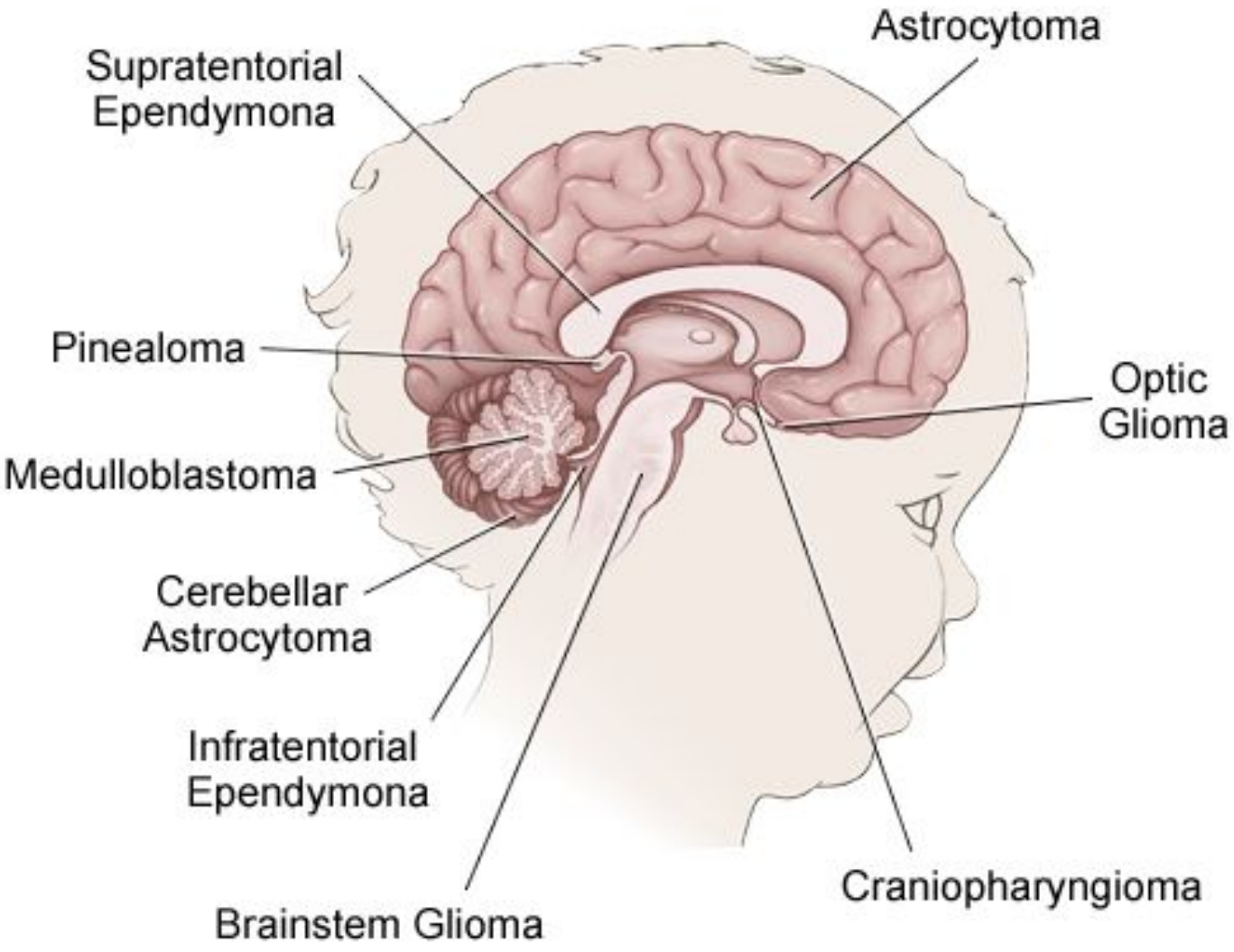
Formazione in oncoematologia pediatrica:
dall'organizzazione della rete pediatrica oncologica regionale alla condivisione di protocolli clinico-assistenziali

NOVITÀ IN AMBITO DI NEURO-ONCOLOGIA

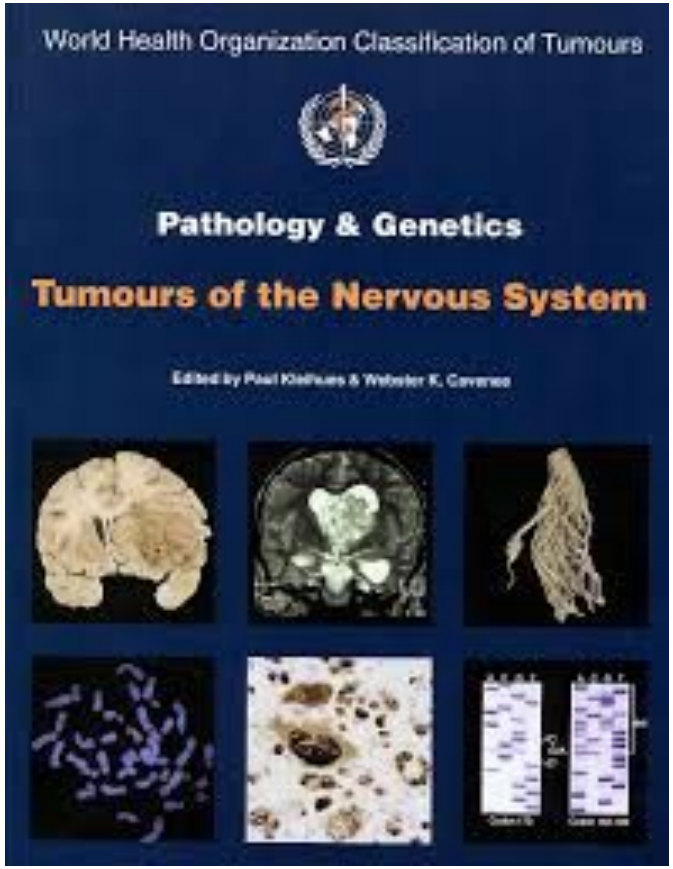
EVA PASSONE
Clinica Pediatrica Udine

Location of Different Types of Brain Tumors



Classificazione WHO

2007



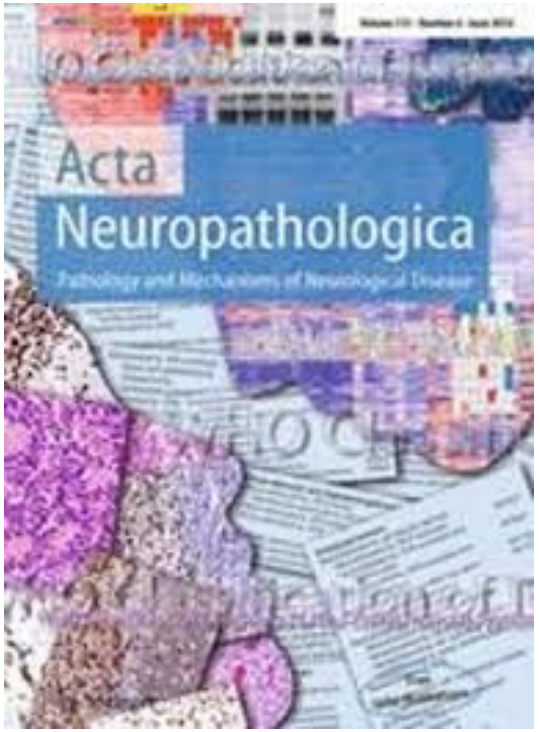
2016

Acta Neuropathol (2016) 131:803–820
DOI 10.1007/s00401-016-1545-1

REVIEW

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis[1] · Arie Perry[2] · Guido Reifenberger[3,4] · Andreas von Deimling[4,5] · Dominique Figarella-Branger[6] · Webster K. Cavenee[7] · Hiroko Ohgaki[8] · Otmar D. Wiestler[9] · Paul Kleihues[10] · David W. Ellison[11]

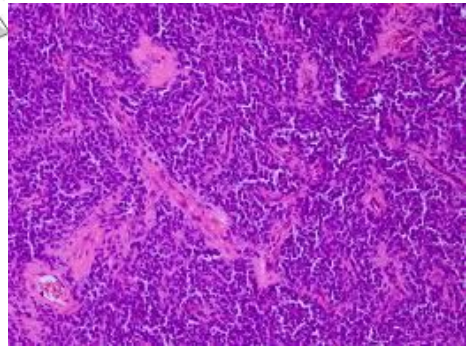


PASSATO

Sede

Caratteristiche istopatologiche

- Grado (I-IV)
- Cellula di origine

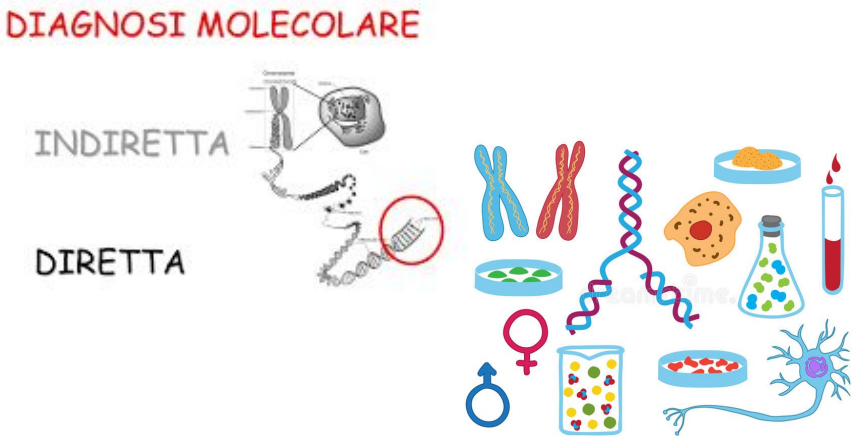


PRESENTE

Come in passato

+

Caratteristiche biologiche



Classificazione WHO 2016

Layer 1: Integrated diagnosis (incorporating all tissue-based information)
Layer 2: Histological classification
Layer 3: WHO grade (reflecting natural history)
Layer 4: Molecular information

Table 3. Diagnosis example: atypical teratoid/rhabdoid tumor.

	A	B
Integrated diagnosis	Atypical teratoid/rhabdoid tumor, WHO grade IV	Embryonal tumor with rhabdoid features, WHO grade IV
Histological classification	Embryonal tumor with rhabdoid features	Embryonal tumor with rhabdoid features
WHO grade	IV	IV
Molecular information	INI1 loss of protein expression/mutation or BRG1 loss of protein expression/mutation	INI1 and BRG1 protein expression retained/not mutated or molecular/immunohistochemical testing not performed

In this example, using the layered diagnosis format, the integrated diagnosis of atypical teratoid/rhabdoid tumor is only possible in the setting of either INI1 or BRG1 loss of protein expression or mutation (column A); without these findings, only a descriptive diagnosis is possible (column B). (Note that this is an example only and that the eventual definition will result from the WHO classification updating process.)

Brain Pathology ISSN 1015-6305

MISCELLANEOUS

International Society of Neuropathology-Haarlem Consensus Guidelines for Nervous System Tumor Classification and Grading

David N. Louis[1]; Arie Perry[2]; Peter Burger[3]; David W. Ellison[4]; Guido Reifenberger[5,6]; Andreas von Deimling[6,7]; Kenneth Aldape[8]; Daniel Brat[9]; V. Peter Collins[10]; Charles Eberhart[3]; Dominique Figarella-Branger[11]; Gregory N. Fuller[12]; Felice Giangaspero[13,14]; Caterina Giannini[15]; Cynthia Hawkins[16]; Paul Kleihues[17]; Andrey Korshunov[6,18]; Johan M. Kros[19]; M. Beatriz Lopes[20]; Ho-Keung Ng[21]; Hiroko Ohgaki[22]; Werner Paulus[23]; Torsten Pietsch[24]; Marc Rosenblum[25]; Elisabeth Rushing[26]; Figen Soylemezoglu[27]; Otmar Wiestler[28]; Pieter Wesseling[29,30]

Table 5. Example: integrated diagnoses for WHO grade II adult diffuse gliomas.[#]

		Histologic classification		
		Diffuse astrocytoma	**Oligodendroglioma**	**"Oligoastrocytoma" or ambiguous histology**
Molecular information	**IDH-mut, 1p/19q-nondel, ATRX loss**	*Diffuse astrocytoma, ATRX loss of expression*	*Diffuse glioma* (oligodendroglioma phenotype), 1p/19q non-deleted, ATRX loss of expression*	*Diffuse astrocytoma, ATRX loss of expression*
	IDH-mut, 1p/19q-codel, ATRX intact	*Diffuse glioma (astrocytoma phenotype), 1p/19q-codeleted*	*Oligodendroglioma, 1p/19q-codeleted*	*Oligodendroglioma, 1p/19q-codeleted*
	IDH wild type	*Diffuse astrocytoma, IDH wild type**	*Diffuse glioma* (oligodendroglioma phenotype), IDH wild type**	*Diffuse astrocytoma, IDH wild type**
	Testing not performed	*Diffuse astrocytoma, NOS*	*Oligodendroglioma, NOS*	*"Diffuse glioma, NOS"*

This example shows how the integrated diagnostic terms for adult WHO grade II diffuse gliomas (names in italics in boxes) could involve a combination of histological and molecular data, although an NOS (not otherwise specified) diagnosis would be made in the absence of molecular information (bottom row). Highlighted in light gray are the common, narrowly histologically and molecularly defined, "classic" diffuse astrocytoma and oligodendroglioma. Note that in this suggested scheme, the term "oligoastrocytoma" does not appear in a diagnostic box, with the last column showing the alternative diagnoses for what has been inconsistently termed "oligoastrocytoma."

[#]A similar classification scheme would apply for WHO grade III, anaplastic gliomas.

*This tumor type may include gliomas that carry genetic alterations similar to primary glioblastoma (eg, +7/–10, EGFR gene amplification) and are associated with poor prognosis, in particular in the setting of anaplastic (WHO grade III) histology. (Note that this table is an example only; the eventual definitions would result from the WHO classification updating process.)

Abbreviations: 1p/19q-codel = whole-arm 1p and 19q co-deletion; ATRX intact = retained nuclear expression by immunohistochemistry; ATRX loss = loss of nuclear expression in tumor cells (with retained expression in non-neoplastic cells as positive control); Mut = mutant form.

Classificazione WHO 2016

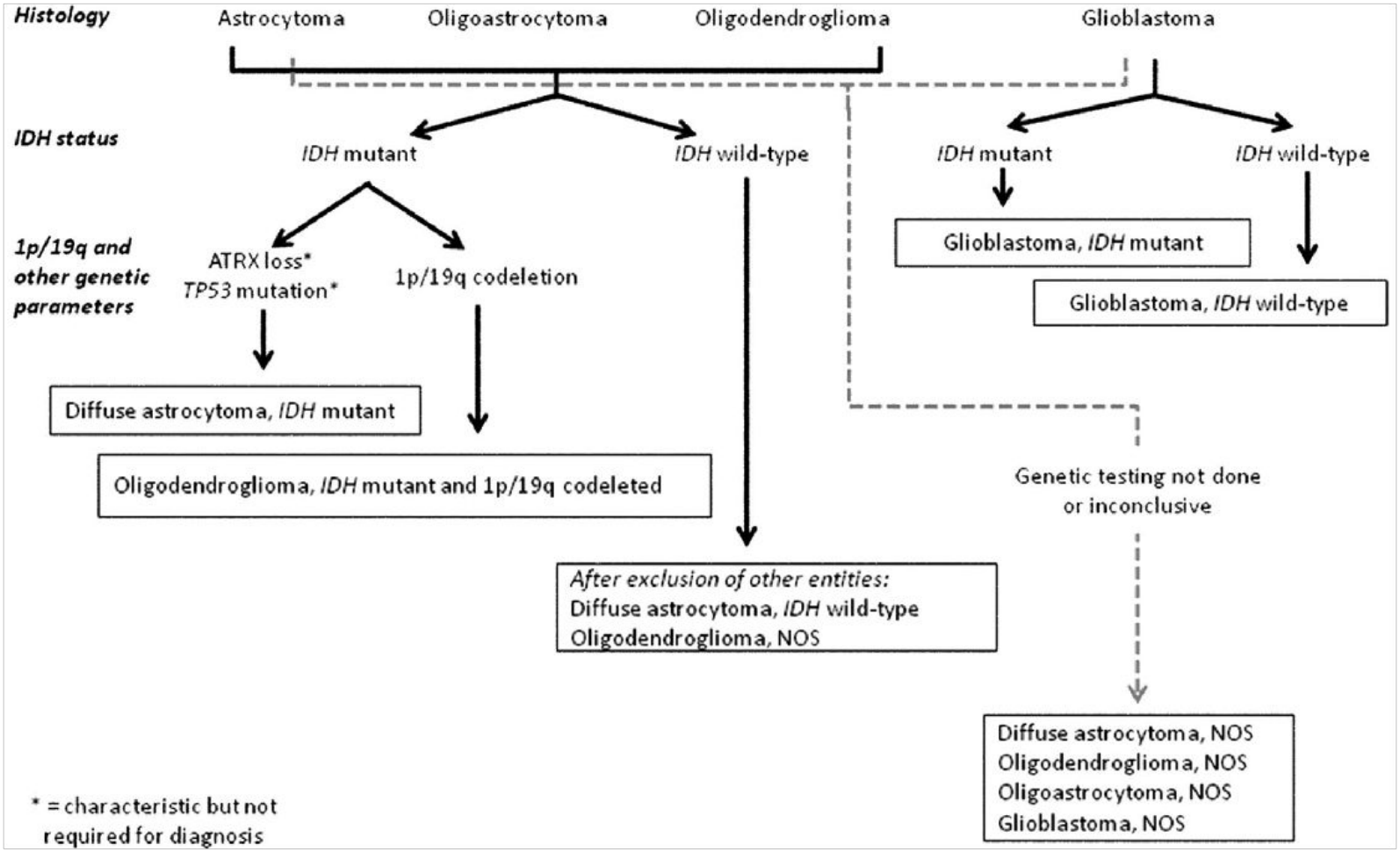


Fig. 1 A simplified algorithm for classification of the diffuse gliomas based on histological and genetic features (see text and 2016 CNS WHO for details). A caveat to this diagram is that the diagnostic "flow" does not necessarily always proceed from histology first to molecular genetic features next, since molecular signatures can sometimes outweigh histological characteristics in achieving an "integrated" diagnosis. A similar algorithm can be followed for anaplastic-level diffuse gliomas; * Characteristic but not required for diagnosis. Reprinted from [27], with permission from the WHO

Differenze classificative

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours	
Pilocytic astrocytoma	9421/1[1]
Pilomyxoid astrocytoma	*9425/3**
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Cellular	9391/3
Papillary	9393/3
Clear cell	9391/3
Tanycytic	9391/3
Anaplastic ependymoma	9392/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	*9390/1**
Choroid plexus carcinoma	9390/3
Other neuroepithelial tumours	
Astroblastoma	9430/3
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	*9431/1**
Neuronal and mixed neuronal-glial tumours	
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Desmoplastic infantile astrocytoma/ganglioglioma	9412/1
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Central neurocytoma	9506/1
Extraventricular neurocytoma	*9506/1**
Cerebellar liponeurocytoma	*9506/1**
Papillary glioneuronal tumour	*9509/1**
Rosette-forming glioneuronal tumour of the fourth ventricle	*9509/1**
Paraganglioma	8680/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	*9395/3**
Embryonal tumours	
Medulloblastoma	9470/3
Desmoplastic/nodular medulloblastoma	9471/3
Medulloblastoma with extensive nodularity	*9471/3**
Anaplastic medulloblastoma	*9474/3**
Large cell medulloblastoma	9474/3
CNS primitive neuroectodermal tumour	9473/3
CNS Neuroblastoma	9500/3
CNS Ganglioneuroblastoma	9490/3
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Atypical teratoid / rhabdoid tumour	9508/3
TUMOURS OF CRANIAL AND PARASPINAL NERVES	
Schwannoma (neurilemoma, neurinoma)	9560/0
Cellular	9560/0
Plexiform	9560/0
Melanotic	9560/0
Neurofibroma	9540/0
Plexiform	9550/0

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) (6144) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours and /1 for borderline or uncertain behaviour.

* The italicised numbers are provisional codes proposed for the 4th edition of ICD-O. While they are expected to be incorporated into the next ICD-O edition, they currently remain subject to change.

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II

Classificazione WHO 2016

Table 2 Summary of the major changes in the 2016 CNS WHO

Formulating concept of how CNS tumor diagnoses are structured in the molecular era
Major restructuring of diffuse gliomas, with incorporation of genetically defined entities
Major restructuring of medulloblastomas, with incorporation of genetically defined entities
Major restructuring of other embryonal tumors, with incorporation of genetically defined entities and removal of the term "primitive neuroectodermal tumor"
Incorporation of a genetically defined ependymoma variant
Novel approach distinguishing pediatric look-alikes, including designation of novel, genetically defined entity
Addition of newly recognized entities, variants and patterns
IDH-wildtype and IDH-mutant glioblastoma (entities)
Diffuse midline glioma, H3 K27M–mutant (entity)
Embryonal tumour with multilayered rosettes, C19MC-altered (entity)
Ependymoma, RELA fusion–positive (entity)
Diffuse leptomeningeal glioneuronal tumor (entity)
Anaplastic PXA (entity)
Epithelioid glioblastoma (variant)
Glioblastoma with primitive neuronal component (pattern)
Multinodular and vacuolated pattern of ganglion cell tumor (pattern)
Deletion of former entities, variants and terms
Gliomatosis cerebri
Protoplasmic and fibrillary astrocytoma variants
Cellular ependymoma variant
"Primitive neuroectodermal tumour" terminology
Addition of brain invasion as a criterion for atypical meningioma
Restructuring of solitary fibrous tumor and hemangiopericytoma (SFT/HPC) as one entity and adapting a grading system to accommodate this change
Expansion and clarification of entities included in nerve sheath tumors, with addition of hybrid nerve sheath tumors and separation of melanotic schwannoma from other schwannomas
Expansion of entities included in hematopoietic/lymphoid tumors of the CNS (lymphomas and histiocytic tumors)

Most Common Brain and CNS Tumors by Age

CBTRUS Statistical Report: NPCR and SEER Data from 2004-2006

Age	Most common histology	Second most common histology
0-4	Embryonal/ medulloblastoma	Pilocytic astrocytoma
5-9	Pilocytic astrocytoma	Malignant glioma, NOS
10-14	Pilocytic astrocytoma	Neuronal/glial
15-19	Pituitary	Pilocytic astrocytoma

CBTRUS, Central Brain Tumor Registry of the United States


GOD... THE HUMAN GENOME CODE'S BEEN UNRAVELLED
DAMN HACKERS!!! NOW, I HAVE TO CHANGE THE PASSWORD

PROGETTO PENSIERO

REVISIONE CENTRALIZZATA ISTOLOGIA

DIAGNOSI

TC

RMN 1.5 T-3T

SPETTROSCOPIA

PET

standardizzazione

CENTRALIZZAZIONE

FOLLOW UP IN TRATTAMENTO

Pediatric Radiology
https://doi.org/10.1007/s00247-018-4194-9

REVIEW

CrossMark

Current concepts in radiologic assessment of pediatric brain tumors during treatment, part 1

Felice D'Arco[1] &Sinead Culleton[1] &Laurens J. L. De Cocker[2] &Kshitij Mankad[1] &Jorge Davila[3] &Benita Tamrazi[4]

Criteri di Macdonald

RANO

RAPNO

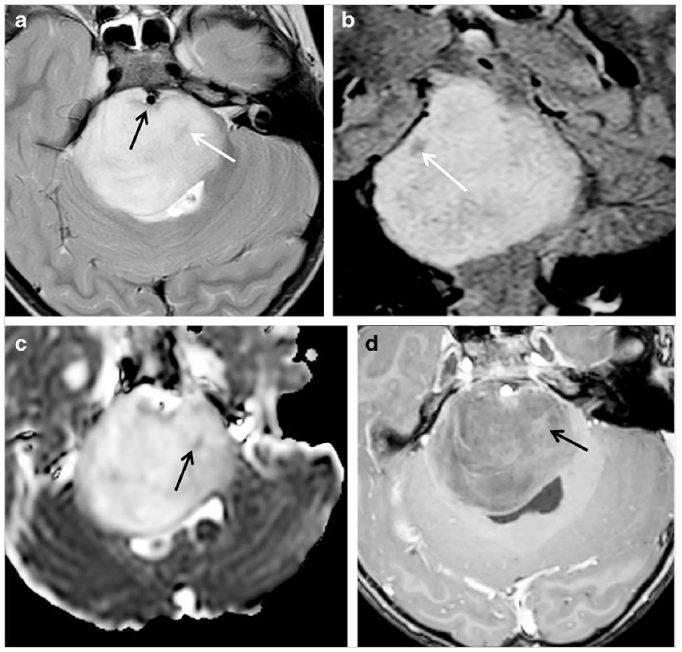


Fig. 5 Pontine diffuse midline glioma in a 7-year-old boy. **a** Axial T2-weighted MR image (repetition time/echo time [TR/TE] 4,500/100 ms) shows a typical pontine diffuse midline glioma with expansion of the pons and encasement of the basilar artery (*black arrow*). Ill-defined and patchy areas of low signal are thought to represent more aggressive tumor areas (*white arrow*). **b** Coronal fluid-attenuated inversion recovery-weighted image shows a hyperintense tumor with similar patchy areas of low signal (*arrow*). **c** Axial apparent diffusion coefficient (ADC) map shows corresponding areas of low ADC values (*arrow*) in a context of non-restricting mass. **d** Axial T1-weighted image (TR/TE 700/12 ms) after gadolinium administration shows faint enhancement (*arrow*) corresponding to areas of low T2-signal intensity and more restricted diffusion

Response Assessment in Pediatric Neuro-Oncology: Implementation and Expansion of the RANO Criteria in a Randomized Phase II Trial of Pediatric Patients with Newly Diagnosed High-Grade Gliomas

T. Jaspan, P.S. Morgan, M. Warmuth-Metz, E. Sanchez Aliaga, D. Warren, R. Calmon, J. Grill, D. Hargrave, J. Garcia, and G. Zahlmann

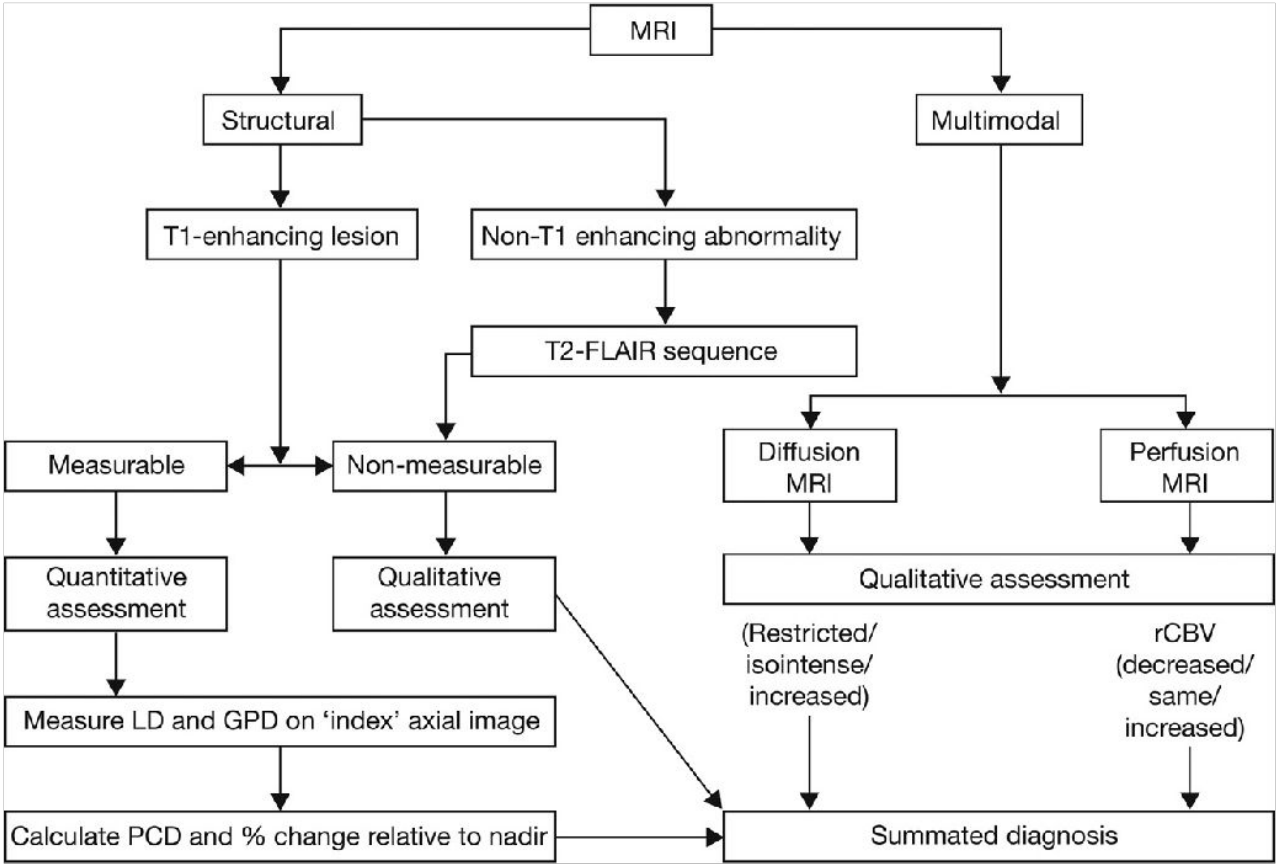


FIG 1. Structural and multimodal imaging used in the HERBY study. LD indicates longest diameter; GPD, greatest perpendicular diameter; PCD, product of cross-sectional enhancing diameters.

Childhood Cancer Survival Rates

(SEER Pediatric Monograph, 1999)

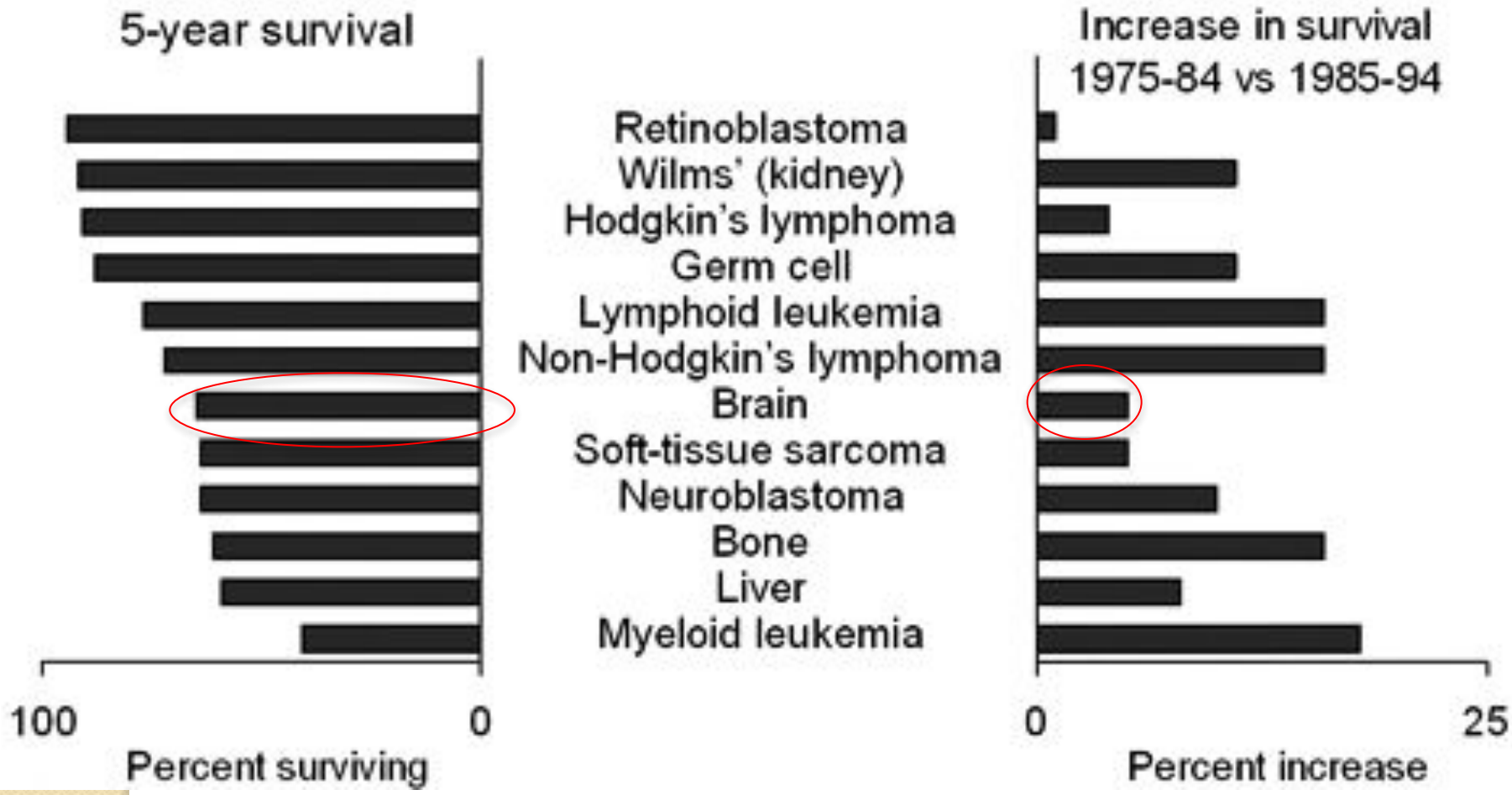
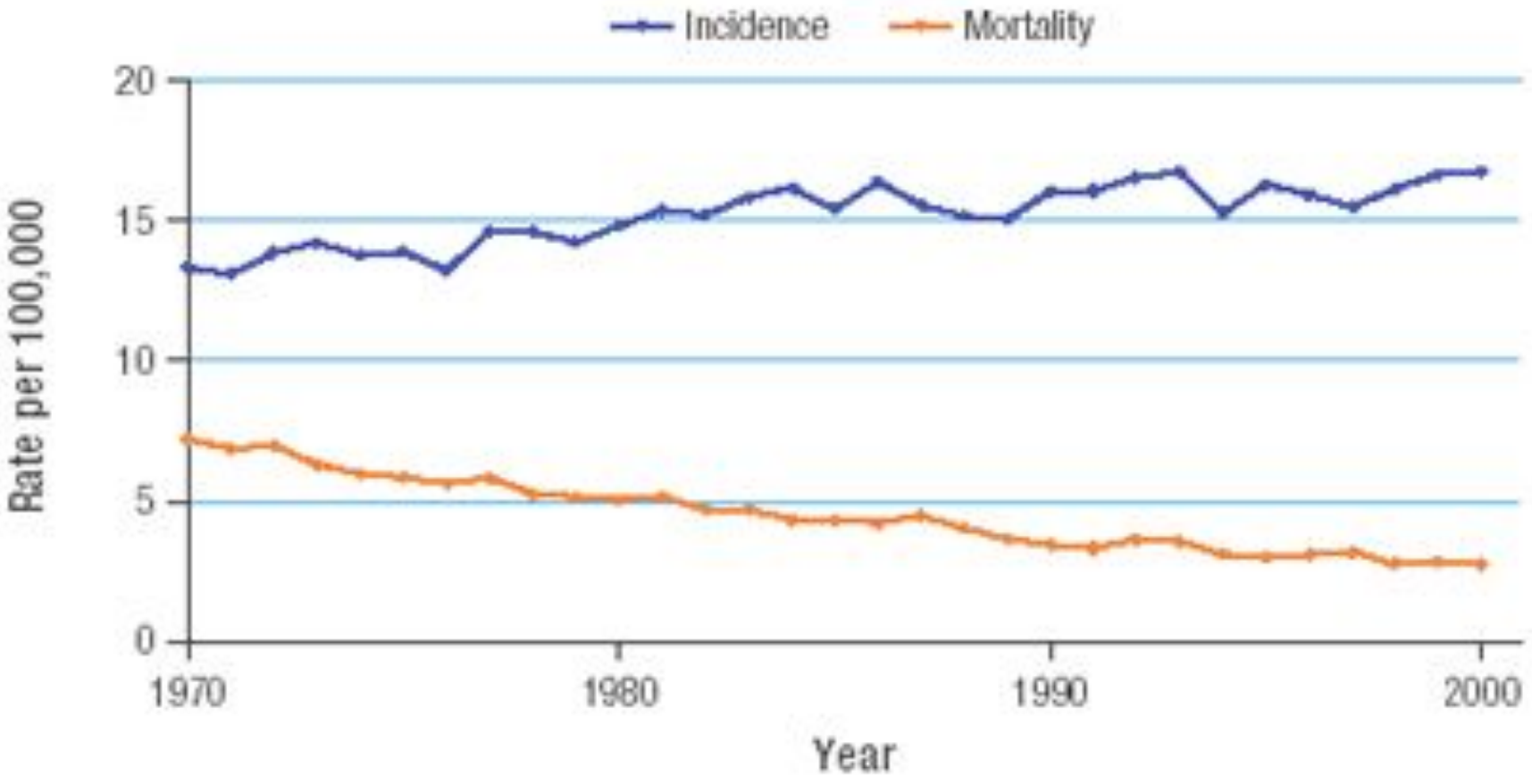


Figure 9.

Age-standardized incidence and mortality rates for all cancers in children and youth, ages 0–19 years, Canada, 1970–2000

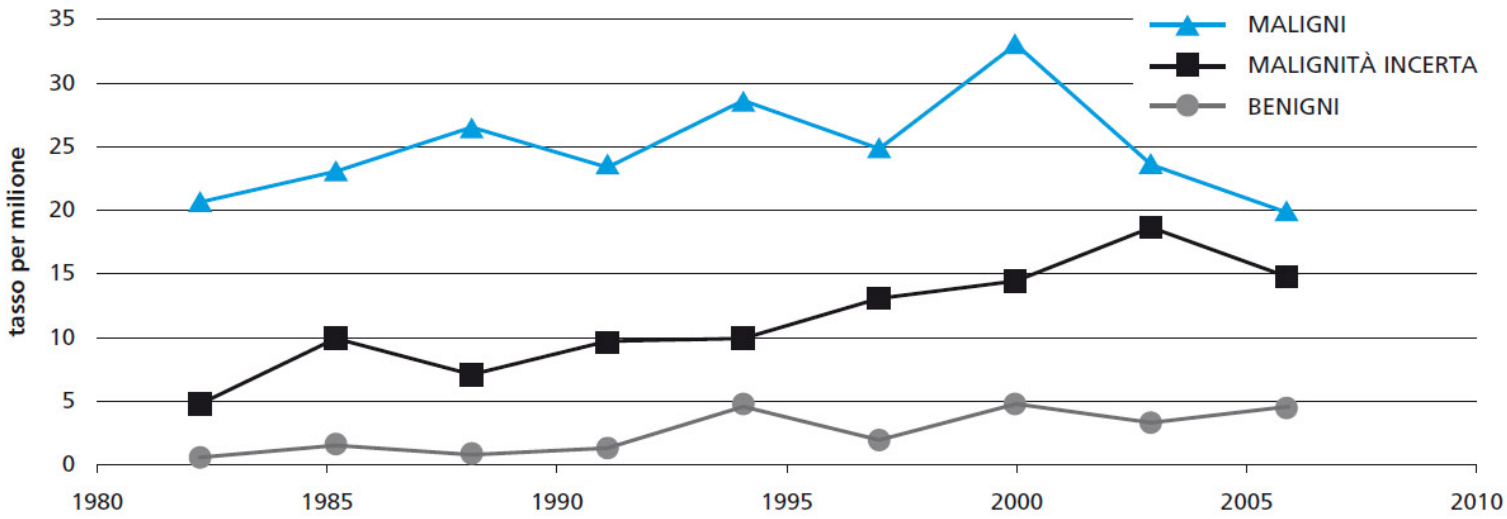


Associazione italiana registri tumori

A cura di
Paola Pisani,
Maria Luisa Mosso,
Carlotta Buzzoni,
Paolo Crosignani,
Maria Michiara,
Rosario Tumino
e AIRTUM Working Group

www.registri-tumori.it

Buone notizie per i bambini italiani: dopo il 2000 si arresta anche la crescita dei tumori maligni del sistema nervoso centrale



● Nell'ultimo aggiornamento della banca dati AIRTUM la crescita dei tumori infantili, persistente dai primi anni Ottanta, subiva una battuta di arresto (*Epidemiol Prev* 2010; 34(1-2): 4). ● Questo grafico mostra un aggiornamento delle tendenze temporali delle neoplasie del sistema nervoso centrale (SNC), il secondo sottogruppo di neoplasie infantili per numerosità dopo le leucemie (22% del totale). ● I risultati confermano un aumento dell'incidenza del complesso dei tumori del SNC, dovuto principalmente ad anticipazione diagnostica in soggetti sintomatici e alla maggiore attenzione riservata dai registri generali alle patologie non maligne, ma nello stesso tempo mostra che le neoplasie maligne (in azzurro) non sono aumentate.

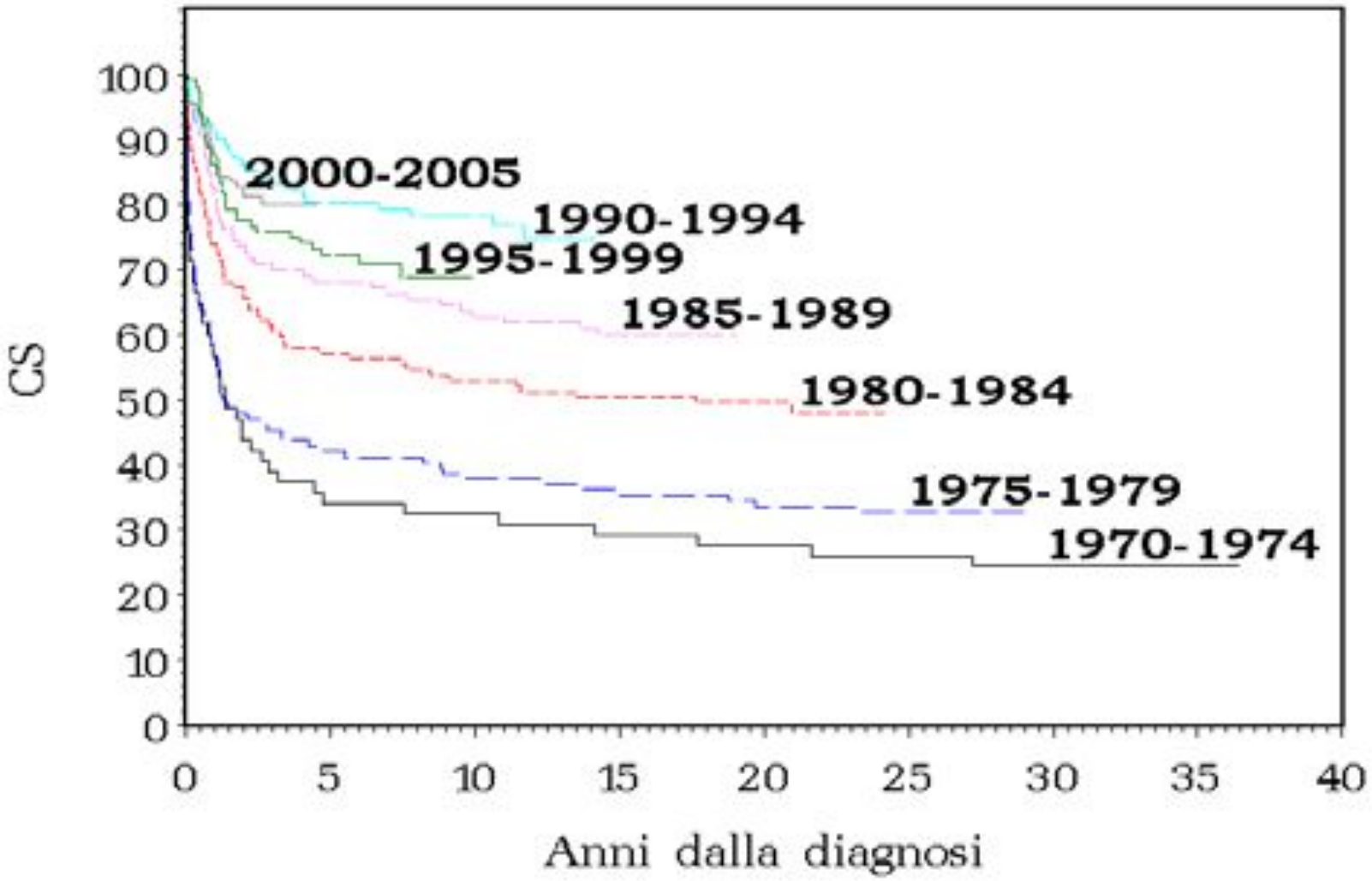
Per i metodi e l'approfondimento vedi www.epiprev.it/rubriche/numeri-come-notizie/intro

Registro dei Tumori Infantili del Piemonte 1970-2005

Bambini 0-14 anni

Sopravvivenza

cumulativa (CS) per tumori SNC



Protocolli

PASSATO

Medulloblastoma

Ependimoma

Gliomi di basso grado

PRESENTE

Medulloblastoma

Ependimoma

Gliomi di basso grado

Medulloblastoma

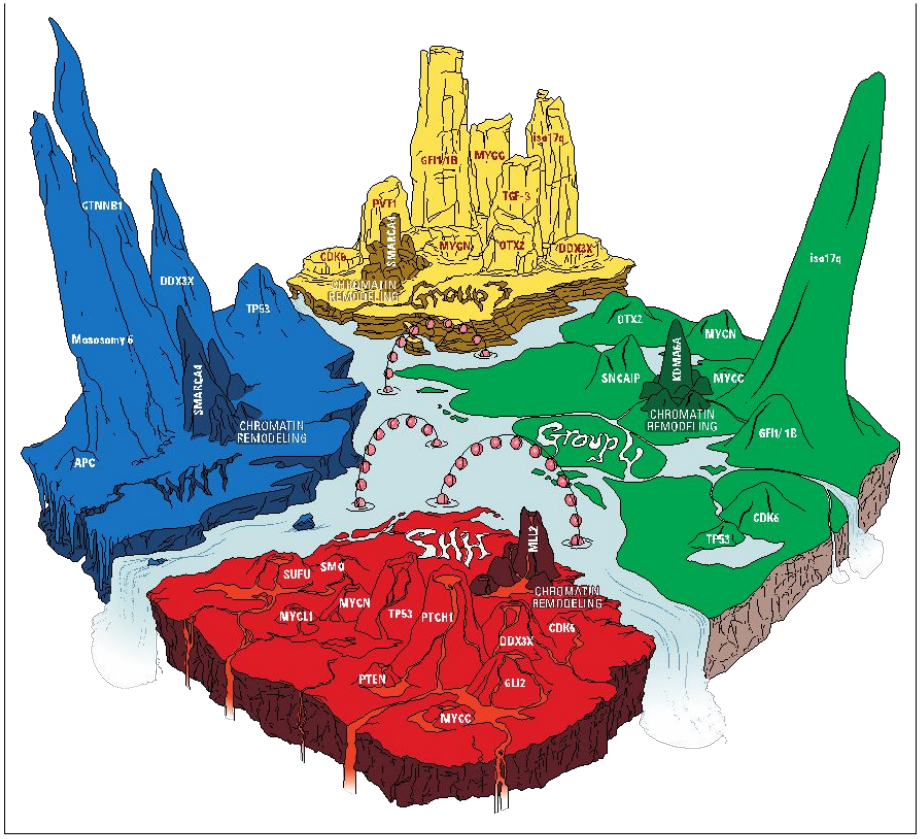


Fig 1. The genetic landscape of medulloblastoma. Recurrent genetic aberrations identified in medulloblastoma (derived from Northcott in 2012,[2,3] Robinson et al,[1] Pugh et al,[7] Jones et al,[8] and Northcott et al in 2014[9]) averaged and displayed proportionally by height of terrain peaks. The figure reveals the unique subgroup-specific molecular aberration and highlights chromatin remodeling mutations as the unifying theme among all four medulloblastoma subgroups. Wingless (WNT) medulloblastoma (left; blue sky landscape), the most molecularly homogenous group, consists of *CTNNB1* mutations in 85%, monosomy 6 in 80%, *DDX3X* mutation in 60%, *TP53* mutation in 13%, and mutations in chromatin remodeling genes in 49.5% (composed of mutations in *SMARCA4* [25%], *MLL2* [12.5%], *CREBBP* [6%], *TRAPP* [3%], and *MED13* [3%]). For the chromatin remodeling peaks (darker colored shading), only the most commonly mutated gene is labeled. Sonic hedgehog (SHH) medulloblastoma (bottom; red volcanic landscape) consists of *PTCH1* mutation/deletion in 29%, *TP53* mutation in 16%, *DDX3X* mutation in 11%, *GLI2* amplification/mutation in 8%, *MYCN* amplification in 6%, *SUFU* mutation in 6%, *SMO* mutation in 5%, *PTEN* deletion in 2.5%, *MYCL1* amplification in 2%, *CDK6* amplification in 1%, *MYCC* amplification in 0.7%, and mutations in chromatin remodeling genes in 21% (composed of mutations in *MLL2* [12%], *SCOR* [3%], *LDB1* [3%], *NCOR2* [1.5%], and *SMARCA4* [1.5%]). Group 3 medulloblastoma (top; yellow desert rocky terrain) is characterized by *GFI1/1B* structural variants (eg, inversions, duplications) in 41%, isochromosome (iso) 17q in 26%, transforming growth factor (TGF)-β signaling in 20%, *MYCC* amplification in 17%, *PVT1* alterations in 12%, *OTX2* amplification in 8%, *MYCN* amplification in 4%, *DDX3X* mutation in 3%, *CDK6* amplification in 1%, and mutations in chromatin remodeling genes in 28.5% (composed of mutations in *SMARCA4* [10.5%], other *KDM* family members [5%], *MLL2* [4%], *KDM6A* [3%], *GPS2* [3%], *MLL3* [1%], *CREBBP* [1%], and *CHD7* [1%]). Group 4 medulloblastoma (right; green forest mountain terrain) is characterized by iso 17q in 80%, *GFI1/1B* structural variants in 10%, *SNCAIP* tandem duplications in 10%, *OTX2* amplification in 5.5%, *MYCN* amplification in 5%, *CDK6* amplification in 5%, *TP53* mutation in 1%, *MYCC* amplification in 1%, and mutations in chromatin remodeling genes in 30% (composed of mutations in *KDM6A* [13%], other *KDM* family members [4%], *MLL3* [3%], *CHD7* [3%], *ZMYM3* [3%], *MLL2* [2%], *GPS2* [1%], and *SCOR* [1%]).

Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape

Amar Gajjar, Daniel C. Bowers, Matthias A. Karajannis, Sarah Leary, Hendrik Witt, and Nicholas G. Gottardo

VOLUME 33 · NUMBER 27 · SEPTEMBER 20 2015

JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Medulloblastoma

HIT-SIOP PNET IV

Medulloblastoma >3-5 anni

M0

Resezione < 1.5 cm^2

Unica modalità di trattamento

SIOP PNET 5 MB

Medulloblastoma >3-5 anni

< 16 anni per LR

< 22 anni per SR

M0

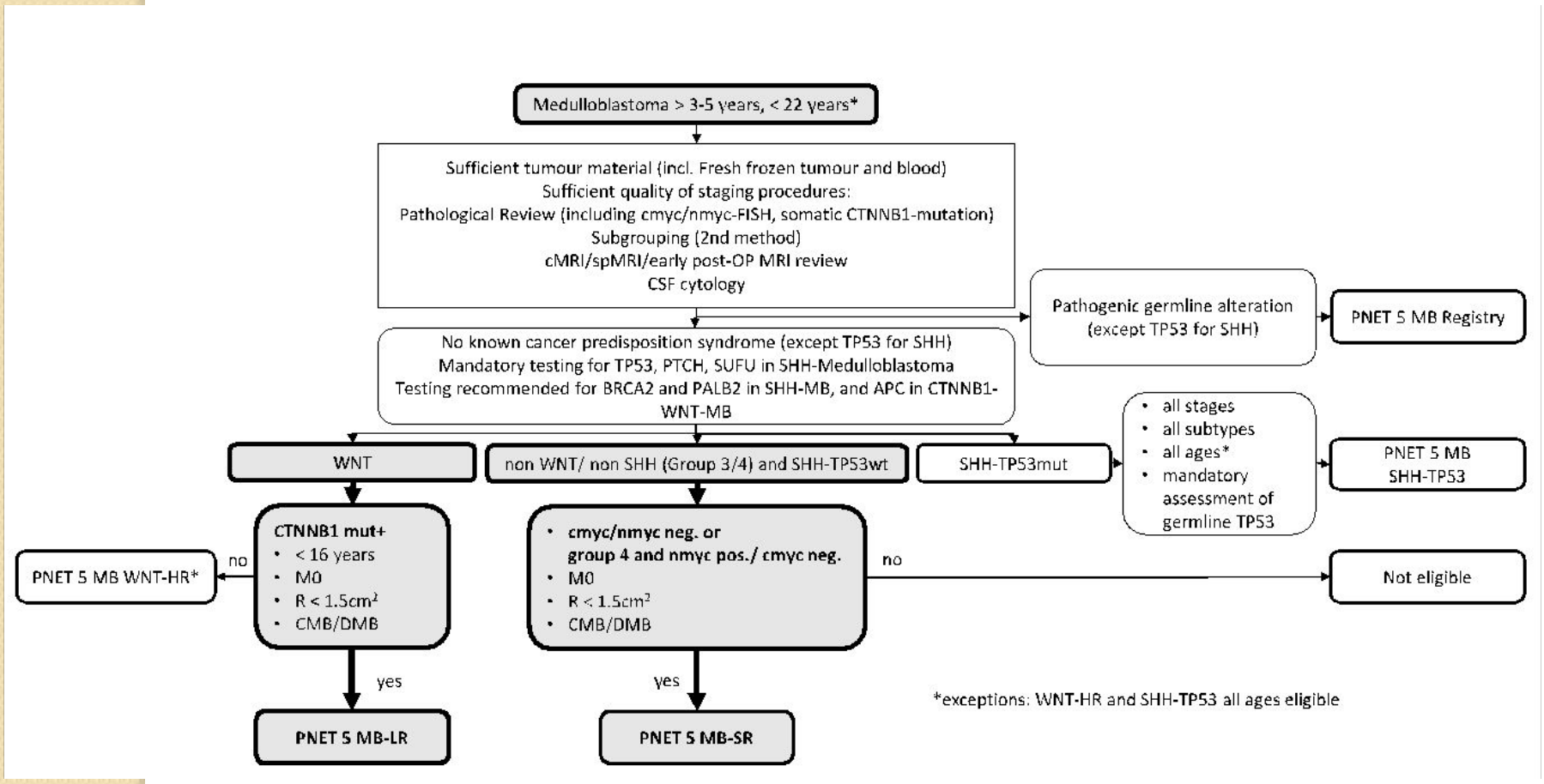
Resezione < 1.5 cm^2

4 categorie con differenti protocolli di terapia

Medulloblastoma

AN INTERNATIONAL PROSPECTIVE TRIAL ON MEDULLOBLASTOMA IN CHILDREN OLDER THAN 3 TO 5 YEARS WITH WNT BIOLOGICAL PROFILE (PNET 5 MB – LR and PNET 5 MB – WNT-HR), AVERAGE-RISK BIOLOGICAL PROFILE (PNET 5 MB -SR), OR TP53 MUTATION AND REGISTRY FOR MB OCCURRING IN THE CONTEXT OF GENETIC PREDISPOSITION

- PNET 5 MB-LR
- PNET 5 MB-SR
- PNET 5 MB-WNT HR
- PNET 5 MB SHH-TP53


Medulloblastoma > 3-5 years, < 22 years*
Sufficient tumour material (incl. Fresh frozen tumour and blood)
Sufficient quality of staging procedures:
Pathological Review (including cmyc/nmyc-FISH, somatic CTNNB1-mutation)
Subgrouping (2nd method)
cMRI/spMRI/early post-OP MRI review
CSF cytology
Pathogenic germline alteration (except TP53 for SHH)
PNET 5 MB Registry
No known cancer predisposition syndrome (except TP53 for SHH)
Mandatory testing for TP53, PTCH, SUFU in SHH-Medulloblastoma
Testing recommended for BRCA2 and PALB2 in SHH-MB, and APC in CTNNB1-WNT-MB
WNT
non WNT/ non SHH (Group 3/4) and SHH-TP53wt
SHH-TP53mut
all stages
all subtypes
all ages*
mandatory assessment of germline TP53
PNET 5 MB SHH-TP53
CTNNB1 mut+
< 16 years
M0
R < 1.5cm²
CMB/DMB
no
PNET 5 MB WNT-HR*
cmyc/nmyc neg. or group 4 and nmyc pos./ cmyc neg.
M0
R < 1.5cm²
CMB/DMB
no
Not eligible
yes
PNET 5 MB-LR
yes
PNET 5 MB-SR
*exceptions: WNT-HR and SHH-TP53 all ages eligible

	PNET 5 MB – LR	PNET 5 MB – SR	PNET 5 MB – WNT-HR	PNET 5 MB – SHH TP53	PNET 5 MB Registry
Mandatory asessments	• Histology by central reference assessment • Early post-operative cranial MRI by central reference assessment • Pre- or postoperative craniospinal MRI by central reference assessment • MYC/MYCN amplification • β-catenin mutation and β-catenin by IHC (Monosomy 6 optional) • Cytology of CSF through lumbar puncture • For all SHH-activated MB: mandatory somatic (blood control) preinclusion sequencing of PTCH, SUFU & TP53 genes • Please see further recommended genetic counselling and assessments on pages 10 and 174				
Inclusion criteria	• CMB or DMB • and CTNNB1 mutation • and < 16 years • and M0 • and R < 1.5 cm^2 • and cmyc/nmyc negative	• CMB or DMB • and Group 3 or 4 MB or SHH TP53 wt • and M0 • and R < 1.5 cm^2 • and cmyc negative • and nmyc negative (and nmyc positive in group 4 MB)	• CMB, DMB or LCA MB • WNT ≥ 16 years or WNT without CTNNB1 mutation • M0 or M+ • R0 or R+ • cmyc/nmyc negative or positive	• All stages • All subtypes • All ages • SHH MB • *TP53* somatic or germline (including mosaicism) mutation	• All stages • All subtypes • All ages • Pathogenic germline alteration (except TP53 for SHH)

Treatment plan PNET 5 MB – LR study

LR-Study

- WNT positive MB (CMB, DMB)
- with CTNNB1 mutation
- age < 16 years
- and M0
- and R < 1.5cm2

Radiotherapy

(to be started within 28 (maximum 40) days after surgery)

Brain – 18.0 Gy in 10 daily fractions of 1.80 Gy

Spine – 18.0 Gy in 10 daily fractions of 1.80 Gy

Primary tumour boost – 36.0 Gy in 20 daily fractions of 1.80 Gy

Total dose to primary tumour – 54.0 Gy in 20 daily fractions of 1.80 Gy

Maintenance Chemotherapy

(to be started 6 weeks after end of radiotherapy)

6 cycles ABA_BAB

Regimen A: Cisplatin 70 mg/m^2 day 1, CCNU 75 mg/m^2 days 1-2, VCR 1.5 mg/m^2 days 1, 8, 15

Regimen B: Cyclophosphamide 1000 mg/m^2 days 1-2, VCR 1.5 mg/m^2 day 1

Ependimoma

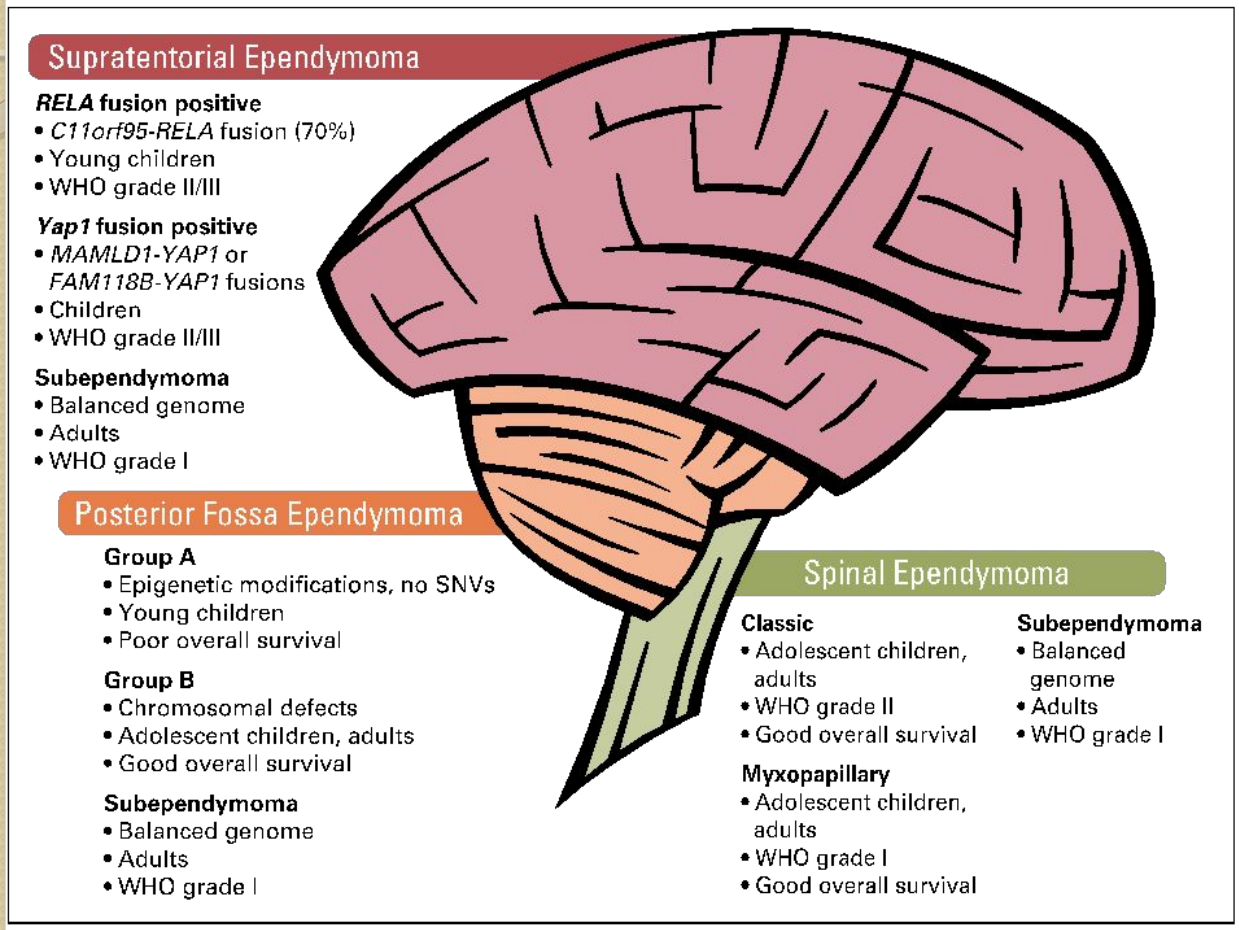


Fig 4. Several subtypes of ependymomas, including WHO grades 1 to 3 disease within all three compartments of the CNS—supratentorial (ST), posterior fossa (PF), and spinal (SP)—are illustrated. *RELA*-positive ependymomas, including *YAP1* fusion–positive ependymomas and subependymomas, arise within the ST region of the brain. Both fusion-positive subtypes display histopathologic features of WHO grades 2 and 3 ependymomas. In the PF, the majority of ependymomas belong to subtype group A, and group B tumors are more infrequent. Both subtypes display the histologic pattern of anaplastic and WHO grade 2 ependymomas; in contrast, subependymomas can be classified as WHO grade 1. SP tumors are diagnosed as classic ependymomas that are WHO grade 2 or 3; myxopapillary ependymoma and spinal subependymomas are WHO grade 1. In children, group A and *RELA*-positive tumors are diagnosed most often and are associated with poor overall survival. SNV, single nucleotide variant.

Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape

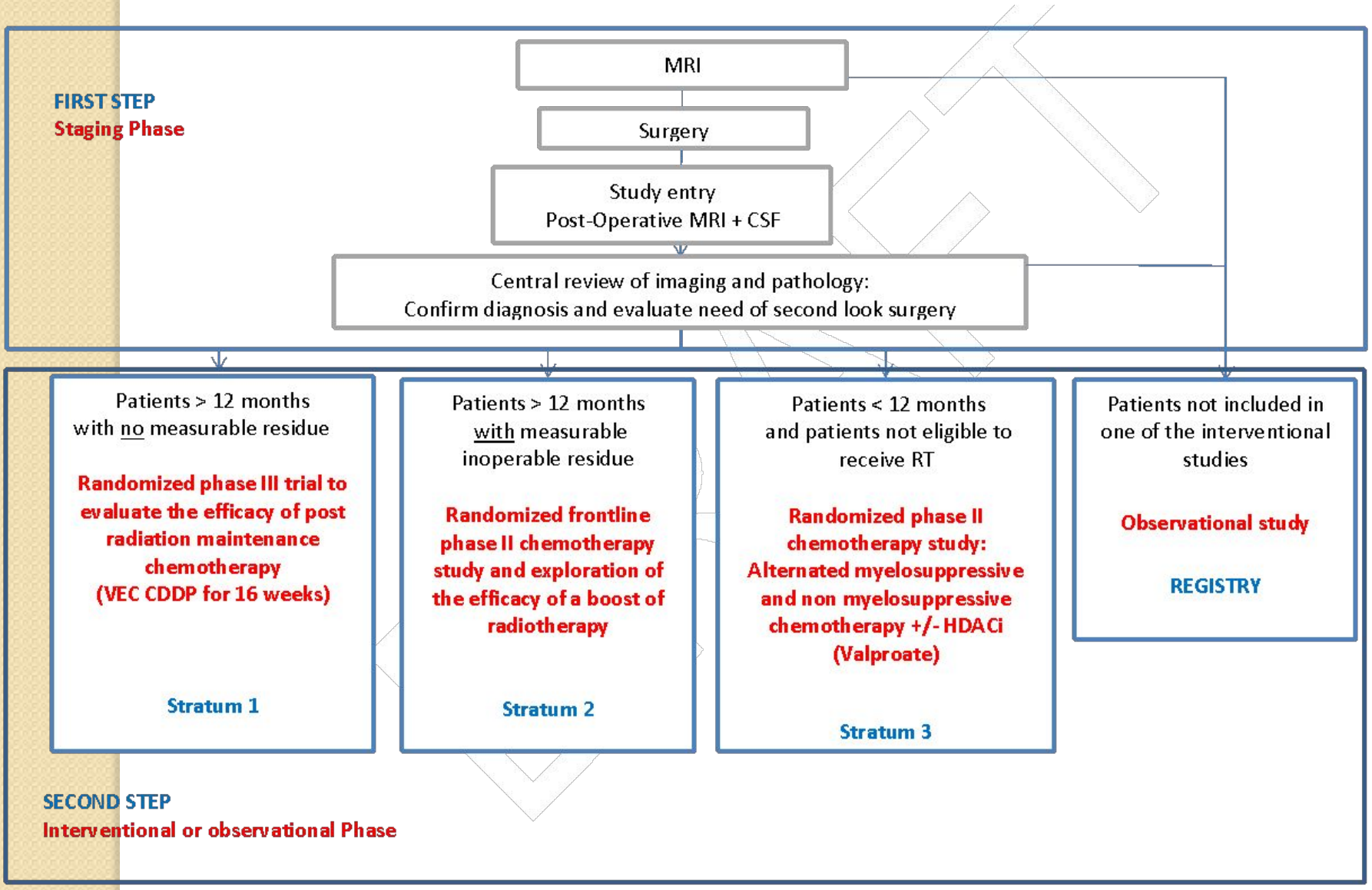
Amar Gajjar, Daniel C. Bowers, Matthias A. Karajannis, Sarah Leary, Hendrik Witt, and Nicholas G. Gottardo

VOLUME 33 · NUMBER 27 · SEPTEMBER 20 2015
JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

SIOP EPENDYMOMA II

An international clinical program for the diagnosis and treatment of children, adolescents and young adults with ependymoma

Final Version 2.0_August 21st, 2014


FIRST STEP
Staging Phase
MRI
Surgery
Study entry
Post-Operative MRI + CSF
Central review of imaging and pathology:
Confirm diagnosis and evaluate need of second look surgery
Patients > 12 months
with no measurable residue
Randomized phase III trial to evaluate the efficacy of post radiation maintenance chemotherapy
(VEC CDDP for 16 weeks)
Stratum 1
Patients > 12 months
with measurable
inoperable residue
Randomized frontline phase II chemotherapy study and exploration of the efficacy of a boost of radiotherapy
Stratum 2
Patients < 12 months
and patients not eligible to receive RT
Randomized phase II chemotherapy study:
Alternated myelosuppressive and non myelosuppressive chemotherapy +/- HDACi
(Valproate)
Stratum 3
Patients not included in one of the interventional studies
Observational study
REGISTRY
SECOND STEP
Interventional or observational Phase

VOLUME 33 · NUMBER 27 · SEPTEMBER 20 2015
JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape

Amar Gajjar, Daniel C. Bowers, Matthias A. Karajannis, Sarah Leary, Hendrik Witt, and Nicholas G. Gottardo

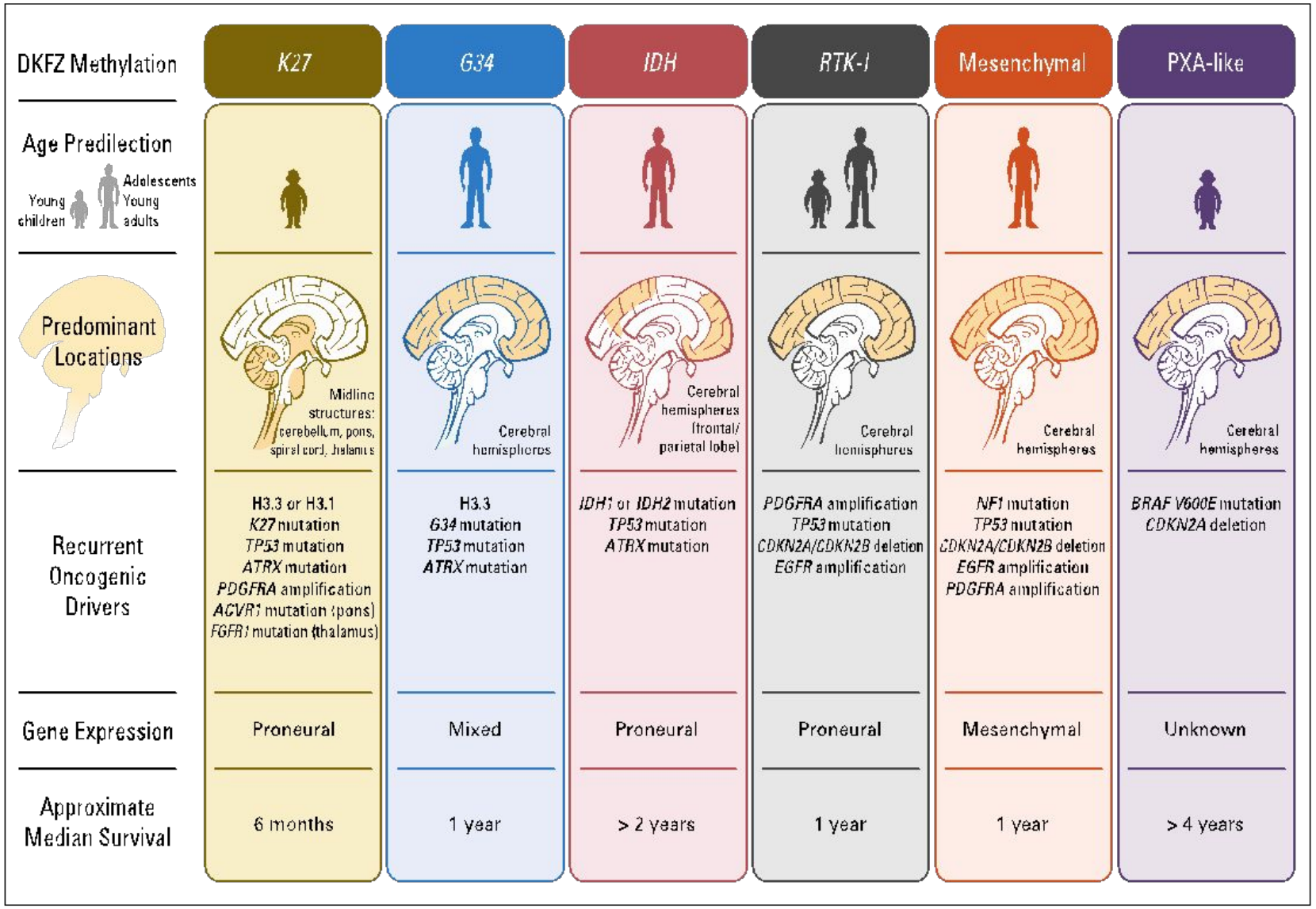


Fig 2. Subgroups of pediatric high-grade glioma that are based on German Cancer Research Center (DKFZ) methylation, age at onset, tumor location, oncogenic drives, gene expression, and median survival. IDH, isocitrate dehydrogenase; PXA, pleomorphic xanthoastrocytoma; RTK-I, receptor tyrosine kinase (subgroup 1).

Gliomi di basso grado

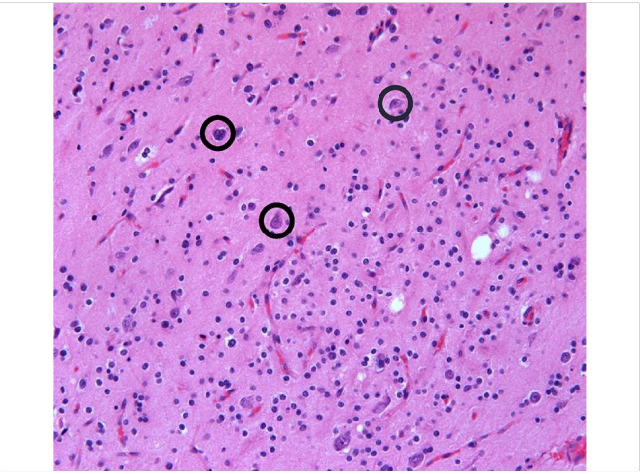


Fig. 1 Classic paediatric low-grade diffuse glioma histology. The absence of mitotic figures, necrosis and microvascular proliferation indicates that this is not a high-grade glioma. The *circled* features represent entrapped nuclei, a hallmark of low-grade diffuse glioma

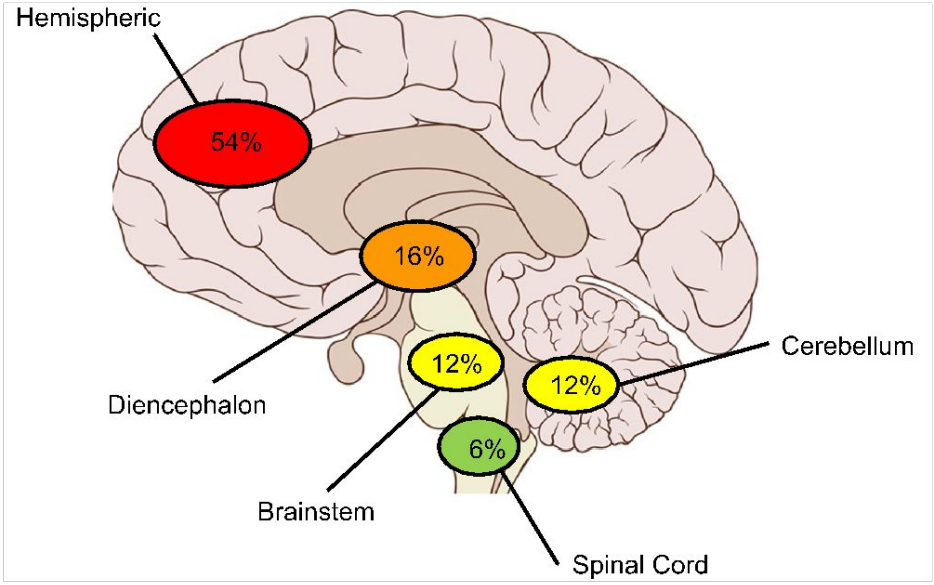


Fig. 2 Prevalence of paediatric low-grade diffuse glioma throughout the brain

Brain Tumor Pathol (2017) 34:51–61

A comprehensive review of paediatric low-grade diffuse glioma: pathology, molecular genetics and treatment

Scott Rvall[1,2] · Uri Tabori[1,3] · Cvnthia Hawkins[1,2,4]

Gliomi di basso grado

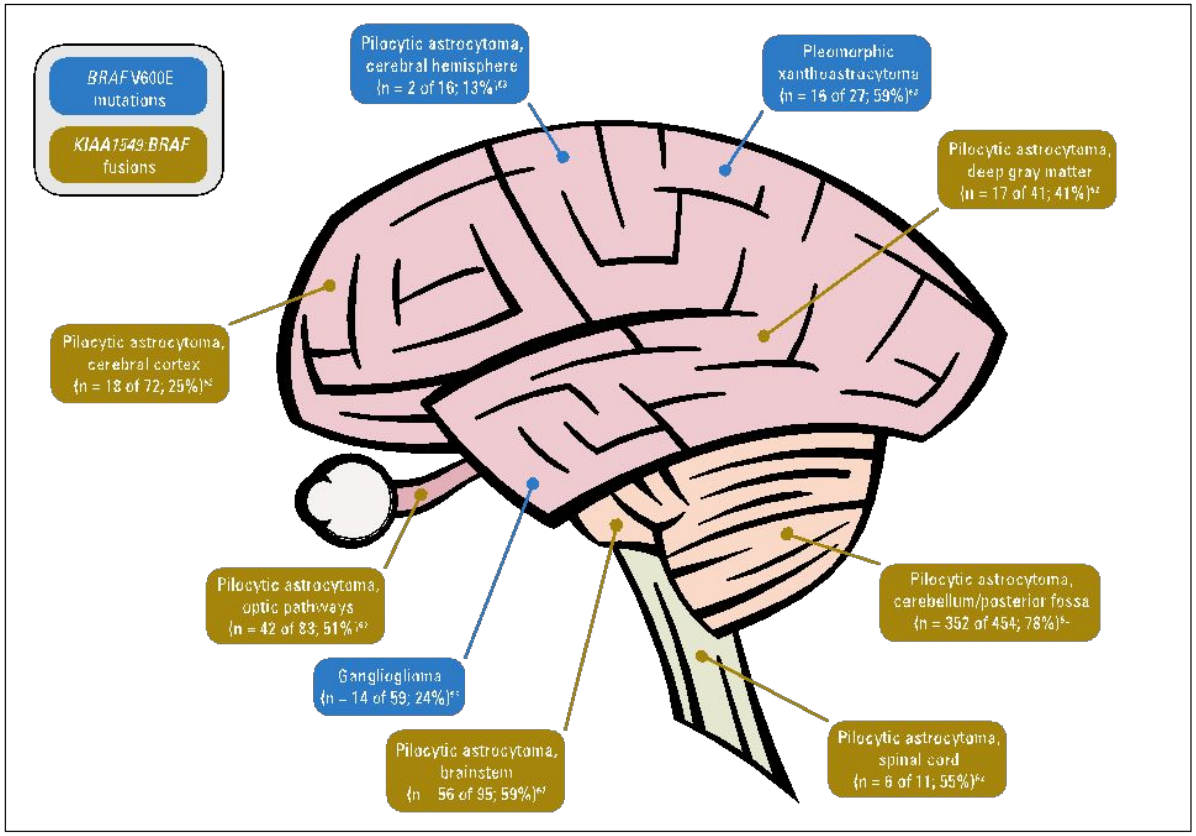


Fig 3. *BRAF* mutations and fusions by tumor histology and tumor location in pediatric low-grade gliomas.

Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape

Amar Gajjar, Daniel C. Bowers, Matthias A. Karajannis, Sarah Leary, Hendrik Witt, and Nicholas G. Gottardo

VOLUME 33 · NUMBER 27 · SEPTEMBER 20 2015
JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Gliomi di basso grado

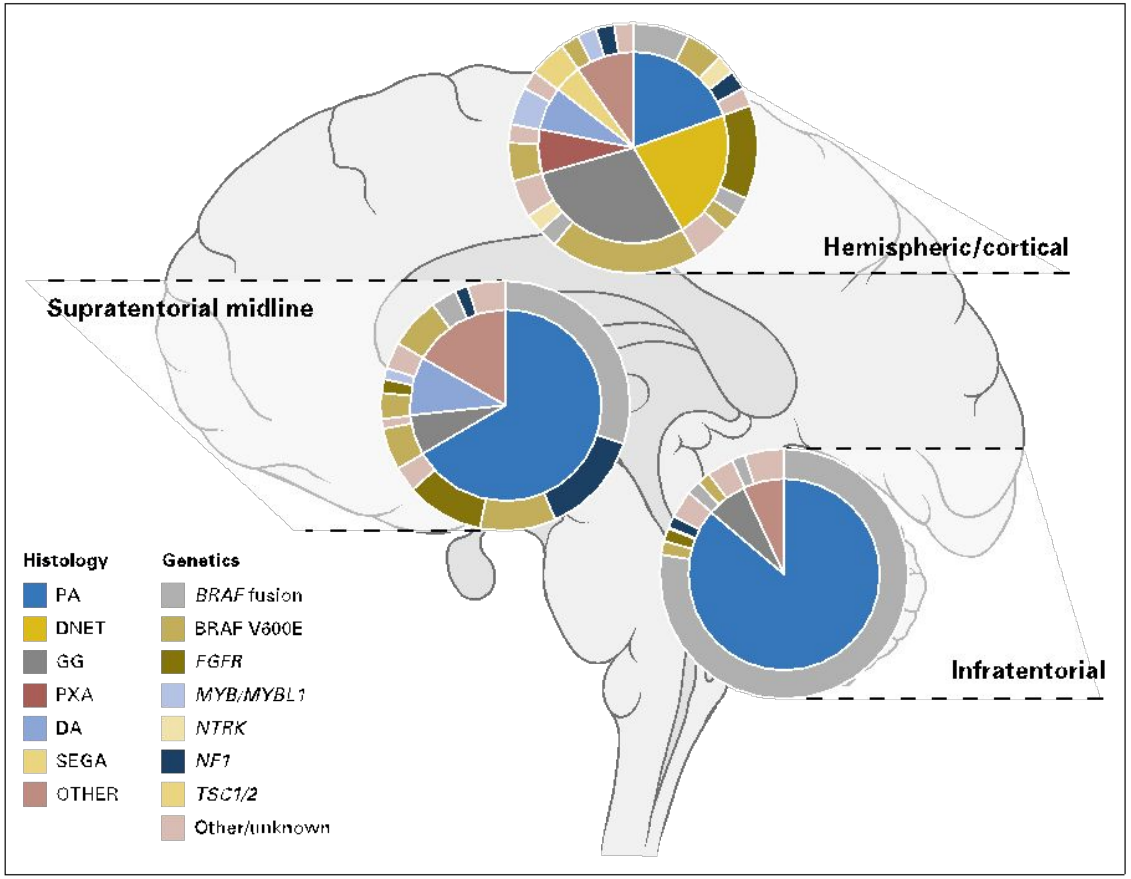


Fig 1. Distribution of pediatric low-grade glioma histologies and molecular genetic alterations by anatomic tumor location. Inner pie charts represent relative frequencies of the most common pediatric low-grade glioma histologic entities represented by colors as indicated. Outer rings represent the most common molecular genetic alterations associated with each histologic entity in a given location. Original data from the German Cancer Research Center in Heidelberg aligned with published data from other studies.[1,2,6,8,12,13,16-21] DA, diffuse astrocytoma; DNET, dysembryoplastic neuroepithelial tumor; GG, ganglioglioma; PA, pilocytic astrocytoma; PXA, pleomorphic xanthoastrocytoma; SEGA, subependymal giant cell astrocytoma.

VOLUME 35 · NUMBER 21 · JULY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Pediatric Gliomas: Current Concepts on Diagnosis, Biology, and Clinical Management

Dominik Sturm, Stefan M. Pfister, and David T.W. Jones

Gliomi di basso grado

SIOP LGG 2004

International Consortium on Low Grade Glioma - ICLGG
of the International Society of Pediatric Oncology - SIOP

Cooperative multicentre Study for Children and Adolescents with Low Grade Glioma

SIOP - LGG 2004

Version I, April 2004

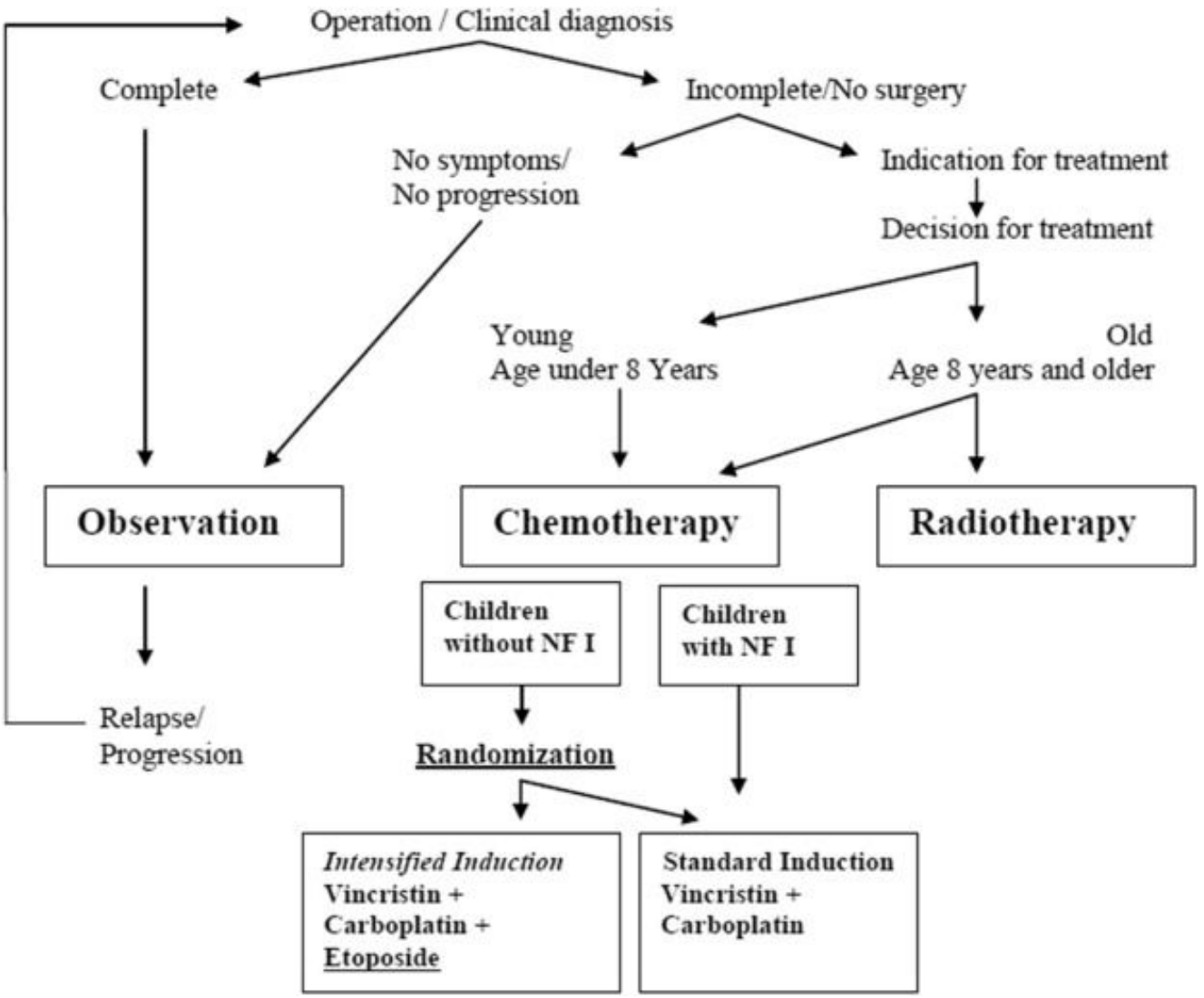
Corrections from:
July 2004
January 2006

gefördert durch:

Deutsche Kinderkrebsstiftung
Stadtstraße 28
53113 Bonn
www. Kinderkrebsstiftung. de

FUTURO??

SIOP LGG 2004



Terapia

CHIRURGIA *fondamentale*

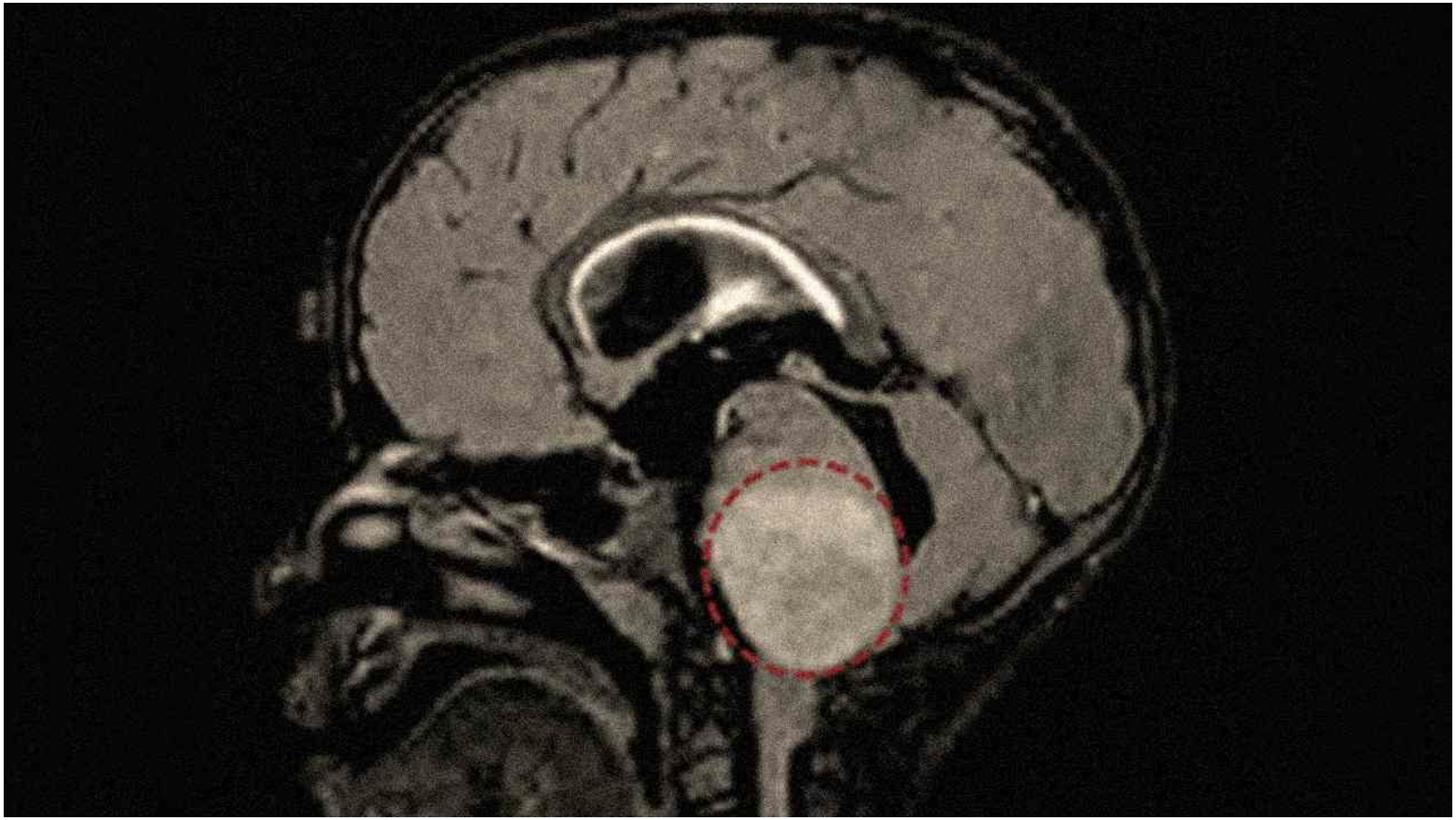
Radioterapia ➡ ETA’

Chemioterapia: RUOLO?

Chirurgia

- Impatto prognostico
- Metodiche
- Sede
- Effetti collaterali

DIPG



Radioterapia

Clinical trial designs generally include one or more hypotheses that address the following radiation oncology tenets:

(1) Reduce the RT target volume to decrease side effects without affecting the rate of local tumor control or pattern of failure.

(2) Concurrently administer chemotherapy and RT to improve disease control with acceptable treatment-related toxicity in patients with high-risk malignancies.

(3) Individualize the treatment of children with specific malignancies on the basis of prior trial results and prognostic factors to include or eliminate RT or reduce radiation doses.

(4) The distribution of radiation dose to an at-risk organ will correlate with that organ's functional outcome.

Pediatr Blood Cancer. 2013 June ; 60(6): 1037–1043.
Children's Oncology Group's 2013 Blueprint for Research: Radiation Oncology
Thomas E. Merchant, DO, PhD1,*, David Hodgson, MD, MPH2, Nadia N.I. Laack, MD, MS3, Suzanne Wolden, MD4, Danny J. Indelicato, MD5, and John A. Kalapurakal, MD6 on behalf of the COG Radiation Oncology Discipline Committee

Protonterapia

Received: 6 March 2017 | Revised: 29 January 2018 | Accepted: 31 January 2018

DOI: 10.1002/pbc.27046

REVIEW

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

Proton therapy for central nervous system tumors in children

Matthew M. Ladra[1] | Shannon M. MacDonald[2] | Stephanie A. Terezakis[1]

The growth in the number of proton centers has been remarkable in the past decade. At present, there are 63 operating proton centers worldwide and 25 in the US.[1] Childhood malignancies are a priority

1. The National Association for Proton Therapy. Source for proton therapy centers map and numbers of centers in operation. http://www.proton-therapy.org/map.htm. 2016.

Palliative care

Effetti collaterali

BREVE TERMINE

Complicanze post-operatorie

SFP

LUNGO TERMINE

ELSEVIER

Seminars in Pediatric Neurology

Neurocognitive Dysfunction in Survivors of Childhood Brain Tumors

Nicole J . Ullrich, MD, PhD,*,† and Leanne Embry, PhD‡

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY REVIEW

Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis

MARIEKE A DE RUITER[1] | ROSA VAN MOURIK[2] | ANTOINETTE Y N SCHOUTEN-VAN MEETEREN[3] | MARTHA A GROOTENHUIS[1] | JAAP OOSTERLAAN[2]

J Neurosurg Pediatrics 10:89–95, 2012

Consensus definitions of complications for accurate recording and comparisons of surgical outcomes in pediatric neurosurgery

Clinical article

James M. Drake, M.B.B.Ch.,[1] Ash Singhal, M.D.,[2] Abhaya V. Kulkarni, M.D., Ph.D.,[1] Gabrielle DeVeber, M.D.,[1] D. Douglas Cochrane, M.D.,[2] and The Canadian Pediatric Neurosurgery Study Group

[1]Division of Neurosurgery, The Hospital for Sick Children, The University of Toronto, Ontario; and [2]Division of Pediatric Neurosurgery, British Columbia Children's Hospital, Vancouver, British Columbia, Canada

TABLE 2: Surgical morbidity data collection form*

CSF Circulation	
Shunt mechanical failure <30 days	___
Shunt infection	___
ETV failure <30 days	___
CSF leak	
minor	___
major	___
pseudomeningocele	
minor	___
major	___
intracranial CSF collection	___
postop hydrocephalus	___
Other Infection	___
wound infection	___
meningitis	
septic	___
aseptic	___
Hemorrhage/Stroke/Deficit	___
new neurological deficit - expected	___
new neurological deficit – unexpected - transient	___
new neurological deficit – unexpected – permanent – (PSOM___)	___
cerebellar mutism (score _____)	___
unexpected intraop hemorrhage	___
postop hemorrhage	
intraventricular	___
subdural	___
extradural	___
intraparenchymal	___
postop infarct/thrombosis	
arterial	___
venous	___
venous sinus thrombosis	___
postop brain edema	___
unexpected seizure	___
intraop death	___
unexpected postop death <30 days	___
other	___
Total	___

* ETV = endoscopic third ventriculostomy.

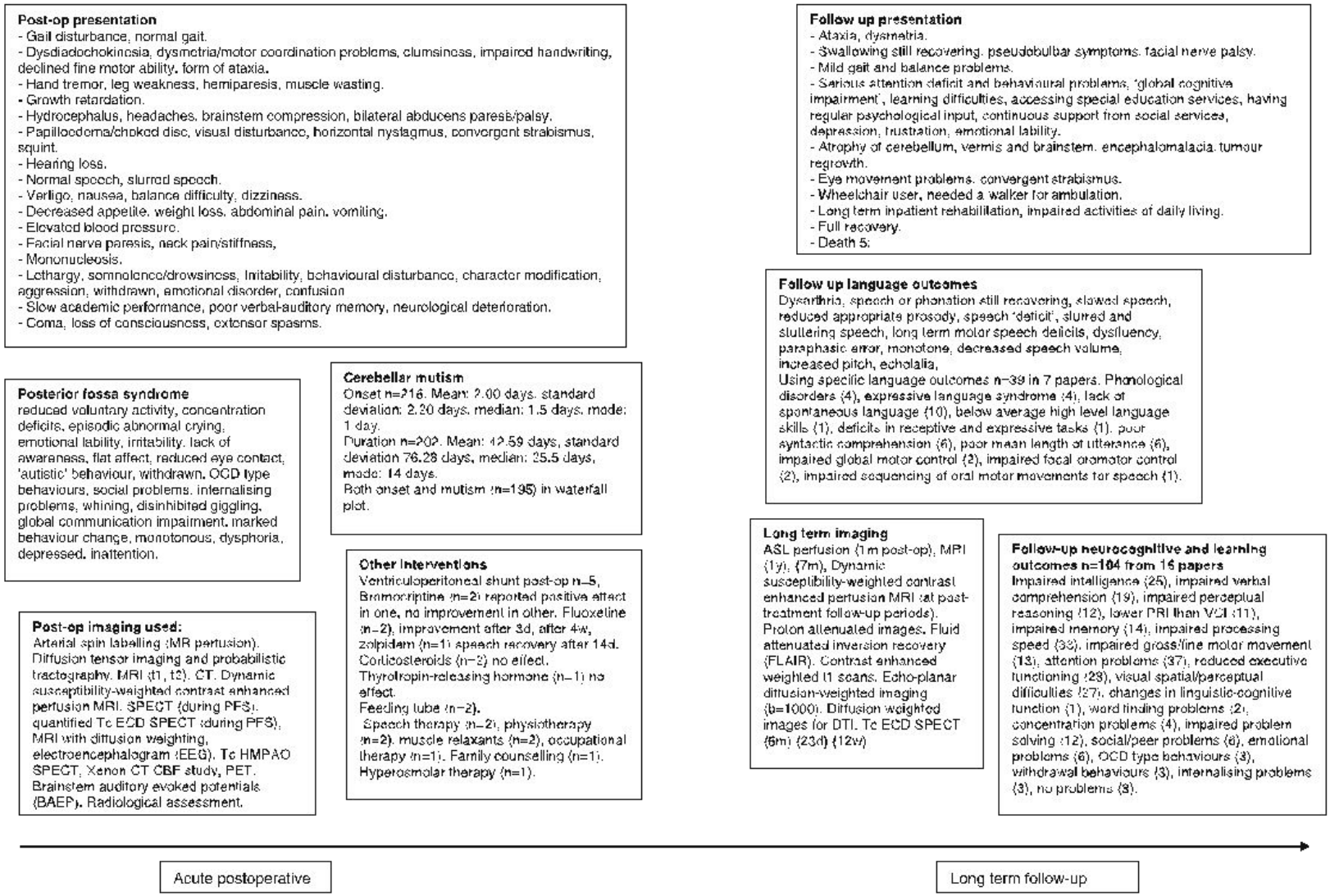


Fig. 3 Logic model presenting acute post-operative and long-term follow-up extracted data

Childs Nerv Syst (2015) 31:1859–1867
DOI 10.1007/s00381-015-2797-0

SPECIAL ANNUAL ISSUE

Posterior fossa syndrome following brain tumour resection: review of pathophysiology and a new hypothesis on its pathogenesis

Shivaram Avula[1] · Conor Mallucci[2] · Ram Kumar[3] · Barry Pizer[4]

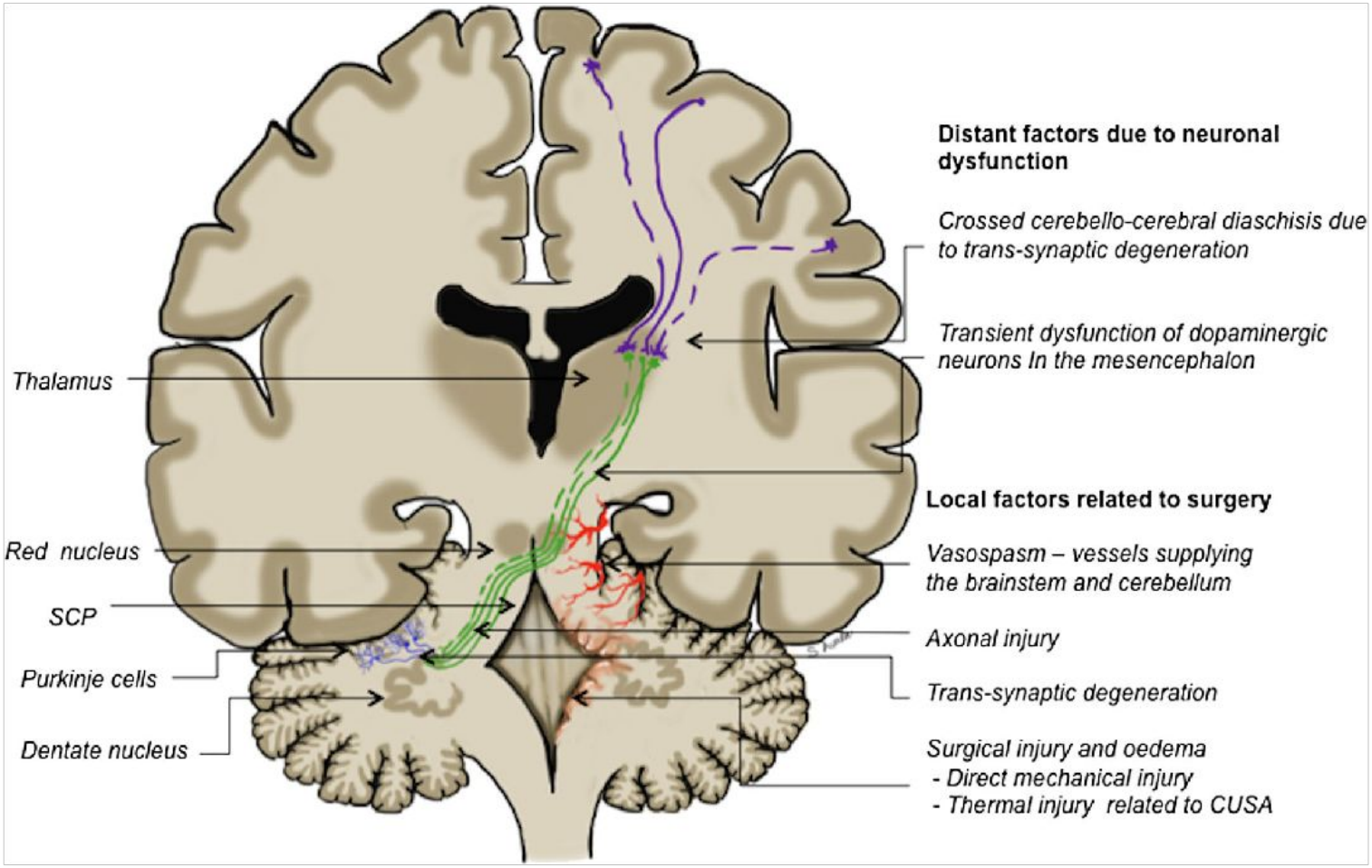


Fig. 3 An Illustration summarising the various factors that have been attributed to the pathogenesis of PFS

ELSEVIER

Seminars in Pediatric Neurology

Neurocognitive Dysfunction in Survivors of Childhood Brain Tumors

Nicole J . Ullrich, MD, PhD,*† and Leanne Embry, PhD‡

Neurotoxic effects, often referred to as "late effects," are thought to fully manifest **between 2 and 5 years** after completion of treatment and are often associated with pronounced and chronic impairment.

Late effects may occur in a variety of domains, including physical, medical, social, emotional, behavioral, and neurocognitive functioning

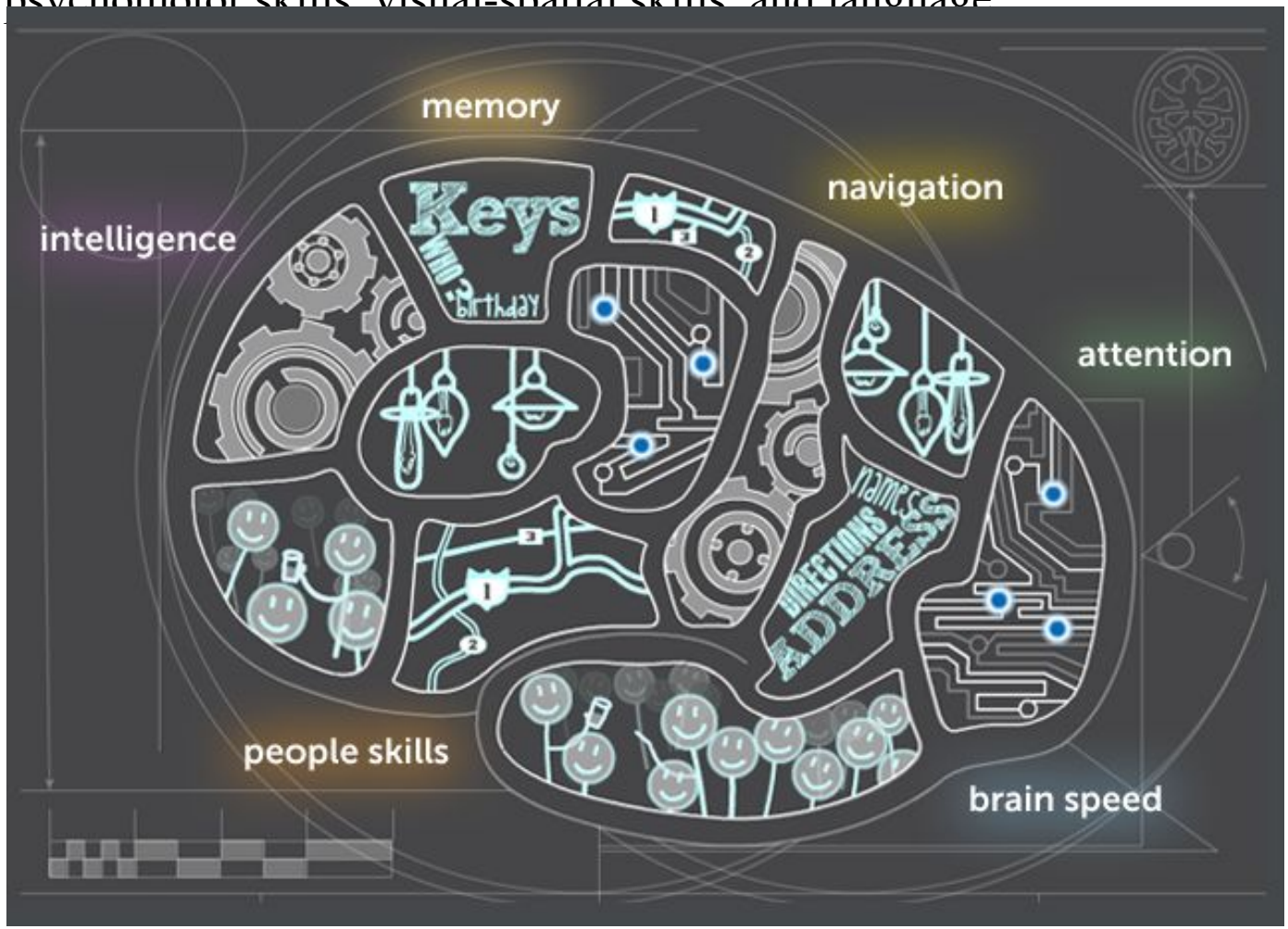
it is estimated **that 40%-100%** of pediatric brain tumor survivors experience deficits in cognitive function related to the tumor and/or its treatment.

Armstrong GT, Liu Q, Yasui Y, et al: Long-term outcomes among adult survivors of childhood central nervous system malignancies in the childhood cancer survivor study. J Natl Cancer Inst 101:946-958, 2009

Moore BD 3rd: Neurocognitive outcomes in survivors of childhood cancer. J Pediatr Psychol 30:51-63, 2005

Turner CD, Chordas CA, Liptak CC, et al: Medical, psychological, cognitive and educational late-effects in pediatric low-grade glioma survivors treated with surgery only. Pediatr Blood Cancer 53:417-423, 2009

Survivors were also found to perform poorly on measures of attention, memory, executive function, processing speed, psychomotor skills, visual-spatial skills, and language.



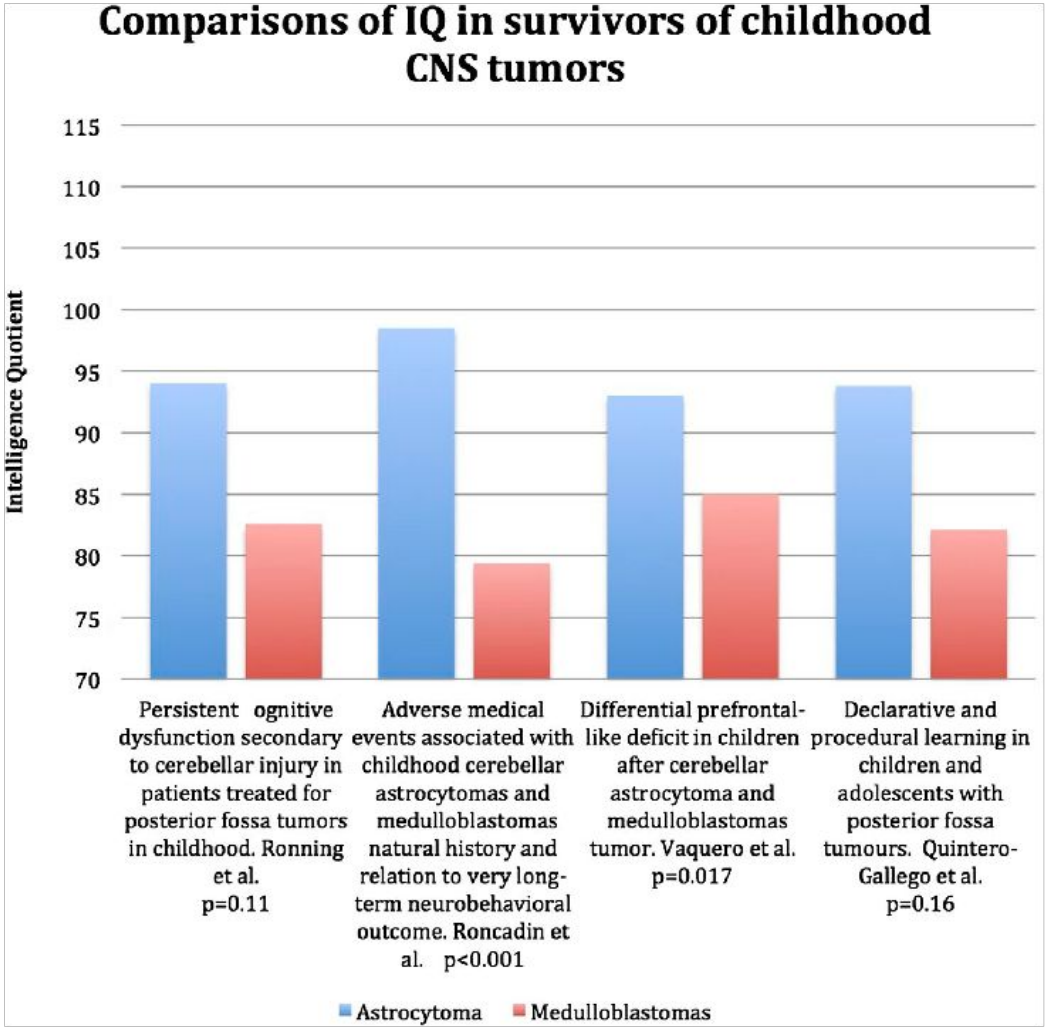


Fig. 1 Comparison of measured IQ and corresponding *p* values in four studies shows medulloblastoma survivors having a lower IQ than the astrocytoma group

Table 1 Risk Factors for Neurocognitive Dysfunction

Tumor-Related Factors	Host Factors
Presence/absence of hydrocephalus	Age at diagnosis
Tumor location	Age at treatment
Tumor size	Gender
Weakness/sensory deficits	Genetic polymorphisms
Cranial nerve deficits	Presence/absence of neurogenetic syndrome
Duration of symptoms	Pretreatment/baseline level of functioning
Presence/absence of seizures	Socioeconomic status
Need for anticonvulsants	Other medical complications/illnesses
Steroid use	Sleep disorders
	Fatigue
	Hypertension
	Sensorineural hearing loss
	Visual impairment
	Endocrine dysfunction

Treatment factors	Environmental/ Psychosocial factors
Surgery	School absences
Neurologic injury	Adequacy of educational supports
Motor/sensory deficits	Access to neuropsychological assessments
Ataxia	Hospital-based school consultation
Perioperative infarction	Educational/vocational supports
Hemorrhage	Technical support
Posterior fossa syndrome	Books on tape
Chemotherapy	Assistive devices
Neuropathy	Computers
Hearing deficit	Loss of socialization/peer experiences
Headaches	Emotional distress (patient/ sibling/family)
Fatigue	Changes to physical appearance
Encephalopathy	Psychological adjustment
Leukoencephalopathy	Self-image/psychological distress
Intrathecal chemotherapy	Depression/anxiety
Steroid use	
"Chemobrain"	
Radiation therapy	
Radiation dose	
Radiation field	
Use of radiosensitizer	
Radiation tissue injury	
White matter injury	
Radiation necrosis	
Stroke or vasculopathy	
Vision changes (cataracts)	

GRAZIE PER L'ATTENZIONE!