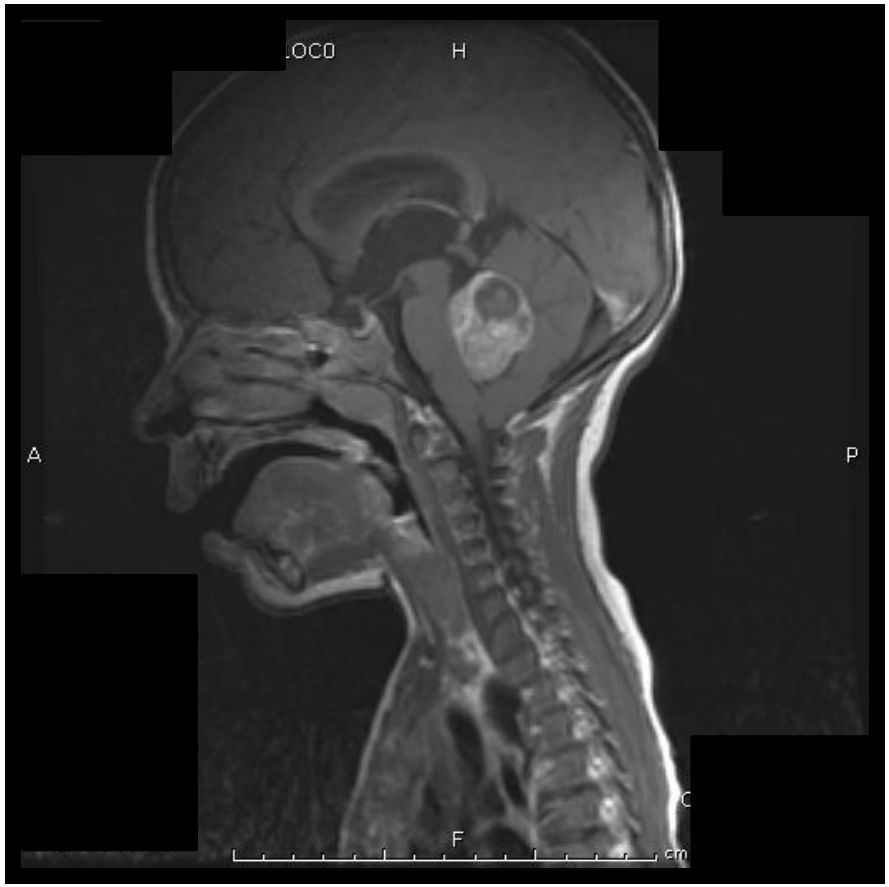
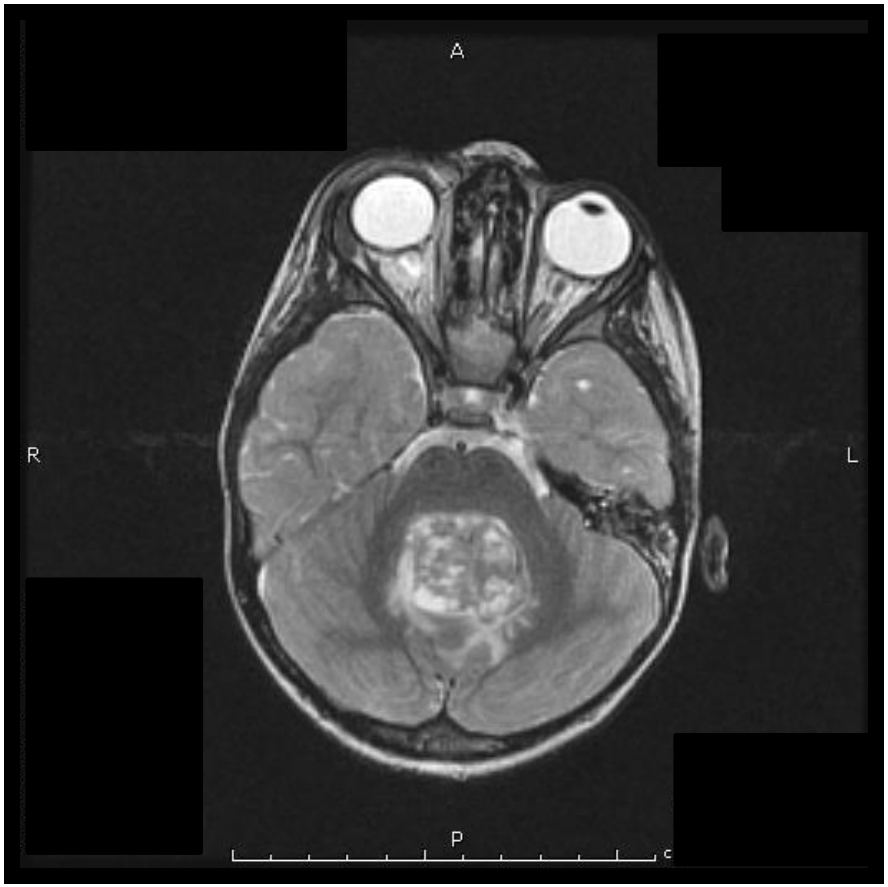
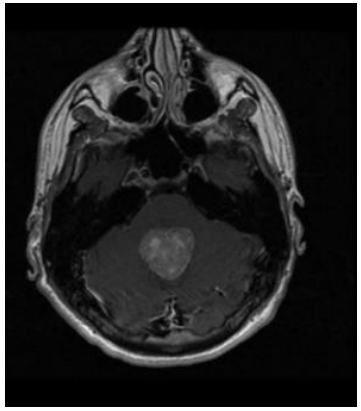
Medulloblastoma

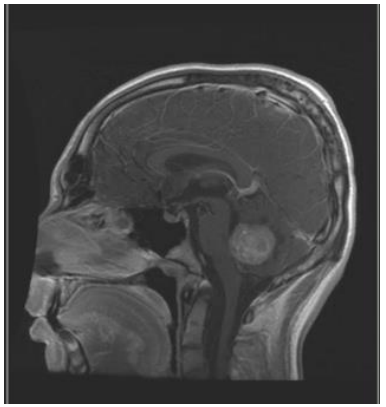




Torunn I. Yock, MD, Massachusetts General Hospital, Harvard Medical School



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

M Stage	Description
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	microscopic tumors cells found in CSF
M2	gross nodular seeding intracranially beyond the primary site (in cerebellar/cerebral subarachnoid space or in third or lateral ventricle)
M3	gross nodular seeding in spinal subarachnoid space
M4	metastasis outside cerebrospinal axis

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)

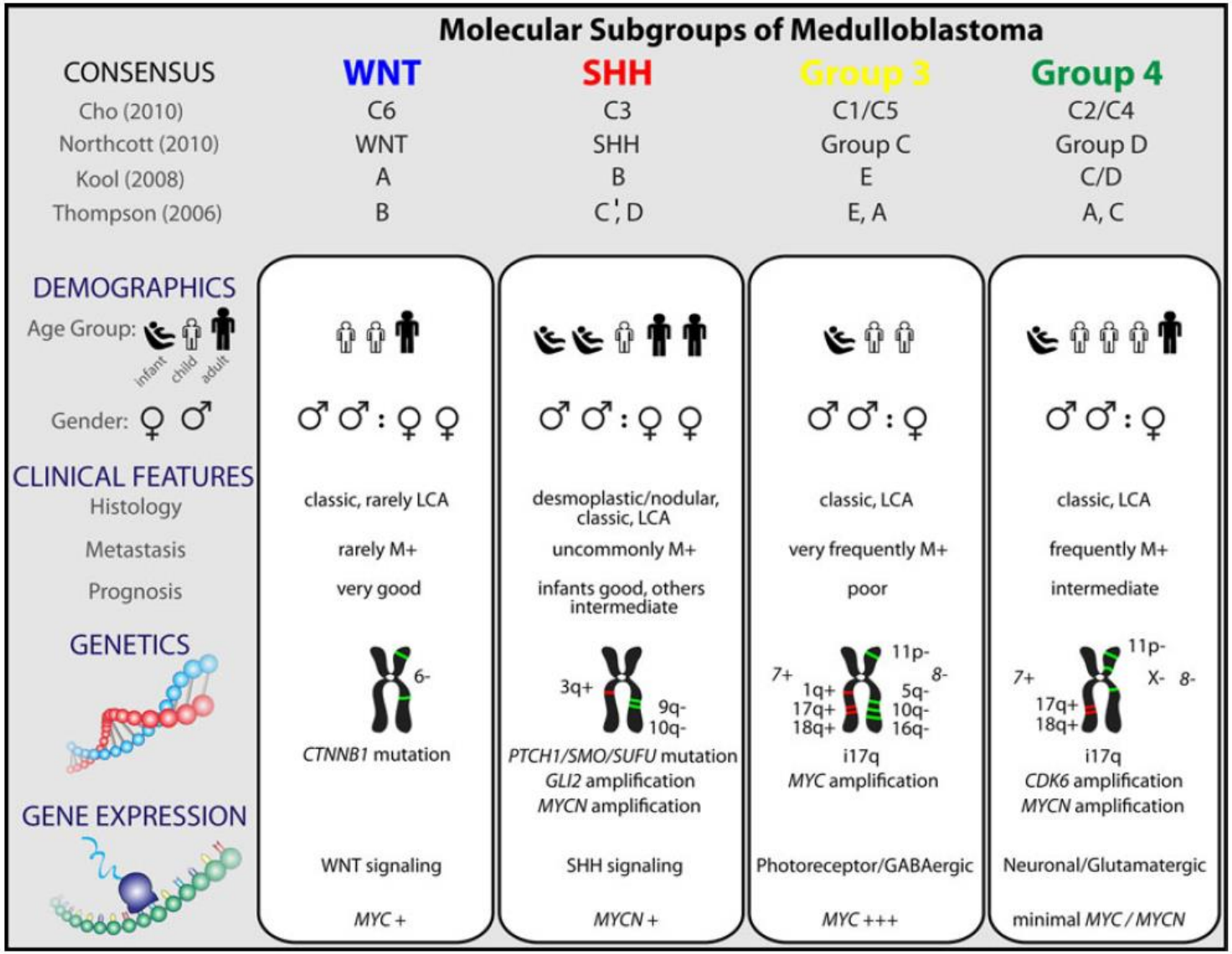
Medulloblastoma: If not SUB Grouped: Treatment Overview (children ~3+)

- 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

Medulloblastoma – evolving landscape



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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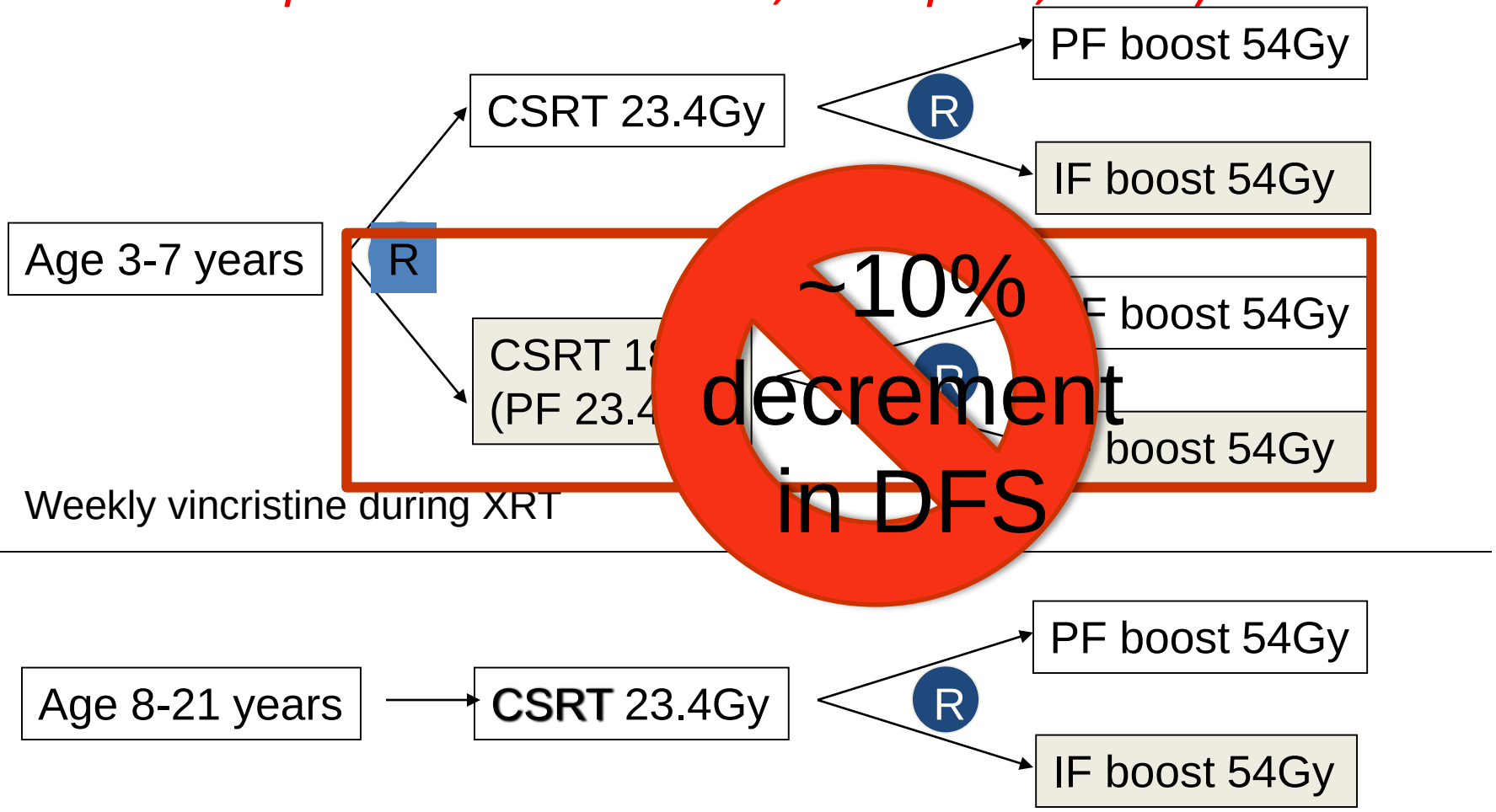
Average Risk Medulloblastoma

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



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

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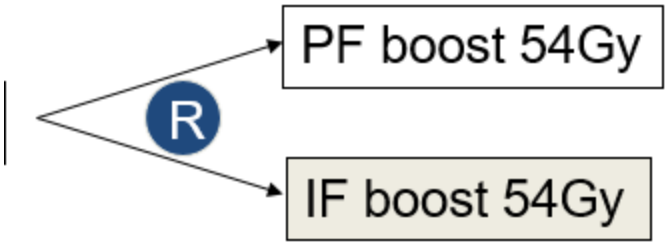
Average Risk Medulloblastoma

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

- NOTE: No difference in the IF vs WPF
- ***Involved field (Tumor bed boost) should be the standard at this point…***



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

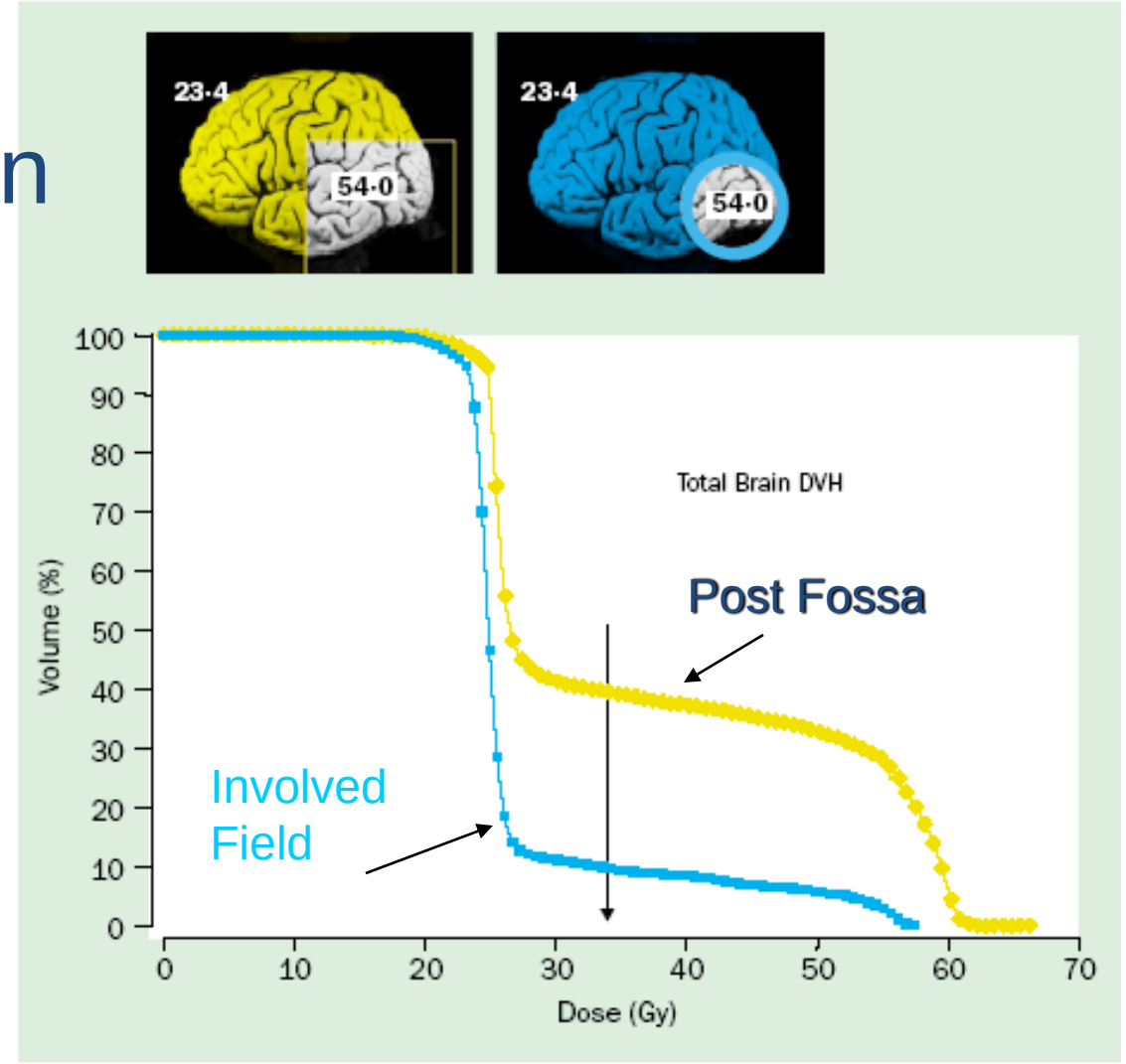


Figure 4. Benefits of dose decreases in planning of radiotherapy to posterior fossa shown with total-brain dose-volume histograms (DVH), comparison of conventional boost (blue) to posterior fossa with conformal boost (yellow) to the primary site after 23·4 Gy craniospinal irradiation.

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)

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Average Risk Medulloblastoma ACNS0331 Chemotherapy Details

Surgery			Chemoradiotherapy								Maintenance								
	31 Days		Radiation Therapy (XRT)							4 wks									
		Cycle									1	2	3	4	5	6	7	8	9
		Week	0	1	2	3	4	5	6		11	17	23	27	33	39	43	49	55
		Day	1	8	15	22	29	36	43										
				Chemotherapy							Maintenance Chemotherapy								
				V	V	V	V	V	V		A	A	B	A	A	B	A	A	B

Maintenance

Cycle A (42 Days)

Cisplatin (75 mg/m^2) IV over 6 hours on Day 1

Lomustine (CCNU) (75 mg/m^2) orally on Day 1

Vincristine (1.5 mg/m^2, maximum dose 2.0 mg) IV push or infusion Days 1, 8, and 15

Cycle B (28 Days)

Cyclophosphamide (1000 mg/m^2) IV over 1 hour on Days 1 and 2

Vincristine (1.5 mg/m^2, maximum dose 2.0 mg) IV push or infusion on Days 1 and 8

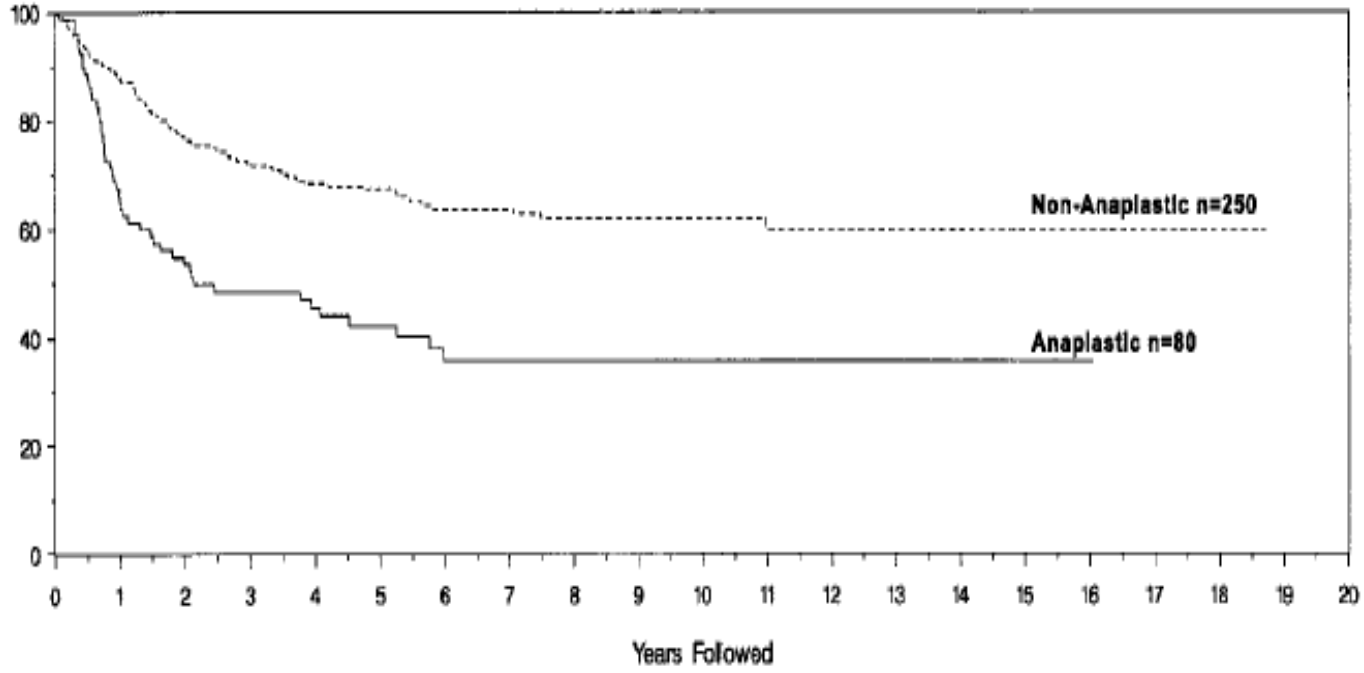
MESNA (360mg/m^2/dose) IV infusion over 15-30 minutes starting 15 minutes prior to or at the same time as cyclophosphamide and repeated at 4 and 8 hours.

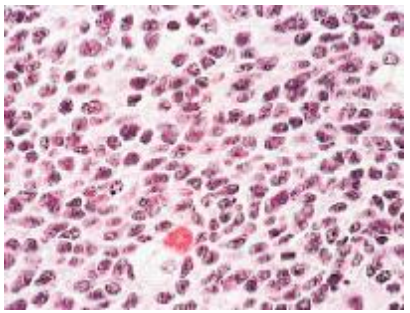
Cumulative cisplatin dose 450 mg/m2

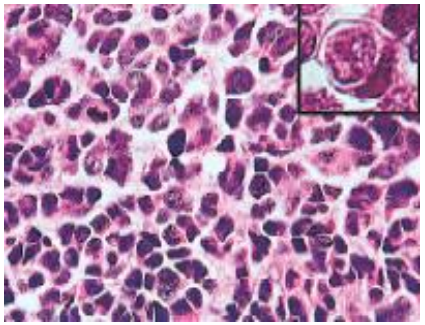
Histology:

(Eberhart, *Cancer* 2002, 94:552)

- Patients with tumors with moderate or severe anaplasia fared worse than those without.

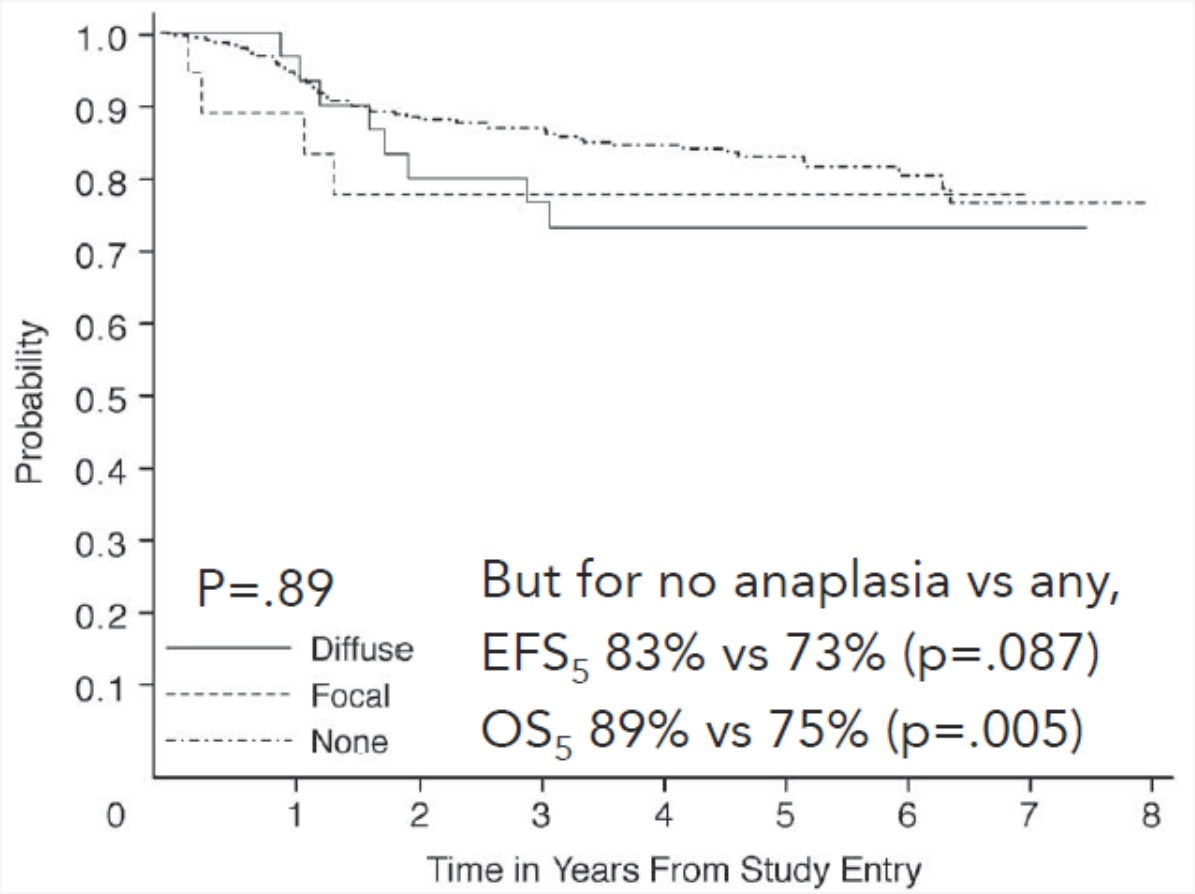






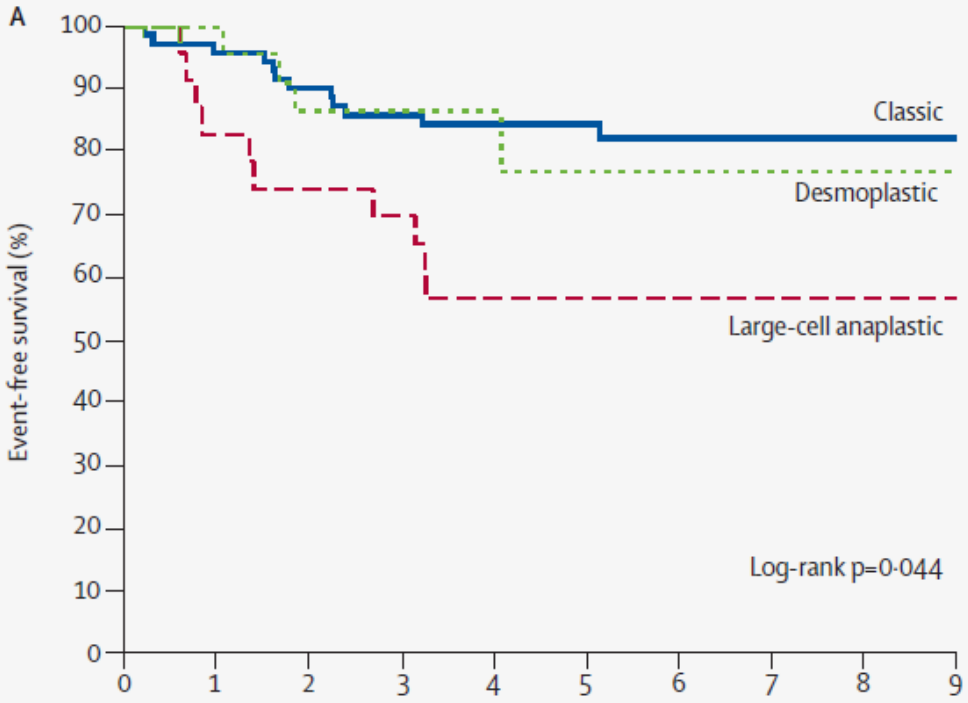
SR Medulloblastoma, CCG A9961

15% with diffuse or focal anaplasia



Packer, JCO 2006

Prognosis by histologic subtype



Number at risk

Classic	71	68	64	59	46	39	27	17	13	3
Nodular demoplastic	22	22	19	14	10	6	5	5	3	2
Large-cell anaplastic	23	19	17	16	11	9	5	1	1	1

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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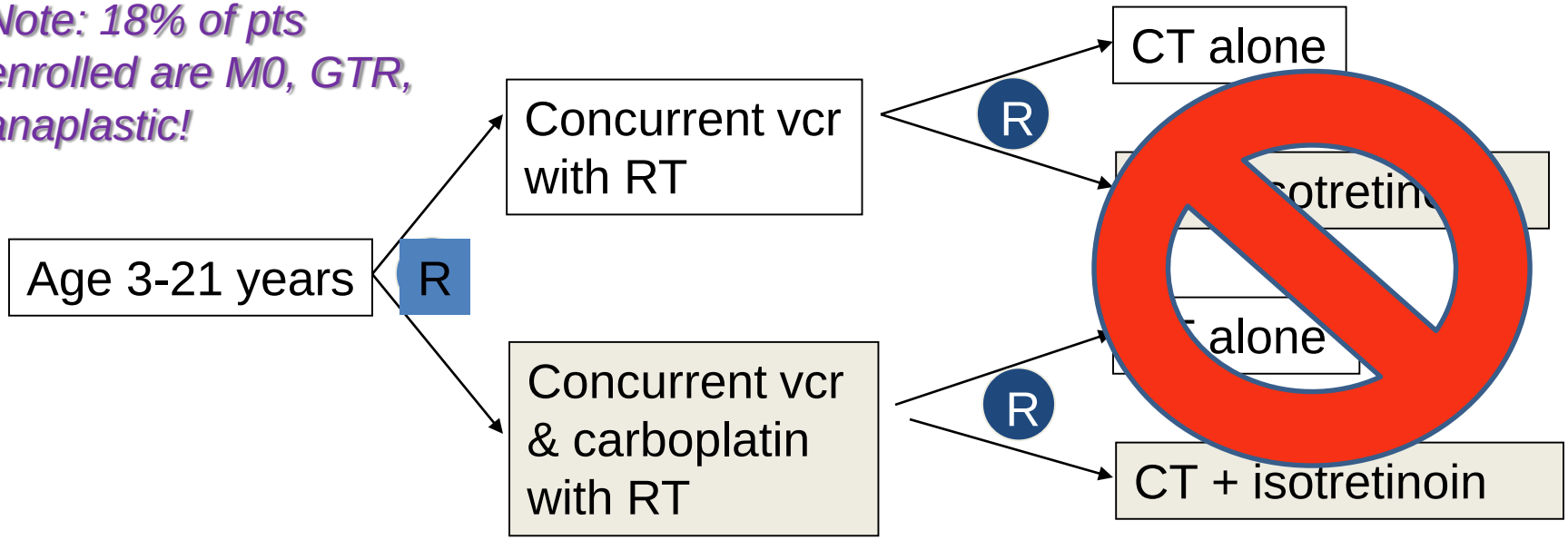
Other Than Average Risk (High) Medulloblastoma

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

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



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

VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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, Tianni Zhou, Emiko J. Holmes, Mehmet Kocak, Arzu Onar, Joel Goldwein, Minesh Mehta, Roger J. Packer, Nancy Tarbell, Charles Fitz, Gilbert Vezina, Joanne Hilden, and Ian F. Pollack

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

VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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…

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

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- Aim: to report outcome of carboplatin as radiosensiter 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.

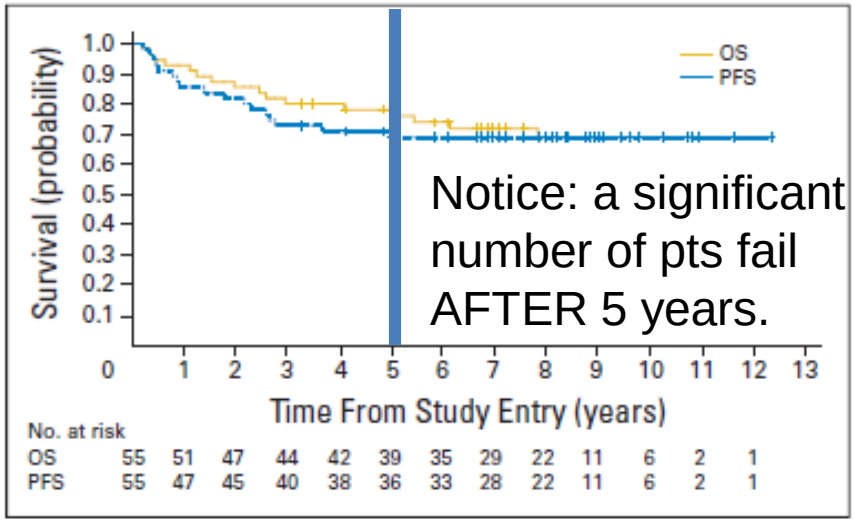


Fig 1. Kaplan-Meier curves showing the overall survival (OS) and progression-free survival (PFS) of patients with centrally reviewed metastatic medulloblastoma treated on regimen A, excluding four patients who were felt to have had pseudoprogression. The numbers below the survival curves reflect the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

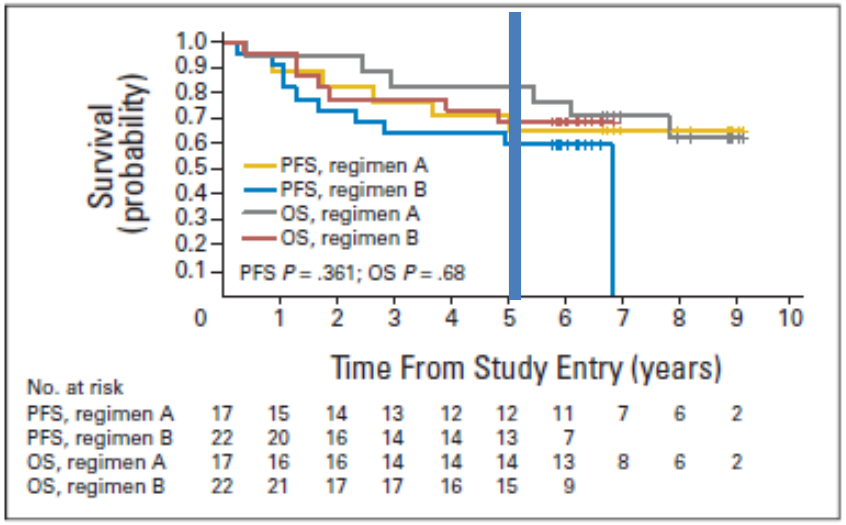


Fig 2. Kaplan-Meier curves showing the overall survival (OS) and progression-free survival (PFS) of patients with centrally reviewed metastatic medulloblastoma treated at the recommended phase II dose of carboplatin on regimen A and regimen B. The numbers below the survival curves reflect the number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

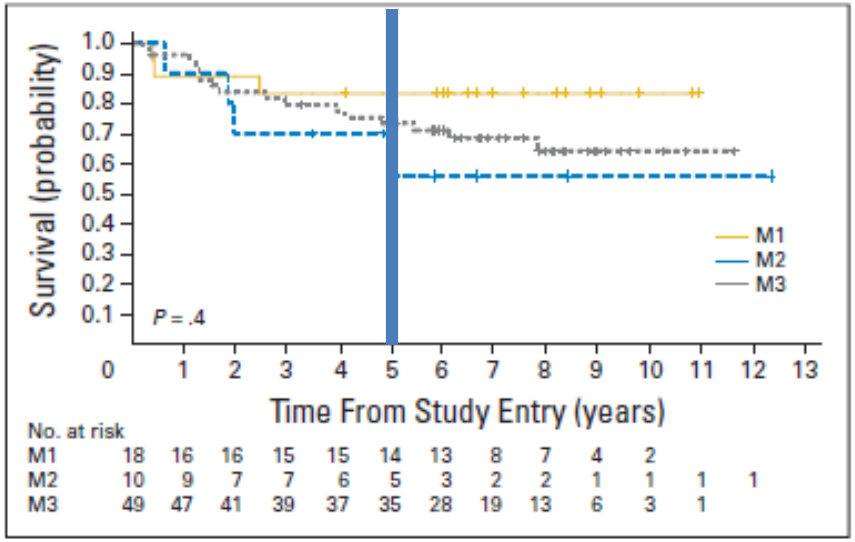


Fig 3. Kaplan-Meier curves showing no significant difference in the overall survival of patients with centrally reviewed metastatic medulloblastoma based on M stage. The numbers below the survival curves reflect the number of patients at risk at any given time point.

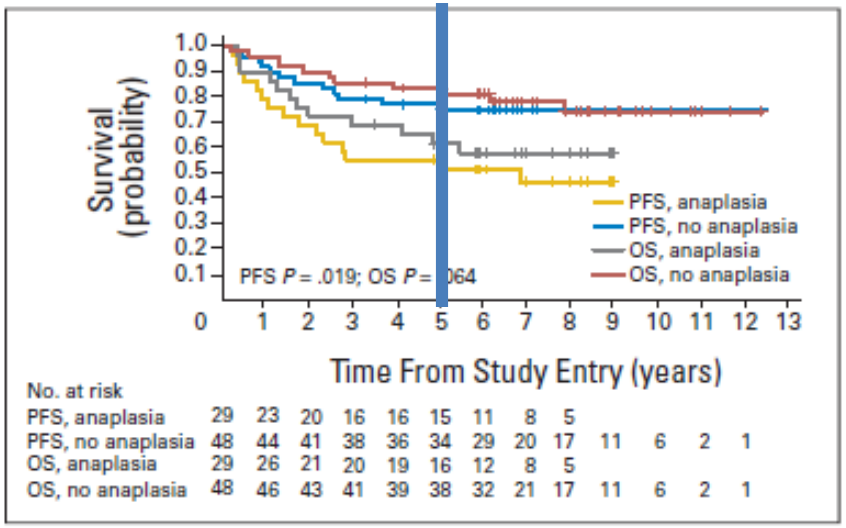


Fig 4. Kaplan-Meier curves showing the overall survival (OS) and progression-free survival (PFS) of patients with centrally reviewed metastatic medulloblastoma with and without anaplasia. The numbers below the survival curves reflect the number of patients at risk at any given time point.

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

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)

Study	Rx Time	5 yr DFS	P-value
Paulino[1]	<50 days	67%	
	>50 days	42%	0.003
DelCharco[2]	<45 days	76%	
	>45 days	45%	0.004

1. Am J Clin Onc, 2003, 2. IJROBP, 1998

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)

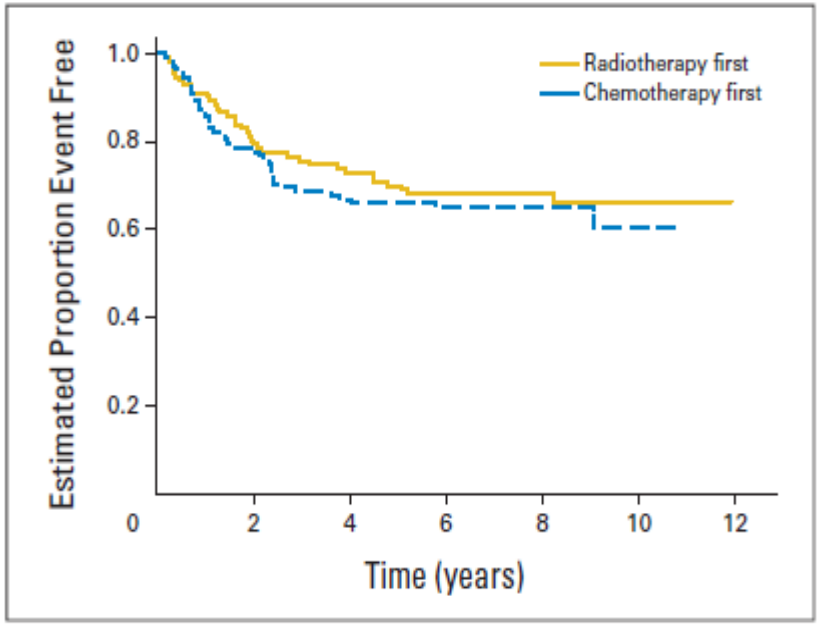


Fig 3. Event-free survival by treatment arm for eligible patients.

- ***<u>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.</u>***

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

- First described in 1979 by Hirsch (Acta Nirochir) 48:1-15.
- 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).

Steinbok et al, Pediatric Neurosurgery 2003, 39:179; Korah et al, 2010, IJROBP 77:106

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)

Fukunaga-Johnson 1998, *IJROBP*, 41:77; Huang 2002, *IJROBP*, 52:599

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

Medulloblastoma (Yock et al. Lanc Onc, 2016)

Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study

Torunn I Yock, Beow Y Yeap, David H Ebb, Elizabeth Weyman, Bree R Eaton, Nicole A Sherry, Robin M Jones, Shannon M MacDonald, Margaret B Pulsifer, Beverly Lavally, Annah N Abrams, Mary S Huang, Karen J Marcus, Nancy J Tarbell

- 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)

	Data (n=59)
Sex	
Male	33 (56%)
Female	26 (44%)
Ethnic origin	
White (non-Hispanic)	53 (90%)
Other	6 (10%)
Age*	
Median (IQR)	6·6 years (5·1–9·9)
<8 years	37 (63%)
≥8 years	22 (37%)
Location	
New England	25 (42%)
Outside New England	34 (58%)
Histological subtype (dominant pattern)	
Classic	45 (76%)
Desmoplastic or nodular variant	6 (10%)
Anaplastic or large cell variant	8 (14%)
Risk	
Standard	39 (66%)
Intermediate†	6 (10%)
High	14 (24%)
Posterior fossa syndrome	
Yes	14 (24%)
No	45 (76%)
Ventriculoperitoneal shunt?	
Yes	12 (20%)
No	47 (80%)
Children's Oncology Group protocol enrolment?‡	
Yes	12 (20%)
No	47 (80%)

(Table 1 continues in next column)

	Data (n=59)
(Continued from previous column)	
Boost field	
Tumour bed involved field	36 (61%)
Posterior fossa	23 (39%)
Boost dose	
54 GyRBE	57 (97%)
>54 GyRBE	2 (3%)
Craniospinal radiation dose§	
Median (IQR)	23·4 (23·4–27·0)
18–27 GyRBE (median 23·4)	45 (76%)
36 GyRBE	14 (24%)
Hypothalamus mean dose (D50)	
Median (IQR)	28·4 GyRBE (24·2–42·8)
<40 GyRBE	37 (63%)
≥40 GyRBE	22 (37%)
Cochlear mean dose to each ear (D_{50})	
Median (IQR)	30·4 GyRBE (25·7–38·7)
<30 GyRBE	61 (52%)
≥30 GyRBE	57 (48%)
Cisplatin cumulative dose (n=51)¶	
Median (IQR)	348 mg/m² (275–429)
≤300 mg/m²	17 (33%)
>300 mg/m²	34 (67%)
Use of photons for <20% radiation dose?	
Yes	6 (10%)
No	53 (90%)

*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 M0 patients with <1·5 cm² of residual disease but with anaplastic or large cell variant. ‡ACNS0331, eight patients; ACNS0332, two patients; ACNS0334, one patient; A9961, one patient. RBE=radiobiological equivalent. §Craniospinal 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%

	Progression-free survival			Overall survival		
	5 years (95% CI)	7 years (95% CI)	p value	5 years (95% CI)	7 years (95% CI)	p value
All patients	80% (67–88)	75% (61–84)		83% (70–90)	81% (67–89)	
Risk			0·364			0·195
Standard	85% (69–93)	81% (64–91)		86% (70–94)	86% (70–94)	
Intermediate*	67% (19–90)	67% (19–90)		67% (19–90)	67% (19–90)	
High	71% (41–88)	63% (32–83)		79% (47–93)	70% (38– 88)	
Risk (2008 revision)			0·349			0·071
Standard	85% (69–93)	81% (64–91)		86% (70–94)	86% (70–94)	
Intermediate–high	70% (45–85)	63% (37–81)		75% (50–89)	68% (42–84)	
Histology			0·657			0·320
Classic or desmoplastic	80% (67–89)	75% (61–85)		84% (70–92)	82% (67–90)	
Anaplastic or large cell	75% (31–93)	75% (31–93)		75% (31–93)	75% (31–93)	

*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.

Table 6: **Survival outcomes**

COG/St Jude studies: Packer, JCO 2006; Gajjar, Lanc Onc 2006; Jackacki, JCO 2012; Tarbell, JCO 2013;

Proton vs Photon Medulloblastoma

(Eaton, IJROBP, 2015)

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‡

*Departments of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia; †Department of Biostatistics and Bioinformatics, Cedars-Sinai Medical Center, Los Angeles, California; ‡Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; §Department of Pediatrics, Aflac Cancer and Blood Disorders Center, Atlanta, Georgia; and ‖Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts

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.

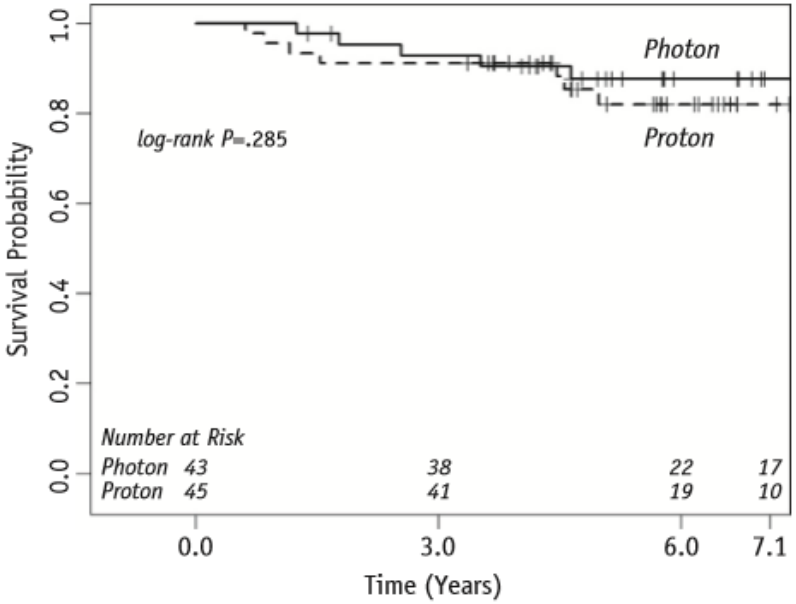


Fig. 1. Kaplan-Meier curves of overall survival for medulloblastoma patients treated with photon and proton radiation therapy.

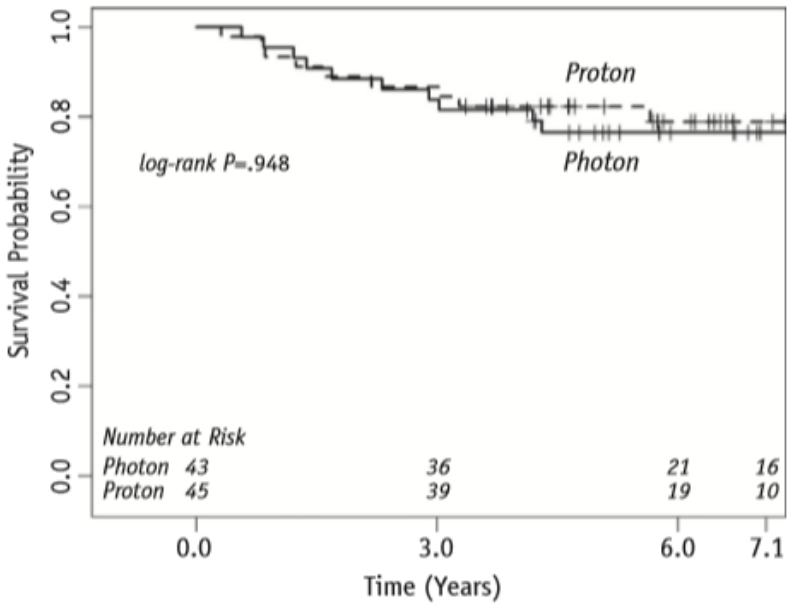


Fig. 2. Kaplan-Meier curves of relapse-free survival for medulloblastoma patients treated with photon and proton radiation therapy.

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.

	Cumulative incidence (95% CI)			p value*
	3 years	5 years	7 years	
All patients	12% (4–25)	16% (6–29)	16% (6–29)	
Risk				0·372
Standard	15% (4–31)	20% (7–38)	20% (7–38)	
Intermediate-high	7% (0–29)	7% (0–29)	7% (0–29)	
Sex				0·080
Male	4% (0–19)	4% (0–19)	4% (0–19)	
Female	20% (6–40)	27% (9–49)	27% (9–49)	
Age (years)				0·357
<8	15% (5–32)	20% (7–38)	20% (7–38)	
≥8	6% (0–25)	6% (0–25)	6% (0–25)	
Age (years)				0·584
<6	12% (2–33)	21% (4–47)	21% (4–47)	
≥6	12% (3–29)	12% (3–29)	12% (3–29)	
Vetriculoperitoneal shunt?				0·337
Yes	22% (3–53)	22% (3–53)	22% (3–53)	
No	10% (2–24)	14% (4–29)	14% (4–29)	
Cisplatin total dose				0·682
≤300 mg/m²	18% (2–46)	18% (2–46)	18% (2–46)	
>300 mg/m²	12% (3–28)	17% (5–35)	17% (5–35)	
Cochlear mean dose (D50)				0·638
<30 GyRBE	14% (2–37)	22% (5–47)	22% (5–47)	
≥30 GyRBE	11% (3–27)	11% (3–27)	11% (3–27)	

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.

	Number of patients	Baseline mean score (95% CI)	Mean change per year (95% CI)	p value
FSIQ	54	104·5 (101·3 to 107·7)	−1·5 (−2·1 to −0·9)	<0·0001
Risk				0·525
Standard	36	104·5 (100·6 to 108·5)	−1·4 (−2·1 to −0·7)	
Intermediate-high	18	104·4 (98·7 to 110·1)	−1·8 (−2·8 to −0·7)	
Sex				0·586
Male	30	104·1 (99·6 to 108·5)	−1·4 (−2·1 to −0·6)	
Female	24	105·0 (100·1 to 109·8)	−1·7 (−2·5 to −0·8)	
Age				0·006
<8 years	34	105·7 (101·6 to 109·7)	−2·0 (−2·7 to −1·3)	
≥8 years	20	102·1 (96·7 to 107·5)	−0·2 (−1·3 to 0·9)	
Craniospinal irradiation dose				0·949
18–27 GyRBE	42	105·1 (101·5 to 108·8)	−1·5 (−2·2 to −0·8)	
36 GyRBE	12	102·1 (95·1 to 109·1)	−1·5 (−2·8 to −0·3)	
Boost field				0·049
Involved field	34	105·6 (101·5 to 109·7)	−2·1 (−2·9 to −1·3)	
Whole posterior fossa	20	103·0 (97·7 to 108·3)	−1·0 (−1·7 to −0·2)	

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

- **<u>CSI in developing kids has an neurocognitive effect. Period. Protons or photons.</u>**

	Number of patients	Baseline mean score (95% CI)	Mean change per year (95% CI)	p value
FSIQ	54	104·5 (101·3 to 107·7)	−1·5 (−2·1 to −0·9)	<0·0001
VCI	53	109·2 (106·0 to 112·4)	−1·3 (−2·0 to −0·7)	<0·0001
Risk				0·435
Standard	36	108·3 (104·4 to 112·1)	−1·2 (−2·0 to −0·4)	
Intermediate-high	17	111·4 (105·7 to 117·1)	−1·7 (−2·9 to −0·6)	
PRI	53	103·5 (100·2 to 106·8)	−0·4 (−1·0 to 0·3)	0·249
Risk				0·555
Standard	36	103·2 (99·2 to 107·3)	−0·3 (−1·0 to 0·5)	
Intermediate-high	17	104·0 (98·1 to 110·0)	−0·7 (−1·9 to 0·5)	
Working memory	41	98·7 (94·0 to 103·3)	−0·8 (−1·8 to 0·3)	0·169
Risk				0·523
Standard	28	96·9 (91·1 to 102·8)	−0·5 (−1·9 to 1·0)	
Intermediate-high	13	101·8 (93·7 to 110·0)	−1·2 (−2·9 to 0·5)	
Processing speed	49	95·3 (91·5 to 99·2)	−2·4 (−3·2 to −1·6)	<0·0001
Risk				0·064
Standard	33	98·2 (93·5 to 102·8)	−3·0 (−4·0 to 2·0)	
Intermediate-high	16	90·0 (83·5 to 96·6)	−1·5 (−2·8 to −0·1)	

Risk is for the 2008 revision. VCI=verbal comprehension index. PRI=perceptual reasoning index. FSIQ=Full Scale Intelligence Quotient. GyRBE=Gray radiobiological equivalents.

Table 3: **Neurocognitive outcomes**

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).*

	3 years	5 years	7 years	p value
Any hormone deficit	27% (16–39)	55% (41–67)	63% (48–75)	
Risk				0·495
Standard	28% (15–43)	58% (40–72)	68% (49–82)	
Intermediate-high	25% (9–46)	50% (26–70)	50% (26–70)	
Growth hormone deficit	22% (12–33)	46% (33–59)	55% (40–68)	
Risk				0·368
Standard	23% (11–37)	50% (33–65)	62% (42–76)	
Intermediate-high	20% (6–40)	40% (18–61)	40% (18–61)	
Thyroid deficiency	12% (5–22)	21% (11–32)	26% (15–38)	
Risk				0·901
Standard	10% (3–22)	21% (10–35)	25% (12–40)	
Intermediate-high	15% (4–34)	20% (6–40)	29% (9–53)	
Adrenal or cortisol deficit	5% (1–13)	9% (3–17)	9% (3–17)	
Risk				0·075
Standard	3% (0–12)	3% (0–12)	3% (0–12)	
Intermediate-high	10% (2–28)	20% (6–40)	20% (6–40)	
Sex hormone deficit	3% (1–11)	3% (1–11)	3% (1–11)	
Risk				0·638
Standard	3% (0–12)	3% (0–12)	3% (0–12)	
Intermediate-high	5% (0–21)	5% (0–21)	5% (0–21)	

Data are cumulative incidence (95% CI). Risk is for the 2008 revision.

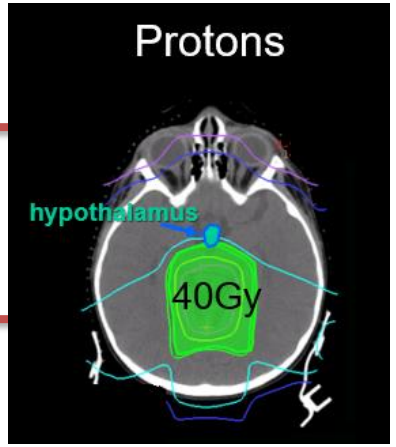
Table 4: **Neuroendocrine outcomes**

Medulloblastoma: Endocrine outcomes (Yock et al. Lanc Onc, 2016)

	3 years	5 years	7 years	p value
Sex				0·592
Male	33% (18–50)	58% (38–73)	64% (41–79)	
Female	19% (7–36)	52% (30–69)	62% (38–79)	
Age (years)				0·499
<8	27% (14–42)	59% (41–74)	69% (48–83)	
≥8	27% (11–47)	47% (24–67)	54% (28–74)	
Craniospinal irradiation dose				0·471
18–27 GyRBE	24% (13–38)	52% (36–66)	62% (44–76)	
36 GyRBE	36% (12–61)	64% (31–84)	64% (31–84)	
Boost field				0·292
Involved field	22% (10–37)	48% (31–64)	58% (37–75)	
Whole posterior fossa	35% (16–54)	65% (41–81)	70% (45–85)	
Hypothalamus mean dose (D50)				0·054
<40 GyRBE	19% (8–33)	44% (27–60)	58% (37–74)	
≥40 GyRBE	41% (20–61)	73% (47–88)	73% (47–88)	

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**



Protons v. Photons Endocrine Comparison (Eaton, Neuro-ongology, 2016)

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

Protons v. Photons Endocrine Comparison (Eaton, Neuro-ongology, 2016)

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 ($p<0.01$)

Protons v. Photons Endocrine Comparison (Eaton, Neuro-ongology, 2016)

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.)

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

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**