esiashvili, Sungjin Kim, Briana Patterson, Elizabeth A. Weyman, Lauren T. Thornton, Claire Mazewski, Tobey J. MacDonald, David Ebb, Shannon M. MacDonald, Nancy J. Tarbell, and Torunn I. Yock

Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia (B.R.E., N.E.); Pediatrics, Emory University School of Medicine and Aflac Cancer and Blood Disorders Center of Children’s Healthcare of Atlanta, Atlanta, Georgia (B.P., C.M., T.J.M.); Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, California (S.K.); Pediatrics, Massachusetts General Hospital, Boston, Massachusetts (D.E.); Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts (B.R.E., E.A.W., L.T.T., S.M.M., N.J.T., T.I.Y.)

- **Population:** standard risk Medulloblastoma
- **Outcome measures:** endocrine deficiency and growth metrics in Emory photon cohort and MGH proton cohort
Results:

• **Median age**: PRT 6.2 and XRT 8.3 years \( (p<0.01) \).
• Cohorts were similar with respect to gender, histology, CSI dose, and total RT dose and boost volume.
• **Median follow-up**: protons 5.8 vs. XRT 7.0 years \( (p<0.01) \).
Results:

- PRT was associated with...
  - a reduced risk of hypothyroidism (23% vs 69%, P<.001), (NO exit dose to thyroid. All risk is now due to dose to the hypothalamic/pituitary axis with protons)
  - a reduced risk of sex hormone deficiency (3% vs 19%, P=.025),
  - requirement for any endocrine replacement therapy (55% vs 78%, P=.030),
  - a greater height as measured by mean standard deviation score, P=.020) on both univariate and multivariate and propensity score adjusted analysis.

Conclusions: Proton radiation appears to decrease or delay the need for hormone replacement in Medulloblastoma patients.
Medulloblastoma: Other Late Effects
(Yock et al. Lanc Onc, 2016)

- **Late effects actually compare favorably to photon literature.**
- **No late GI, cardiac, pulmonary issues.**
- No late seizure disorders
- **No second tumors, COG A9921 3% at 7 years; (Packer, A9961, N-O, 2013).**
- **1.7% brainstem necrosis** (topic to be discussed in more detail later as it is a hot topic in the pediatric neuro-oncology community.)

<table>
<thead>
<tr>
<th>Late toxic effects (n=58)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>11 (19%)</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Obesity</td>
<td>0</td>
<td>5 (10%)</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>16 (27%)</td>
<td>4 (7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS brainstem injury</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Ataxia</td>
<td>24 (41%)</td>
<td>4 (8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headaches</td>
<td>7 (12%)</td>
<td>4 (7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>3 (5%)</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>5 (9%)</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (3%)</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Scoliosis (present at radiotherapy)</td>
<td>4 (7%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Truncal muscle weakness</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>10 (17%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Graded by Common Toxicity Criteria (version 3.0). 190 acute grade 2 toxic effects occurred in 59 patients, 55 acute grade 3 toxic effects occurred in 37 patients, and 12 grade 4 toxic effects occurred in 12 patients. 26 late grade 2 toxic effects occurred in 19 patients, eight late grade 3 toxic effects occurred in seven patients, and one late grade 4 toxic effect occurred in one patient. Only acute toxic effects possibly, probably or definitely related to radiation were reported. We used the highest reportable grade per patient. *One patient progressed within 90 days after finishing radiotherapy and was therefore excluded from the analysis of late effects.

Table 7: Acute and late toxic effects