AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

XLVIII
CONGRESSO NAZIONALE
AIEOP
Bologna
2-4 Ottobre 2023

tumori embrionari del sistema nervoso centrale: overview

Medulloblastoma

Maura Massimino

Fondazione IRCCS Istituto Nazionale dei Tumori
Bologna, 3 Ottobre 2023

Il sottoscritto Maura Massimino

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

❑ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*

x - *Novartis*

- *Oncoscience*

pediatric brain tumors
EPIDEMIOLOGICAL PREMISES

- Brain tumors represent, by incidence, the second pediatric tumor after leukemia
- 20/25% of the tumors of this age group
- In italy about 350-400 cases are diagnosed every year
- Mortality, in the last two decades, has reduced from 2 / 100,000 to 0.9 / 100,000 events per year:

THAT MEANS THAT 60% OF AFFECTED CHILDREN CAN BECOME ADULT

Survival improvement

- Embryonal tumors, from 1980 to 2009
  - 37% to 60%, as general assessment

  But, around 2000
  - Gap between South and East Europe with 40% and EUROCARE-5 consortium with 66%
  - **Medulloblastoma, from 1959 to 2009**
    - **29% to 73% as general assessment**
    - In Tunisia less than 27% in 1997
    - In Uganda 0 in 2007

And in the meantime

Neuro-Oncology
XX(XX), 1–21, 2021 | doi:10.1093/neuonc/noab106 | Advance Access date 29 June 2021

The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

A S … cation of F … e Opt …

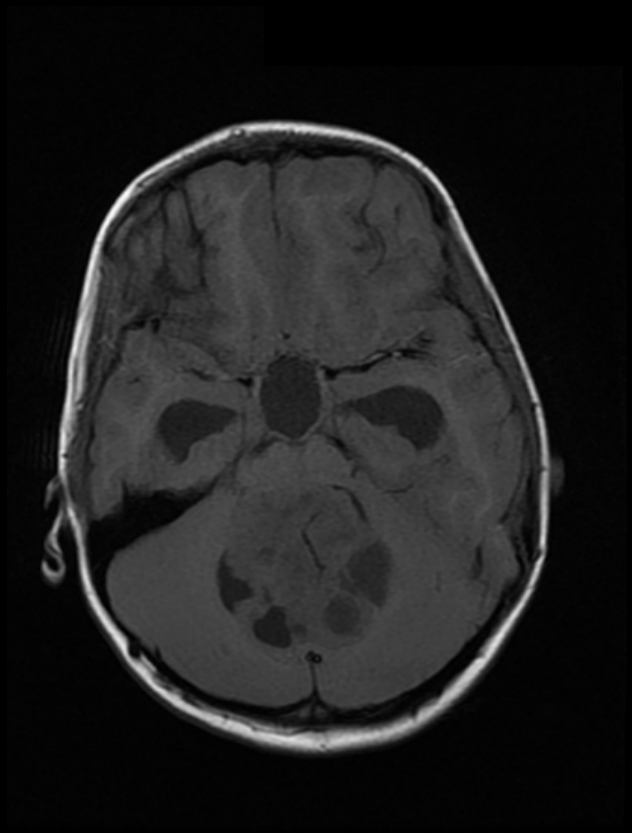
Stefan … ar[8],
Sabrina … Hill[13],
Thomas … g[19,20],
Christia …

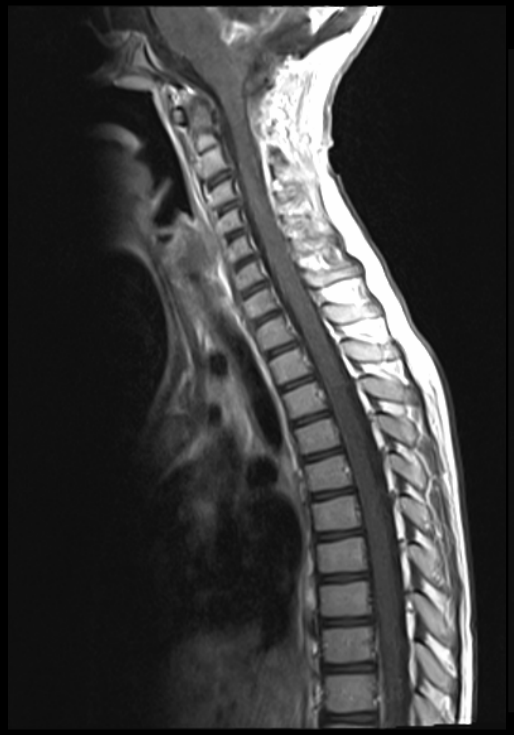
WHO 2016 (rev 4th) classification of brain tumors was a combination of phenotypic and genotypic parameters

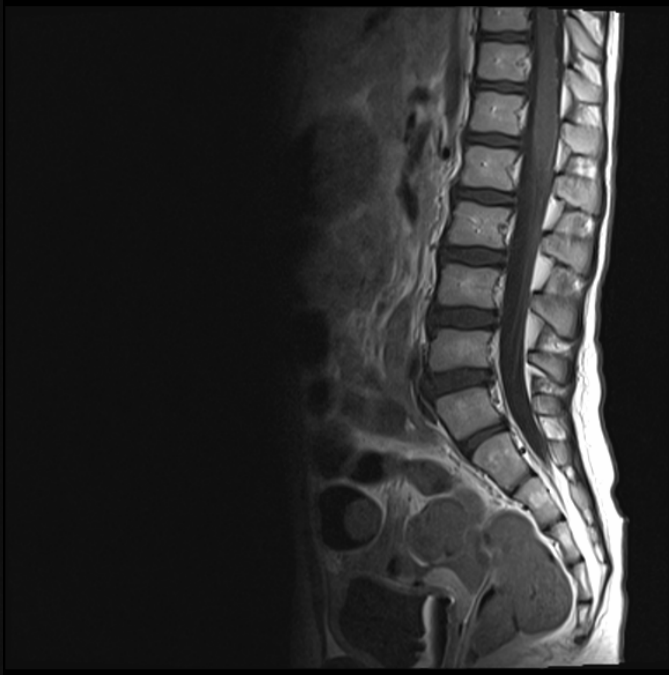
Classification WHO 2021 (5th) introduced molecular criteria essential for diagnosis

Thanks to E. Miele

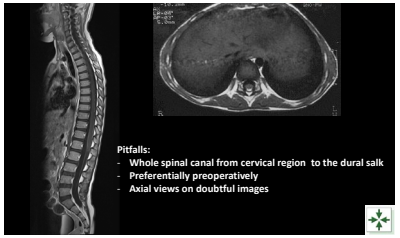
Medulloblastoma



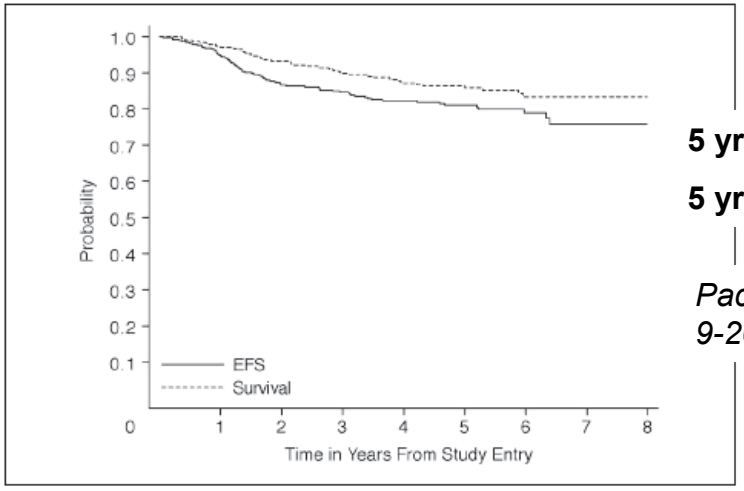




MEDULLOBLASTOMA



- Craniospinal irradiation is needed
  - **Dissemination at diagnosis: 20-35% of patients**
- Craniospinal doses can be reduced in **standard risk conditions** if chemotherapy is thereafter given

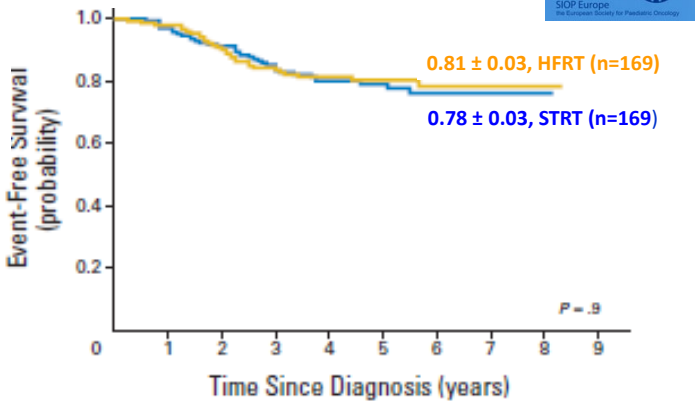


5 yrs EFS 81%

5 yrs OS 86%

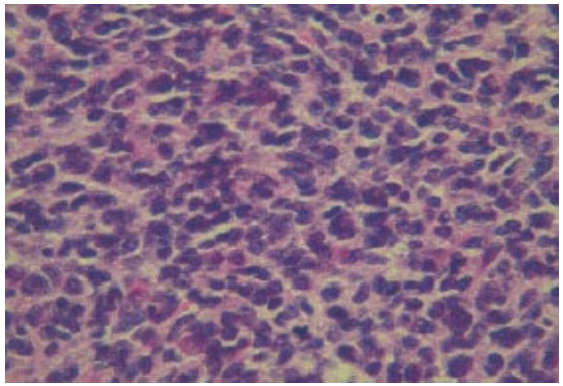
Packer JCO 9-2006

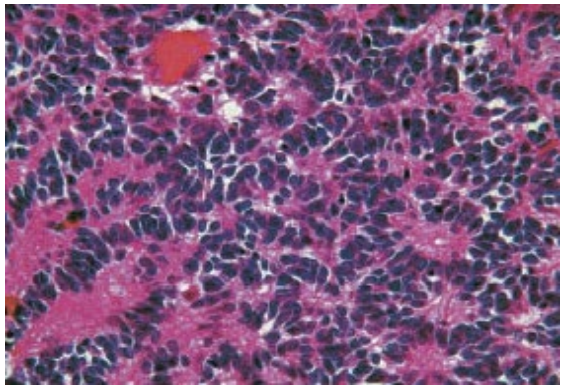
Fig 1. Event-free survival (EFS) and survival from study entry.



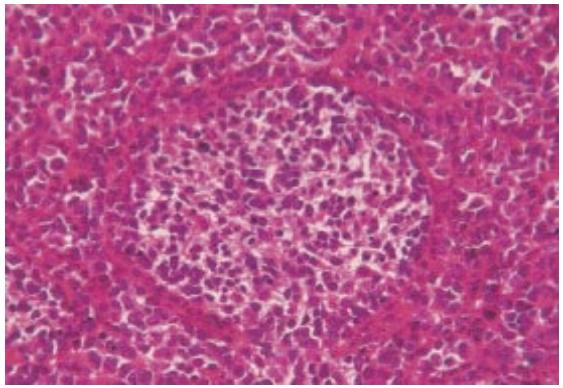
What we have acquired for MEDULLOBLASTOMA
Histological subtypes

Classic (CMB)

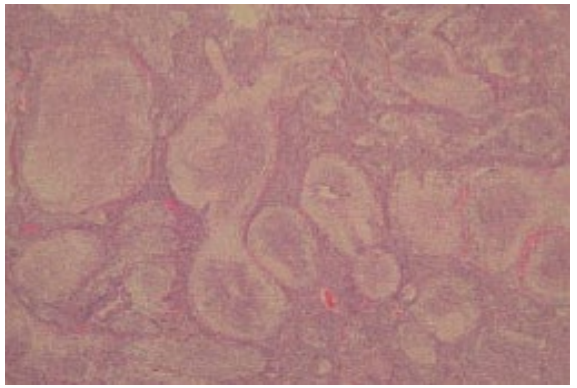




Desmoplastic/nodular (DMB)

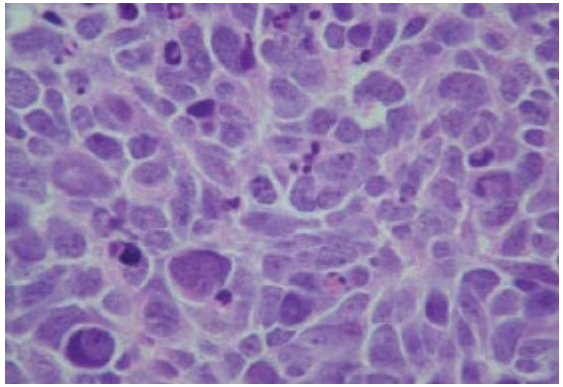


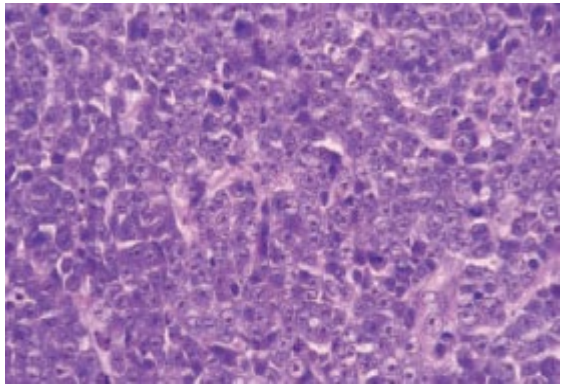
Nodular prevalence (MBEN)



Large cell/ anaplastic (LCA)

bad





Acta Neuropathol (2012) 123:465–472
DOI 10.1007/s00401-011-0922-z

CONSENSUS PAPER

Molecular subgroups of medulloblastoma: the current consensus

Michael D. Taylor · Paul A. Northcott · Andrey Korshunov · Marc Remke · Yoon-Jae Cho · Steven C. Clifford · Charles G. Eberhart · D. Williams Parsons · Stefan Rutkowski · Amar Gajjar · David W. Ellison · Peter Lichter · Richard J. Gilbertson · Scott L. Pomeroy · Marcel Kool · Stefan M. Pfister

Molecular Subgroups of Medulloblastoma

	WNT	SHH	Group 3	Group 4
Northcott (2010)	C6	C3	C1/C5	C2/C4
Kool (2008)	WNT	SHH	Group C	Group D
Thompson (2006)	A	B	E	C/D
	B	C', D	E, A	A, C

DEMOGRAPHICS

Age Group: infant, child, adult

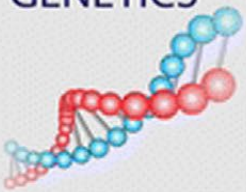
Gender:

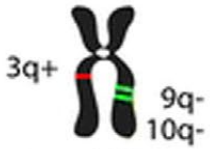
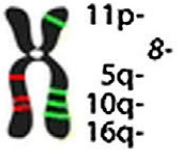
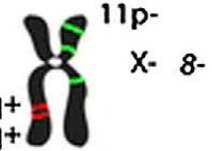
	WNT	SHH	Group 3	Group 4
Age Group				
Gender	♂♂:♀♀	♂♂:♀♀	♂♂:♀	♂♂:♀

CLINICAL FEATURES

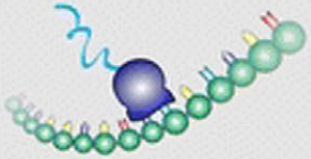
	WNT	SHH	Group 3	Group 4
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate

GENETICS



	WNT	SHH	Group 3	Group 4
	 6-	 3q+ 9q- 10q-	 7+ 1q+ 17q+ 18q+ 11p- 8- 5q- 10q- 16q-	 7+ 17q+ 18q+ 11p- X- 8-
	CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification

GENE EXPRESSION



	WNT	SHH	Group 3	Group 4
	WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
	MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*

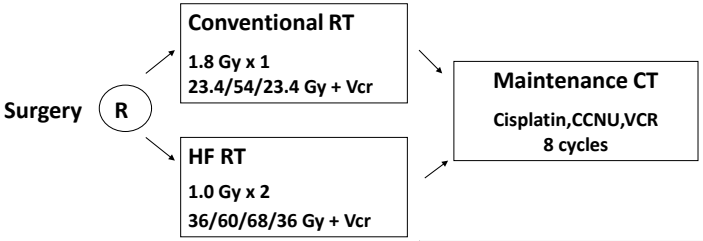
What we have acquired for MEDULLOBLASTOMA
Common strategy in EUROPE

VOLUME 30 · NUMBER 26 · SEPTEMBER 10 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

SIOP Europe
the European Society for Paediatric Oncology

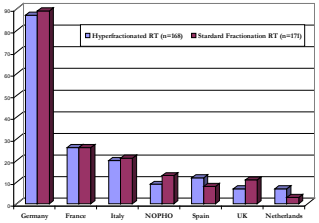
Hyperfractionated Versus Conventional Radiotherapy Followed by Chemotherapy in Standard-Risk Medulloblastoma: Results From the Randomized Multicenter HIT-SIOP PNET 4 Trial

Birgitta Lannering, Stefan Rutkowski, Francois Doz, Barry Pizer, Göran Gustafsson, Aurora Navajas, Maura Massimino, Roel Reddingius, Martin Benesch, Christian Carrie, Roger Taylor, Lorenza Gandola, Thomas Björk-Eriksson, Jordi Giralt, Foppe Oldenburger, Torsten Pietsch, Dominique Figarella-Branger, Keith Robson, Marco Forni, Steven C. Clifford, Monica Warmuth-Metz, Katja von Hoff, Andreas Faldum, Véronique Mosseri, and Rolf Kortmann



Study accrual:

- Jan 2001-December 2006
- 340 patients, 9 Countries, > 122 Centres
- Web-based data collection
- Final evaluation 2010
- Stratification by clinical risk factors



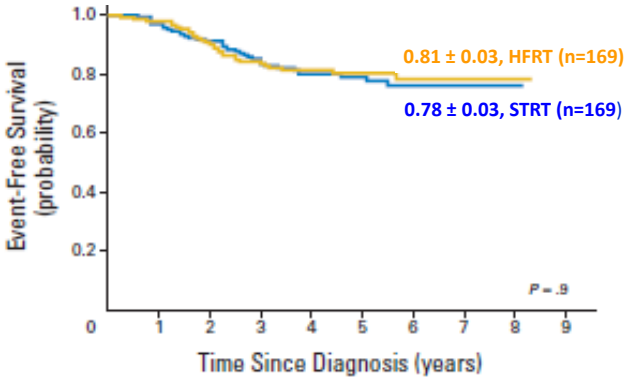


Table 1: Clinical, pathological and molecular characteristics of the HIT-SIOP-PNET4 cohort (n = 338; all patients with available data are shown), and univariate (Cox proportional hazards) analysis of their prognostic associations.

Variable	Categories	n	Five-year pEFS ±SE	Univariate Hazard Ratio (± CI)	p-value
+Gender	Male (M) Female (F) Ratio (M:F)	211 127 1.66:1	0.79 ± 0.03 0.80 ± 0.04	1.0 0.85 (0.52–1.41)	0.533
Age*	Median (years) Min.-Max.	9.0 3–20	–	0.99 (0.93–1.05)	0.754
+Pathology**	All others LCA	320 16	0.80 ± 0.02 0.64 ± 0.14	1.0 1.76 (0.71–4.37)	0.262
+Residual tumor	≤1.5 cm² >1.5 cm²	286 31	0.82 ± 0.02 0.64 ± 0.09	1.0 2.34 (1.22–4.50)	**0.020**
+Time from diagnosis to radiotherapy	<49 days ≥49 days	305 30	0.81 ± 0.02 0.67 ± 0.09	1.0 1.93 (0.99–3.79)	**0.050**
Time from diagnosis to radiotherapy*	Median (days) Min.-Max.	35 15–92	–	1.03 (1.00–1.05)	**0.025**
β-catenin nuclear accumulation	No Yes	196 58	0.75 ± 0.03 0.91 ± 0.04	1.0 0.40 (0.17–0.94)	**0.019**
CTNNB1 mutation	No Yes	164 31	0.75 ± 0.04 0.89 ± 0.06	1.0 0.37 (0.12–1.21)	0.058
MYC/*MYCN* amplification (PCR)	No Yes	160 23	0.79 ± 0.03 0.72 ± 0.09	1.0 1.26 (0.53–3.00)	0.606
MYC amplification (iFISH)	No Yes	157 4	0.81 ± 0.03 1.00	1.0 0.22 (0.02–29.16)	0.542
MYCN amplification (iFISH)	No Yes	147 13	0.82 ± 0.03 0.77 ± 0.12	1.0 1.41 (0.42–4.67)	0.588
17p loss and/or 17q gain (diploid(cen)) (iFISH)	No Yes	127 24	0.85 ± 0.03 0.57 ± 0.10	1.0 3.12 (1.44–6.76)	**0.007**
Polyploid	No Yes	72 85	0.78 ± 0.05 0.83 ± 0.04	1.0 0.81 (0.39–1.68)	0.572
PTCH1 (9q22) loss	No Yes	138 13	0.80 ± 0.03 0.85 ± 0.10	1.0 0.82 (0.19–3.46)	0.781

Or, how low can CSI doses be if giving chemotherapy? How much CSI is needed?

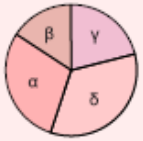
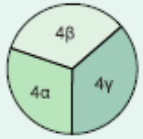
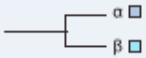
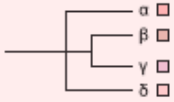
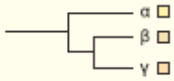
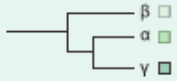
Not really known for every Mbl subtype:

- a 5.4 Gy reduction in the CSI dose (*18 Gy*) was prescribed in patients 3-7 years (COG ACNS0331) with a non-inferiority randomized design
- The 5-year **EFS** in SD-CSI and LD-CSI was **82.5% and 71.4%,** respectively (p 0.028)
- The 5-year **OS** in SD-CSI and LD-CSI was **85.6% and 77.5%**, respectively (p 0.049)
- **decreasing CSI dose to 18 Gy may increase risk of recurrence and is not recommended without subgrouping**

Children's Oncology Group Phase III Trial of Reduced-Dose and Reduced-Volume Radiotherapy With Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma

J Clin Oncol 39:2685-2697. © 2021

How far we can expand this classification?

Subgroup		WNT		SHH				Group 3			Group 4		
Subtype		WNT α	WNT β	SHH α	SHH β	SHH γ	SHH δ	Group 3α	Group 3β	Group 3γ	Group 4α	Group 4β	Group 4γ
Subtype proportion													
Subtype relationship													
Clinical data	Age												
	Histology			LCA Desmoplastic	Desmoplastic	MBEN Desmoplastic	Desmoplastic						
	Metastases	8.6%	21.4%	20%	33%	8.9%	9.4%	43.4%	20%	39.4%	40%	40.7%	38.7%
	Survival at 5 years	97%	100%	69.8%	67.3%	88%	88.5%	66.2%	55.8%	41.9%	66.8%	75.4%	82.5%
Copy number	Broad	6^-		$9q^-$, $10q^-$, $17p^-$		Balanced genome		7^+, 8^-, 10^-, 11^-, i17q		8^+, i17q	$7q^+$, $8p^-$, i17q	i17q	$7q^+$, $8p^-$, i17q (less)
	Focal			*MYCN* amp, *GLI2* amp, *YAP1* amp	*PTEN* loss		$10q22^-$, $11q23.3^-$		*OTX2* gain, *DDX31* loss	*MYC* amp	*MYCN* amp, *CDK6* amp	*SNCAIP* dup	*CDK6* amp
Other events				*TP53* mutations			*TERT* promoter mutations		High *GFI1/1B* expression				

Age (years): 0-3 >3-10 >10-17 >17

Cavalli et al., 2017, Cancer Cell *31*, 737–754
June 12, 2017 © 2017 Elsevier Inc.
http://dx.doi.org/10.1016/j.ccell.2017.05.005

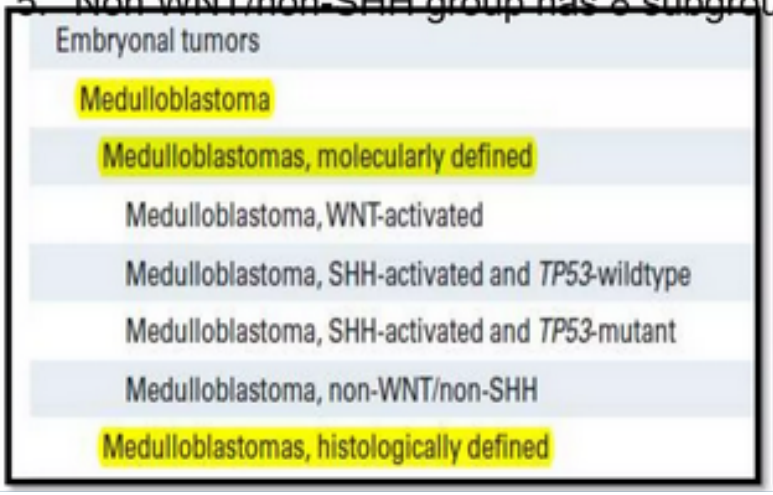
What is standard risk?

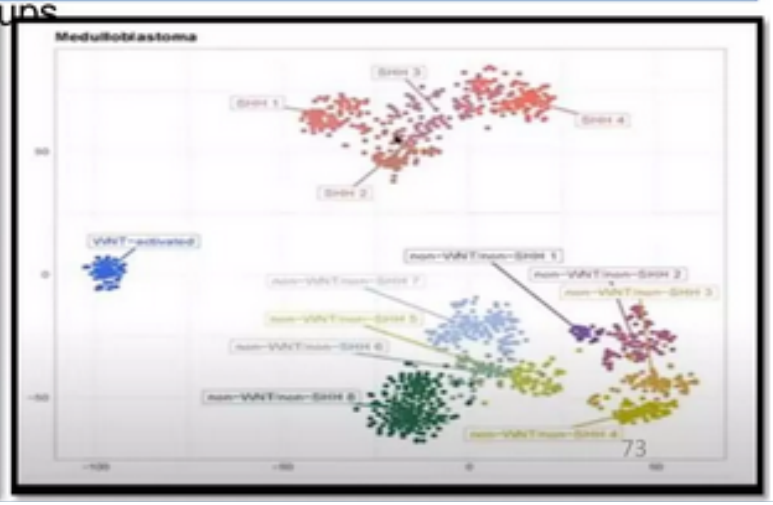
- **standard risk conditions** have changed over time
  - Not residual disease, neither absence of metastases are enough
  - + no LCA histology enough either
  - + no MYC/MYCN amplification
  - + no Tp53 mutation

and (!)…

Changes in Medulloblastoma classification- WHO 5th edition

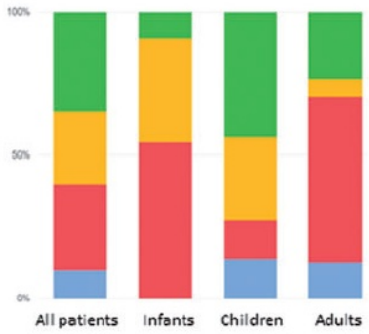
1. The histopathological classification of medulloblastoma listed in the 2016 WHO classification comprised 4 morphologic types: classic, desmoplastic/nodular, medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic.
2. These have now 2021 been combined into 1 section that describes them as morphologic patterns of an inclusive tumor type, Medulloblastoma, histologically defined.
3. WNT activated is a single entity
4. SHH having 4 subgroups
5. Non-WNT/non-SHH group has 8 subgroups

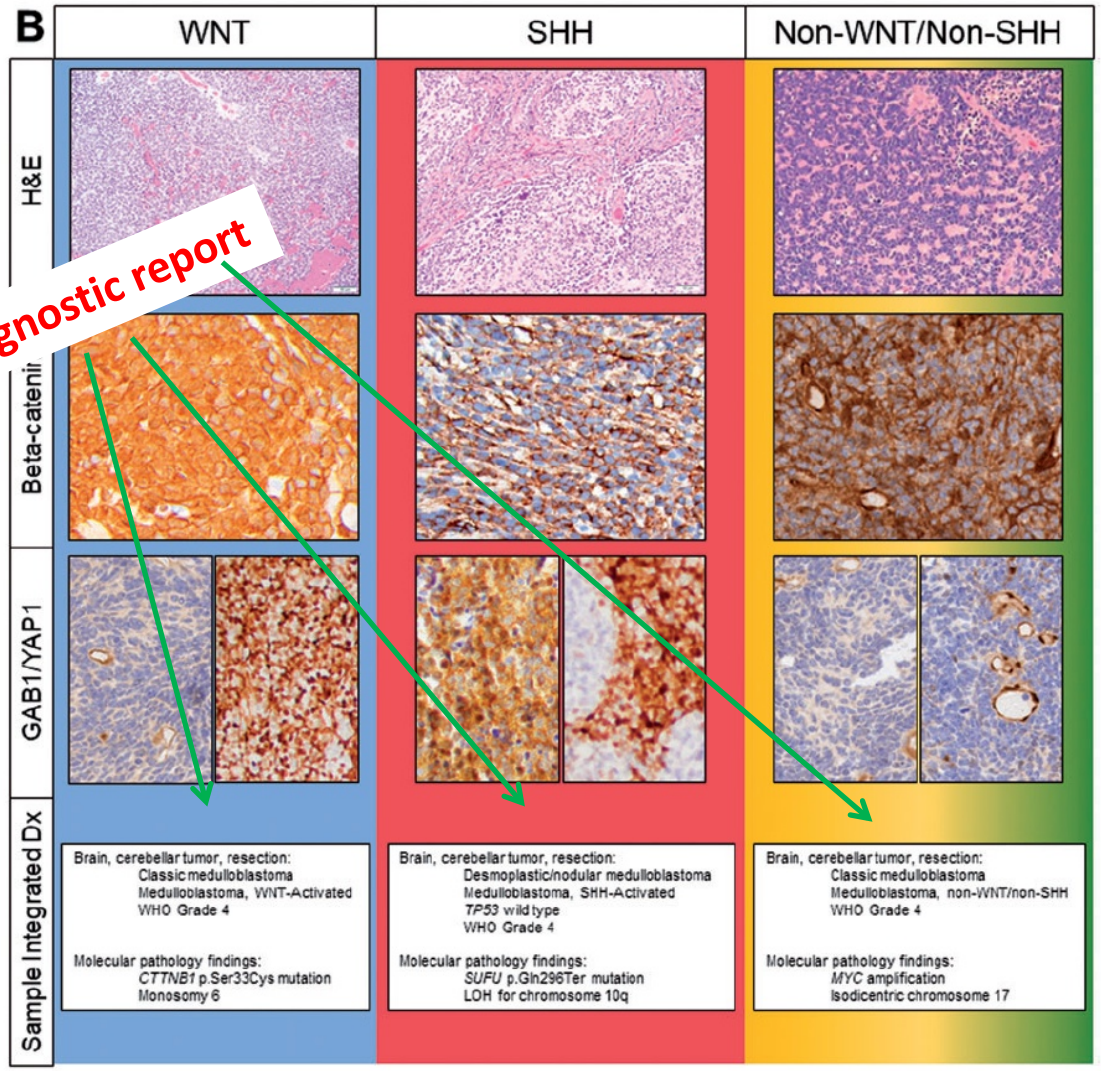




A

	WNT	SHH	Group 3	Group 4
Percent of MB	10	30	25	35
Age Group	Child>Adult	Infant, Adult>Child	Child, Infant	Child>Infant, Adult
Histology	Classic, rarely LC/A	D/N, classic, LC/A, MBEN*	Classic, LC/A	Classic, LC/A
Metastasis	Rarely metastatic	Uncommonly metastatic	Very frequently metastatic	Frequently metastatic
Prognosis	Very good	Infants good, others intermediate	Poor	Intermediate





The ideal diagnostic report

Invited Article

Medulloblastoma: WHO 2021 and Beyond

Jennifer A Cotter[1] and Cynthia Hawkins[2,3,4]

Pediatric and Developmental Pathology
2022, Vol. 25(1) 23–33

DOI: 10.1177/1093526621018931
journals.sagepub.com/home/pdp
SAGE

SIOP-E trials and biological studies: Driving translational advances

SIOP Europe
the European Society for Paediatric Oncology

Clinically-driven

- **Standard** — UKCCSG-SIOP-PNET3 1994-2000 — FFPE
- **Standard** — HIT-SIOP-PNET4 2000-06 — FFPE

Biologically-driven

- **Standard Favourable** — SIOP-PNET5-MB 2014-22 — FFPE + FZ, Blood, CSF
- **High-risk** — SIOP-HR-MB 2021-28 — FFPE + FZ, Blood, CSF
- **Standard Favourable** — SIOP-MB6 In planning — FFPE + FZ, Blood, CSF

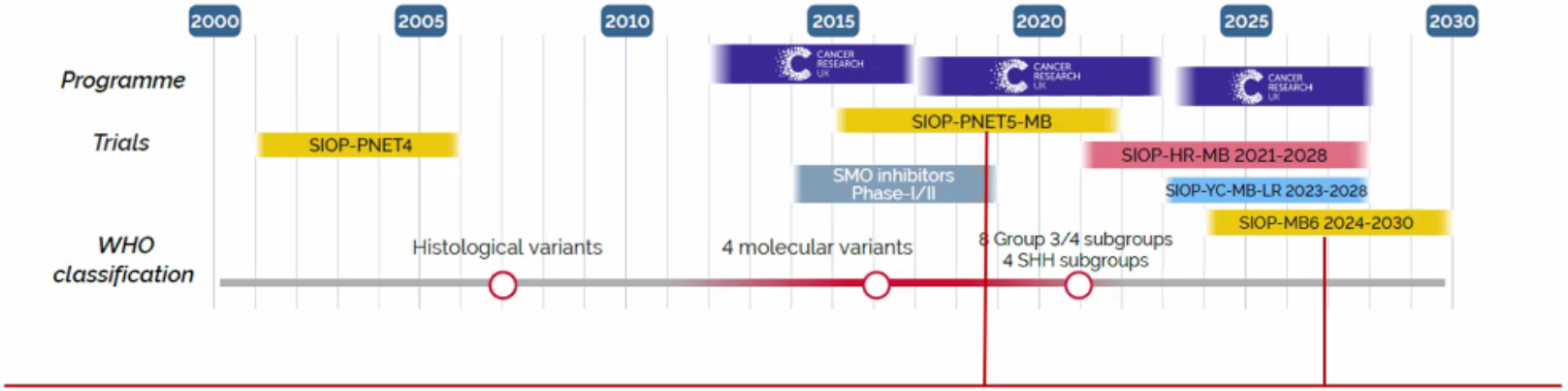
Infant — SIOP-YC-MB-LR 2023-28 — FFPE + FZ, Blood, CSF

Newcastle University / Centre for Cancer

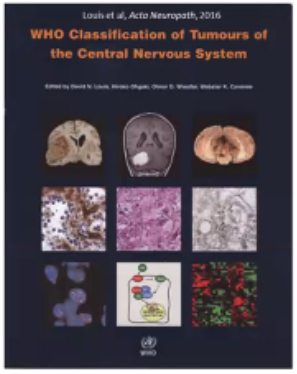
Trials biological studies

CANCER RESEARCH UK

Biomarker chronology: Clinical translation



Trial	Group	Biomarkers		Leads	Date
NON-INFANT (3-16yrs)					
SIOP-PNET5-MB	Favourable-risk	WNT	Selection Stratification	Biology: Clifford Path: Pietsch Cls: Rutkowski, Doz UK Cl: Michalski	To 2022
	Standard-risk	SHH, MYC/N			
SIOP-HR-MB	High-risk	LCA, TP53	Selection Novel agents Randomisation	Biology: Clifford Path: Pietsch Cl: Bailey	2021-28
INFANT (<3yrs)					
SIOP-YC-MB	Favourable-risk	SHH	Selection Stratification	Biology: Clifford Path: Pietsch Cls: Dufour, Rutkowski UK Cl: Bailey	2023-28
	High-risk	DN/LCA, MYC/N			



- First international trials
- A biomarker-driven trial for every medulloblastoma patient
- High-quality biomaterial collection

Newcastle University / Centre for Cancer

SIOP PNET 5 MB

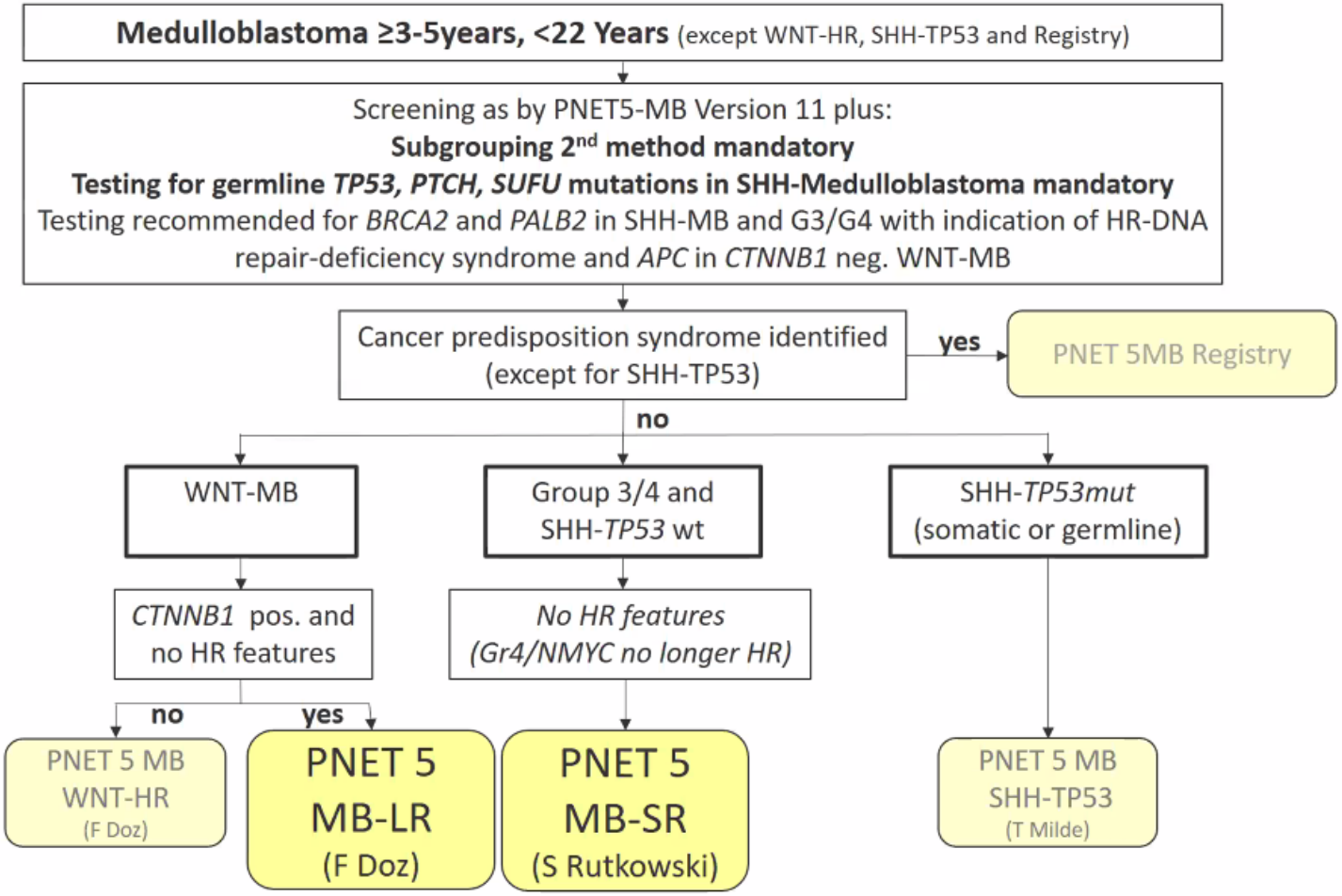
EudraCT-Nr. 2011-004868-30

- European study (16 countries) for children older than 3 to 5 years
- Stratification according to clinical and biological criteria

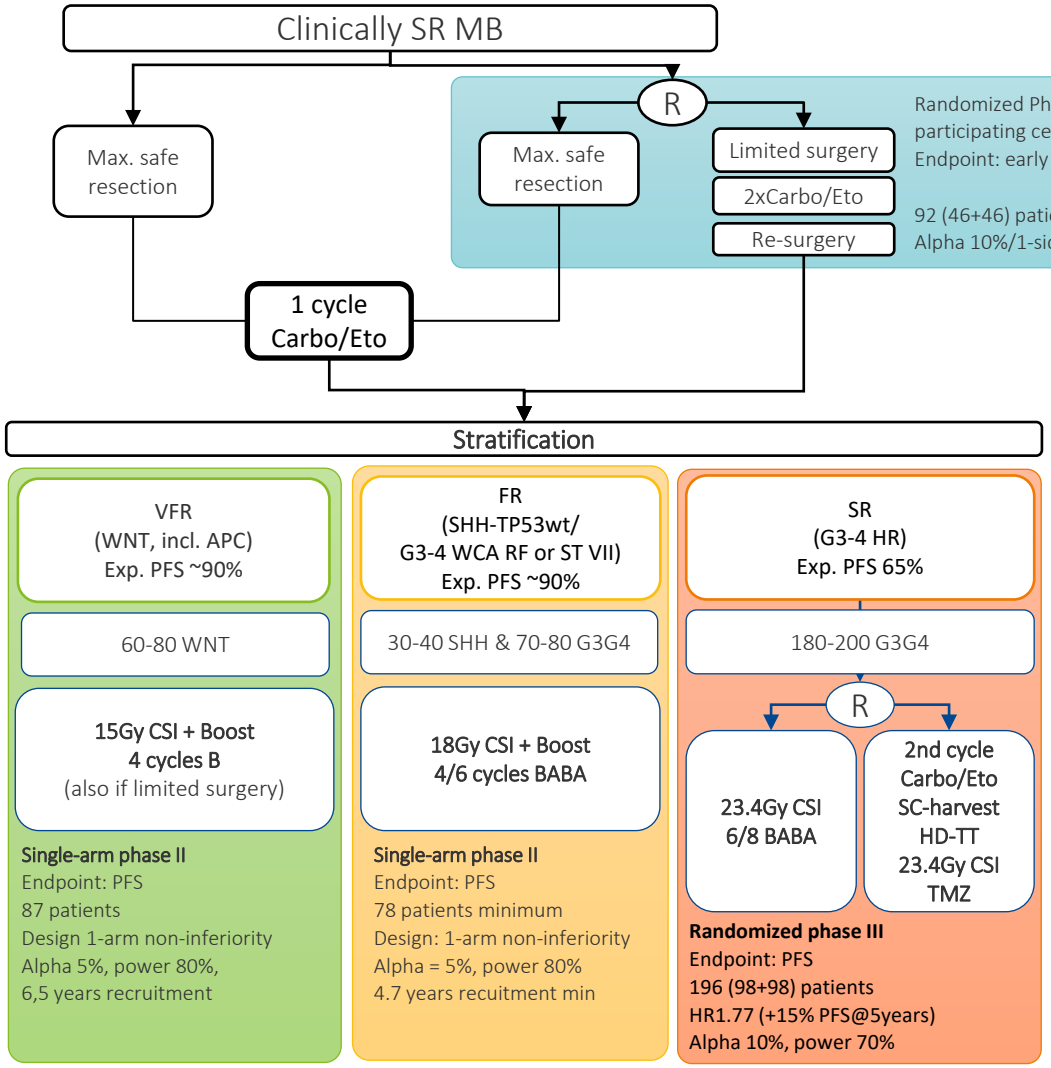
- LR: Low-risk medulloblastoma (Phase II; Co-PI: F. Doz)
- SR: Standard-risk medulloblastoma (Phase III)

KiNDER UKE

PNET5 MB Version 13



SIOP MB6



Total No patients	~380
Trial duration	6 (-8) years
Participating countries	SIOP-E
Sponsor	Germany

Conclusions: What We Have For Standard Risk Medulloblastoma

- **NO NEW DRUGS but**
  - **Risk tailored protocols**
  - **And NEW way of using old drugs**
    - **Less toxicity forecast for «better» disease**
    - **Shorter duration**
    - **Sinergy (RT + CT) evaluation for «less good» diseases**

High-risk medulloblastoma

Screening

SIOP-HRMB is an international, prospective, phase III randomised trial in patients older than age of 3 years with 'high-risk' medulloblastoma (HR-MB).

The trial has two main objectives which are:

- To evaluate whether the outcome in children, young people and adults with HR-MB is improved over standard (once a day) radiotherapy for those treated with:

  (i) hyperfractionated-accelerated (twice a day) radiotherapy (HART), or

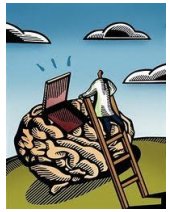
  (ii) high-dose therapy (HDT) with thiotepa followed by conventional RT.

- To evaluate whether the outcome in HR-MB is different for those treated with two different maintenance chemotherapy therapies.

Alternating with VCR/ Cyclo (Total: 8 cycles)	5/28 days x 6 cycles	

medulloblastoma: also….l[illegible] effects

Unwanted, unknown



All patients!

- More severe if young age at diagnosis

Follow-up:

- Rehabilitation (**from the very beginning!)**
- Endocrine/ internistic (hypothalamus/pituitary, gonads)
- Orthopaedic (post spinal RT)
- Ophthalmological (HICP, RT)
- Audiometric (RT, CDDP)
- Neurocognitive/Schooling
- Neurological
- Dermatological
- Risk of second tumour (HGG, meningioma, cavernoma)
- Follow-up after CT (renal, fertility …)
- Cosmetic (hair, height, weight…)
- Social (friends, work, family)

No Time For Revolution

But For Hope…

- **An improved understanding of the molecular genetics, epigenetics, and cellular biology underpinning childhood brain tumours will potentially enable more effective and less toxic treatment strategies to be developed and implemented**
- **This could spare children from the severely detrimental consequences associated with conventional treatment protocols**
- **and improve the outlook for patients with currently incurable disease**

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