Updates in Pediatric CNS Tumors

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2021 WHO Classification of Tumors of the Central Nervous System, fifth edition

Gliomas, glioneuronal tumors, and neuronal tumors
Adult-type diffuse gliomas
Pediatric-type diffuse low-grade gliomas
Pediatric-type diffuse high-grade gliomas
Circumscribed astrocytic gliomas
Circumscribed astrocytic gliomas
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Chordoid glioma
Astroblastoma, MN1-altered

Louis, et al. Neuro-Oncology, 2021, 23(8), 1231–1251

WHO classification of adult-type and pediatric-type diffuse gliomas

Tumor type	CNS WHO grade	Characteristic molecular genetic alterations
Adult-type diffuse gliomas		
Astrocytoma, IDH-mutant	2, 3, 4	*IDH1*, *IDH2*
Oligodendroglioma, IDH-mutant, 1p/19q-codeleted	2, 3	*IDH1*, *IDH2*, 1p/19q
Glioblastoma, IDH-wildtype	4	IDH-wildtype, chromosome 7 and 10, *TERT*, *EGFR*, others
Pediatric-type diffuse low-grade gliomas		
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	1	*MYB*, *MYBL1*
Angiocentric glioma	1	*MYB*
Polymorphous low-grade neuroepithelial tumor of the young	1	*BRAF*, FGFR genes
Diffuse low-grade glioma, MAPK pathway-altered	NA*	MAPK pathway genes
Pediatric-type diffuse high-grade gliomas		
Diffuse midline glioma, H3 K27-altered	4	H3 K27, *EGFR*, *EZHIP*
Diffuse hemispheric glioma, H3 G34-mutant	4	H3 G34
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	4	IDH-wildtype, H3-wildtype, methylome, *EGFR*, *PDGFRA*, *MYCN*
Infant-type hemispheric glioma	NA¶	RTK genes

WHO: World Health Organization; CNS: central nervous system; IDH: isocitrate dehydrogenase; *TERT*: telomerase reverse transcriptase; *EGFR*: epidermal growth factor receptor; *MYB*: MYB proto-oncogene, transcription factor; *MYBL1*: MYB proto-oncogene-like 1; FGFR: fibroblast growth factor receptor; MAPK: mitogen-activated protein kinase; *EZHIP*: EZH inhibitor protein; *PDGFRA*: platelet-derived growth factor receptor alpha; *MYCN*: MYCN proto-oncogene, bHLH transcription factor; NA: not assigned; RTK: receptor tyrosine kinase.

* Low grade.

¶ High grade.

Pediatric Diffuse High-Grade Gliomas

- 14.8% of all intracranial neoplasms are among children and adolescents.
- 5-year overall survival is <20%
- Treatment for pediatric diffuse high-grade gliomas frequently includes surgery, radiation therapy (RT), and chemotherapy.
- Goals of surgery include the safe reduction of tumor-associated mass effect and obtaining adequate tissue for histologic and molecular classification.

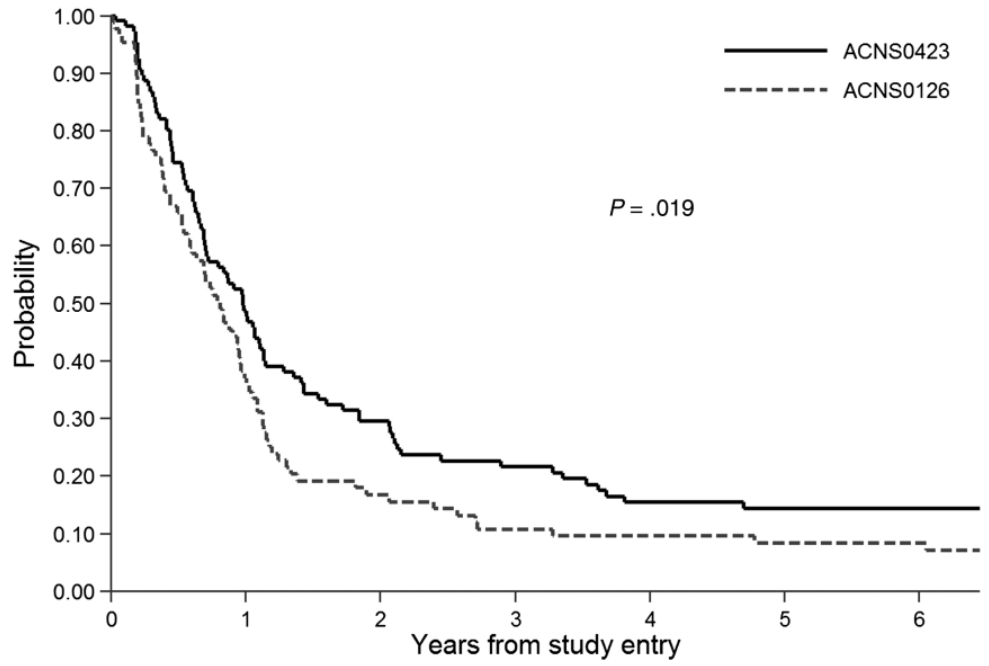
ACNS 0423 – High Grade Glioma – Treatment

- 54.0 Gy to the preoperative tumor volume plus a 2 cm margin in 1.8 Gy fractions if a gross-total resection (GTR) was performed.
- For incomplete resections, residual disease was boosted with 3 additional fractions to a total dose of 59.4 Gy.
- During radiation, participants received temozolomide 90 mg/m2 /day for 42 days.
- Four weeks after completion of radiotherapy, participants started adjuvant therapy with lomustine 90 mg/m2 on day 1 and temozolomide 160 mg/m2 /day×5. Cycles were repeated every 42 days or when counts recovered, for a total of 6 cycles.

Jakacki et al. Neuro-Oncology 2016; 18(10); 1442–1450

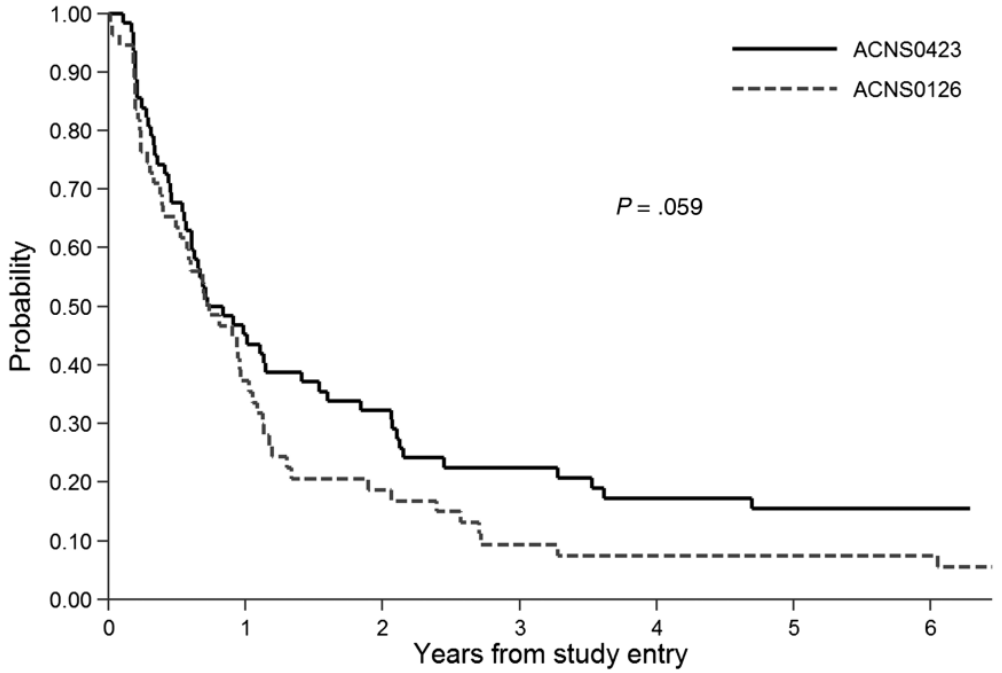
ACNS 0423 – High Grade Glioma – Outcomes

EFS of AA and GBM



risk (n)							
ACNS0423	108	51	30	21	15	8	3
ACNS0126	86	31	14	9	8	7	7

EFS of GBM

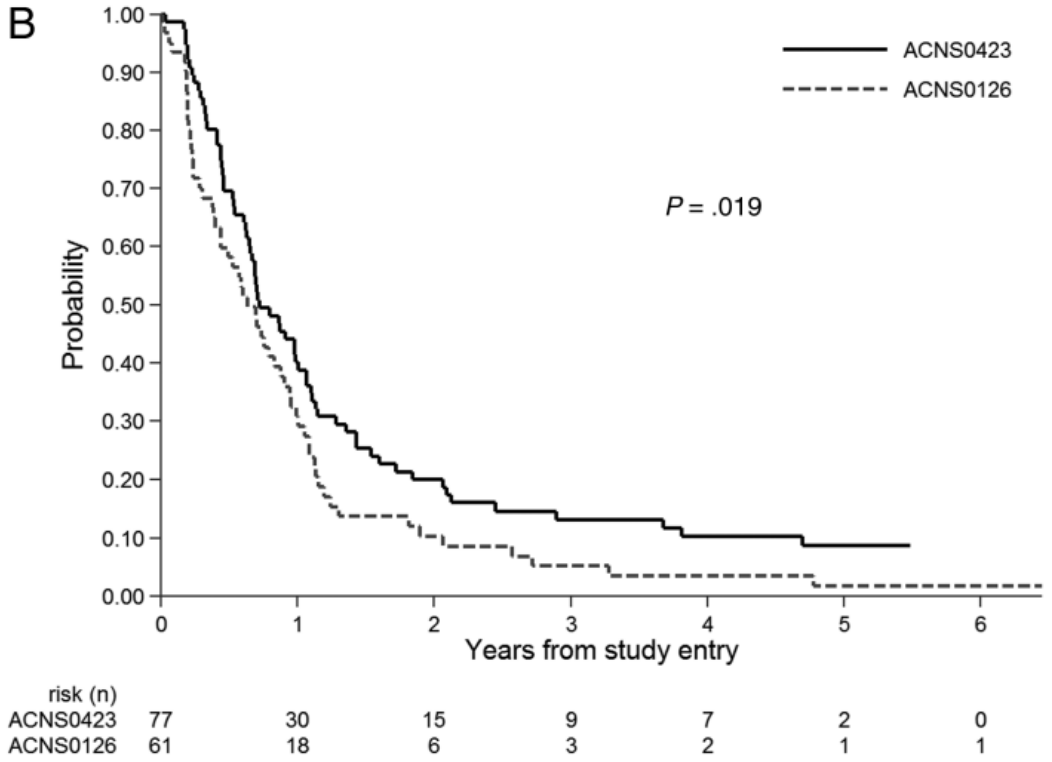


risk (n)							
ACNS0423	62	28	20	13	10	5	2
ACNS0126	55	20	10	5	4	4	4

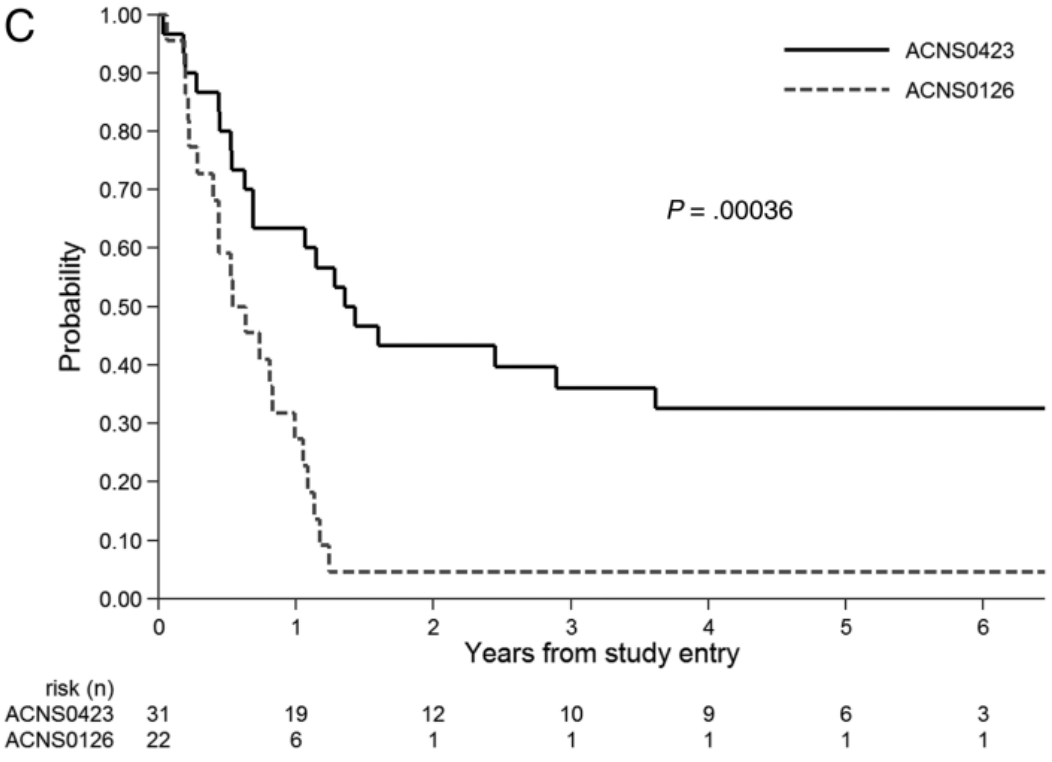
Jakacki et al. Neuro-Oncology 2016; 18(10); 1442–1450

ACNS 0423 – High Grade Glioma – Outcomes

patients had not undergone GTR



patients had MGMT overexpression



Jakacki et al. Neuro-Oncology 2016; 18(10); 1442–1450

Low grade glioma

- Most common pediatric brain tumor (40%)

- Infratentorial low grade astrocytomas in the cerebellum are common, but usually resectable so we rarely see them as Radiation Oncologists except brainstem lesions.

- Most supratentorial low grade astrocytomas occur in the central regions of the diencephalon (hypothalamus, optics, thalamus—not generally resectable), secondly in hemispheres, in temporal and frontal lobes most commonly (often resected thus less common for us to see them).

Low-Grade Glioma

- Extensive resection is the treatment goal for superficial lesions within the cerebral and cerebellar hemispheres.
- After complete resection, 10-year progression-free survival (PFS) exceeds 85%, versus less than 50% if there is radiologically visible residual tumor.
- After complete resection, RT or chemotherapy is rarely warranted
- For unresectable or partially resected tumors, chemotherapy has been used during the last 2 decades to delay or avoid RT in young children

COG A9952 - Low-Grade Glioma – chemotherapy regimens

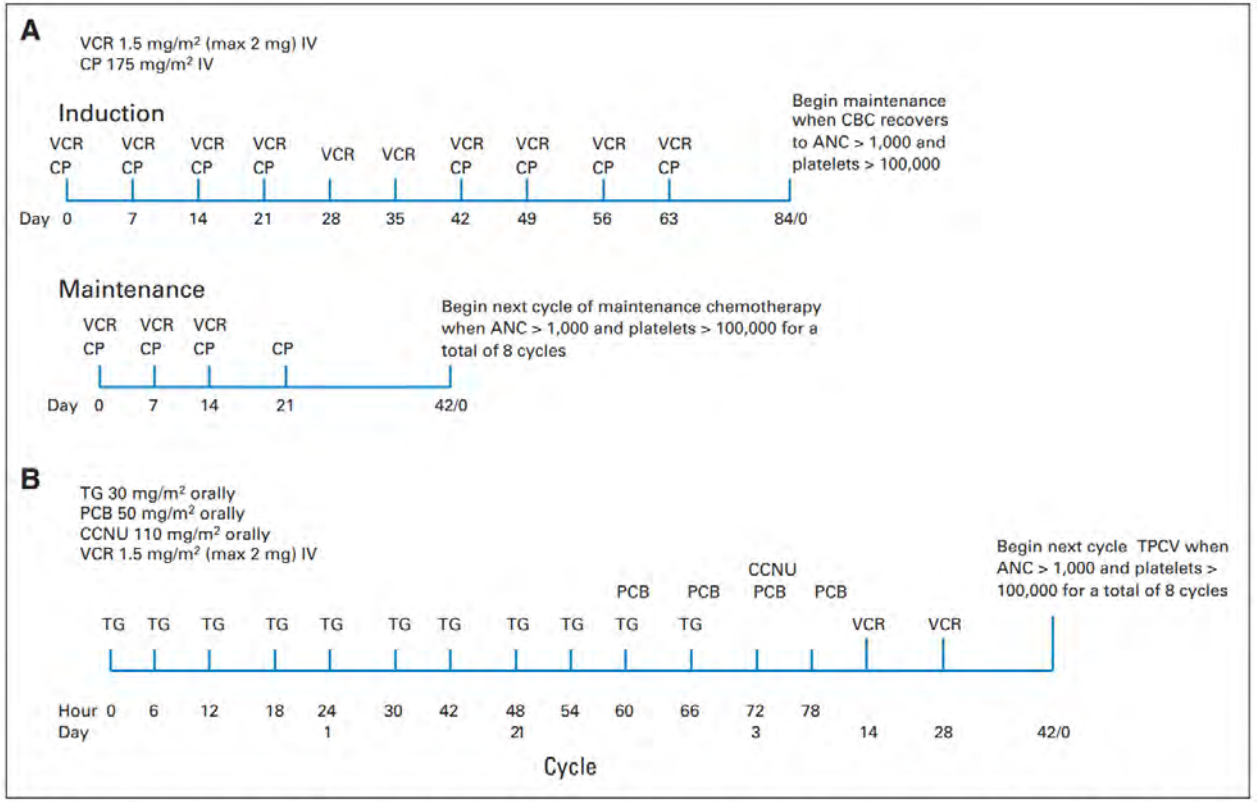


Fig 2. Treatment schema for induction and maintenance therapy for two regimens. Regimen A: carboplatin (CP) and vincristine (VCR). Regimen B: TPCV, thioguanine (TG), procarbazine (PCB), CCNU (lomustine), and vincristine (VCR). ANC, absolute neutrophil count.

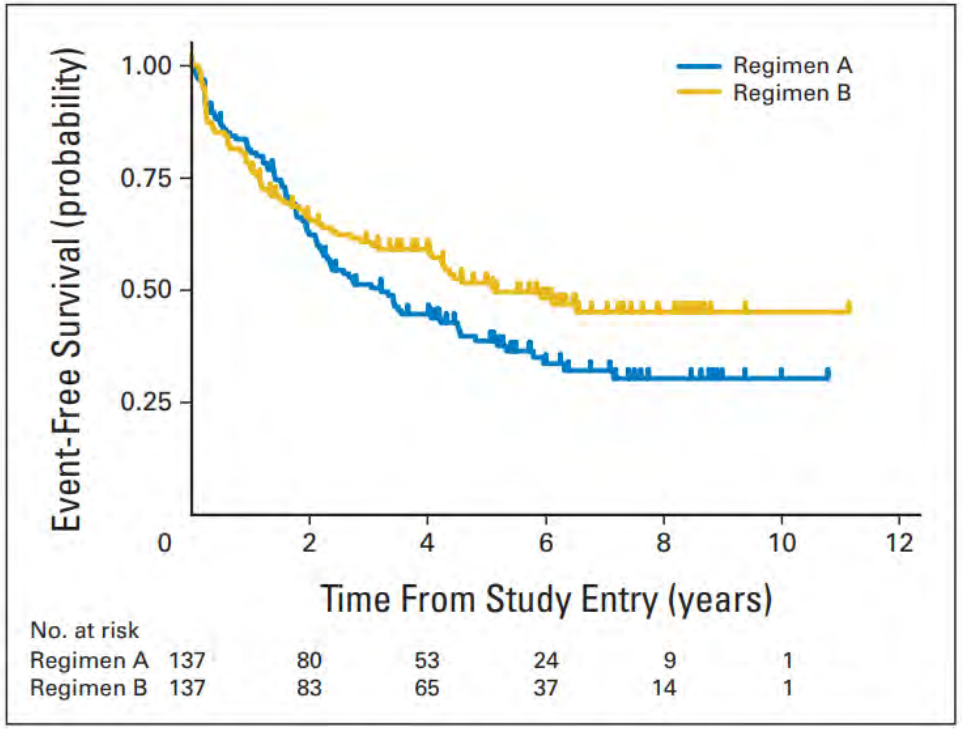


Fig 3. Event-free survival for patients randomly assigned to regimen A (CV: carboplatin and vincristine) or regimen B (TPCV: thioguanine, procarbazine, CCNU [lomustine], and vincristine).

Ater et al. J Clin Oncol 2012, 30:2641-2647

Low-Grade Glioma

- Both regimens are active—carboplatin and vincristine versus thioguanine, procarbazine, lomustine, and vincristine—for unresectable or progressive LGGs in children without NF1.

- Patients with NF1-related gliomas received carboplatin and vincristine given concerns regarding alkylator-related second malignancies.

- Both regimens delayed tumor progression, although children without NF1 generally experienced disease progression within 5 years of therapy, highlighting the need for additional treatment options

Targeted Therapy

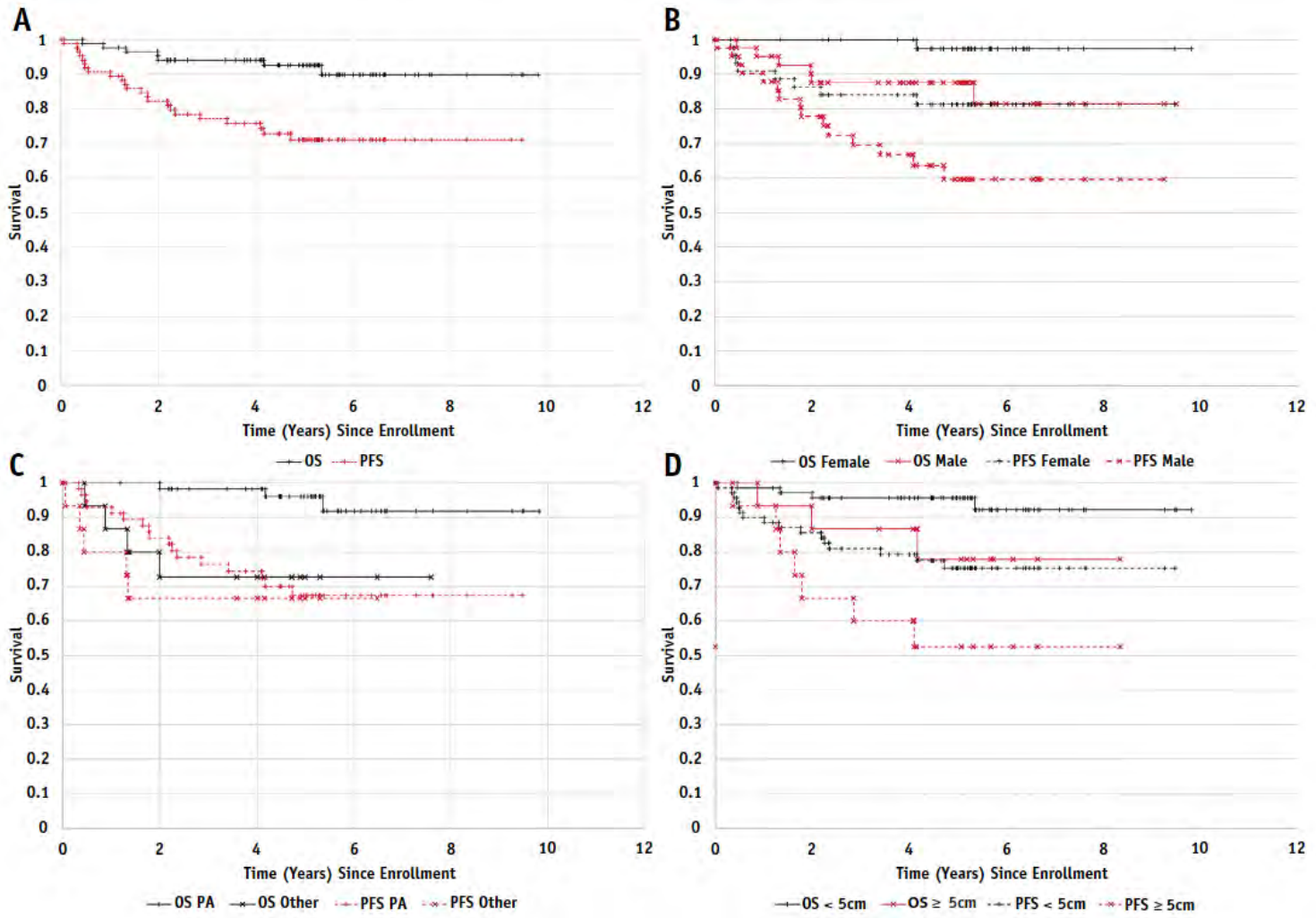
- Selumetinib - inhibit MAPK activation by blocking MEK1/2 (MAPK/ERK kinase)
- trametinib - MEK inhibitor
- Vemurafenib - target tumors with BRAF V600E mutations
- Dabrafenib - target tumors with BRAF V600E mutations
- Everolimus - mTOR inhibitor

ACNS 0221 – Low Grade Glioma – RT

- 54 Gy in 30 fractions of 1.8 Gy each.
- GTV for pilocytic astrocytoma
  - the entire tumor volume seen on gadolinium-enhanced T1-weighted MRI plus any additional abnormality seen on T2-weighted MRI or fluid-attenuated inversion recovery imaging.
- GTV for non- pilocytic astrocytomas,
  - based on T2 or fluid-attenuated inversion recovery imaging. All tumor cysts were included in the GTV.
- CTV was the GTV plus a 5-mm anatomically limited margin (ie, CTV did not extend into the calvarium).
- PTV was the CTV plus a 3- to 5-mm margin.

Cherlow et al. Int J Radiat Oncol Biol Phys 2019; 103 (4): 861-868

ACNS 0221 – Low grade glioma – OS and PFS



Cherlow et al. Int J Radiat Oncol Biol Phys 2019; 103 (4): 861-868

2021 WHO Classification of Tumors of the Central Nervous System, fifth edition

Medulloblastoma
Medulloblastomas, molecularly defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and TP53-wildtype
Medulloblastoma, SHH-activated and TP53-mutant
Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined

Louis, et al. Neuro-Oncology, 2021, 23(8), 1231–1251

Medulloblastoma

- 2nd Medulloblastoma most common pediatric brain tumor, but most common malignant brain tumor.
- Mode and Median age is 5 and 7 years, but 20% present under the age of two.
- Primitive cerebellar tumor of neuroectodermal origin, with gene expression distinct from other PNET.
- It can disseminate through the CSF and therefore necessitates CSI as part of treatment (in non infants).

Medulloblastoma – Modified staging system according to Chang

T-Stage	Tumor Extent
T1	Tumor less than 3 cm in diameter
T2	Tumor greater than 3 cm in diameter
T3a	Tumor greater than 3 cm in diameter with extension into the aqueduct of Sylvius and/or the foramen of Luschka
T3b	Tumor greater than 3 cm in diameter with unequivocal extension into the brain stem
T4	Tumor greater than 3 cm in diameter with extension up past the aqueduct of Sylvius and/or down past the foramen magnum
M-Stage	**Degree of Metastasis**
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells found in the cerebrospinal fluid
M2	Gross nodular seeding demonstrated in the cerebellar/cerebral subarachnoid space or in the third or lateral ventricles
M3	Gross nodular seeding in the spinal subarachnoid space
M4	Metastasis outside the cerebrospinal axis

Medulloblastoma – Risk Stratification

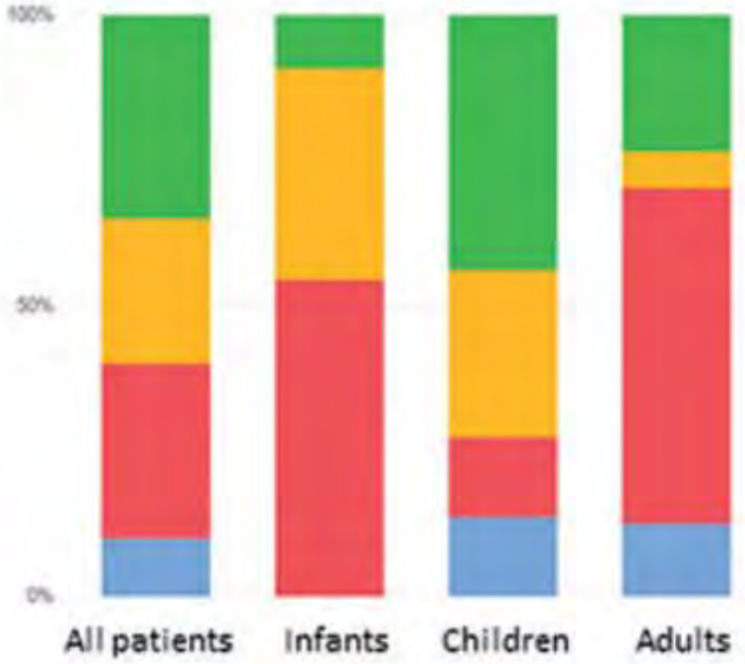
	Average Risk	High risk
Residual gross disease	< 1.5 cm^2	≥ 1.5 cm^2
Metastatic Spread	M0	M1-4
Patient's age	≥ 3 years	< 3 years
Histology	Classic/Desmoplastic	

Other than average risk: Large cell anaplasia histology, M0, and GTR

Demographic and prognostic features of medulloblastoma by subgroup

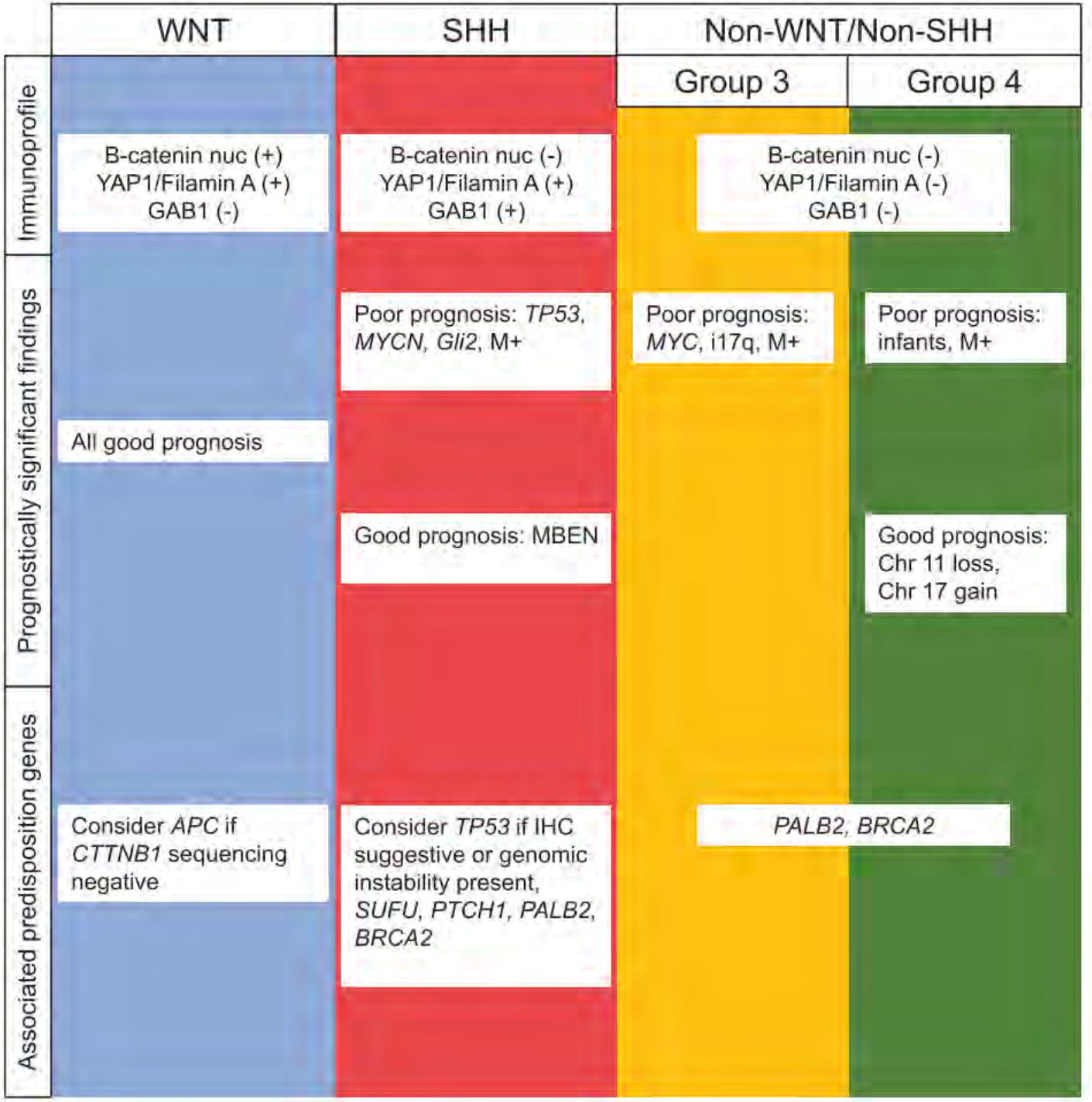
A

	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



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

Medulloblastoma – Key clinicopathologic findings by molecular subgroup

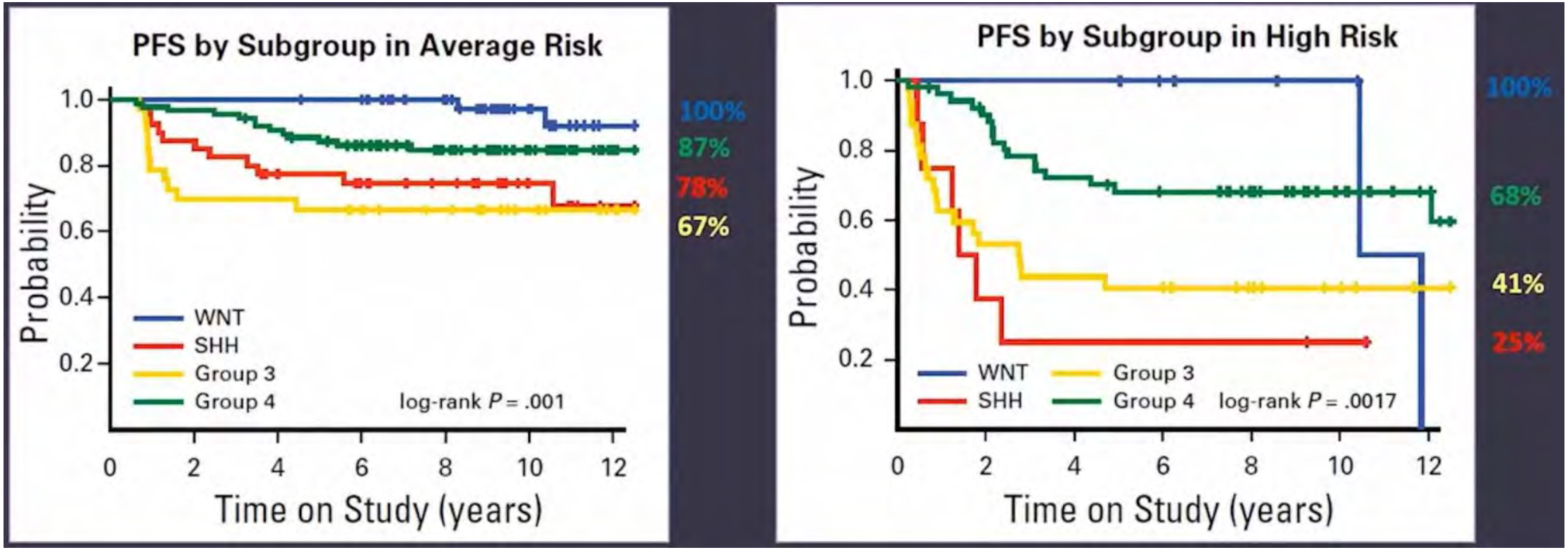


Cotter et al. Pediatric and Developmental Pathology 2022, Vol. 25(1) 23–33

Medulloblastoma – PFS by molecular subtype

PFS by Subgroup in Average Risk

PFS by Subgroup in High Risk



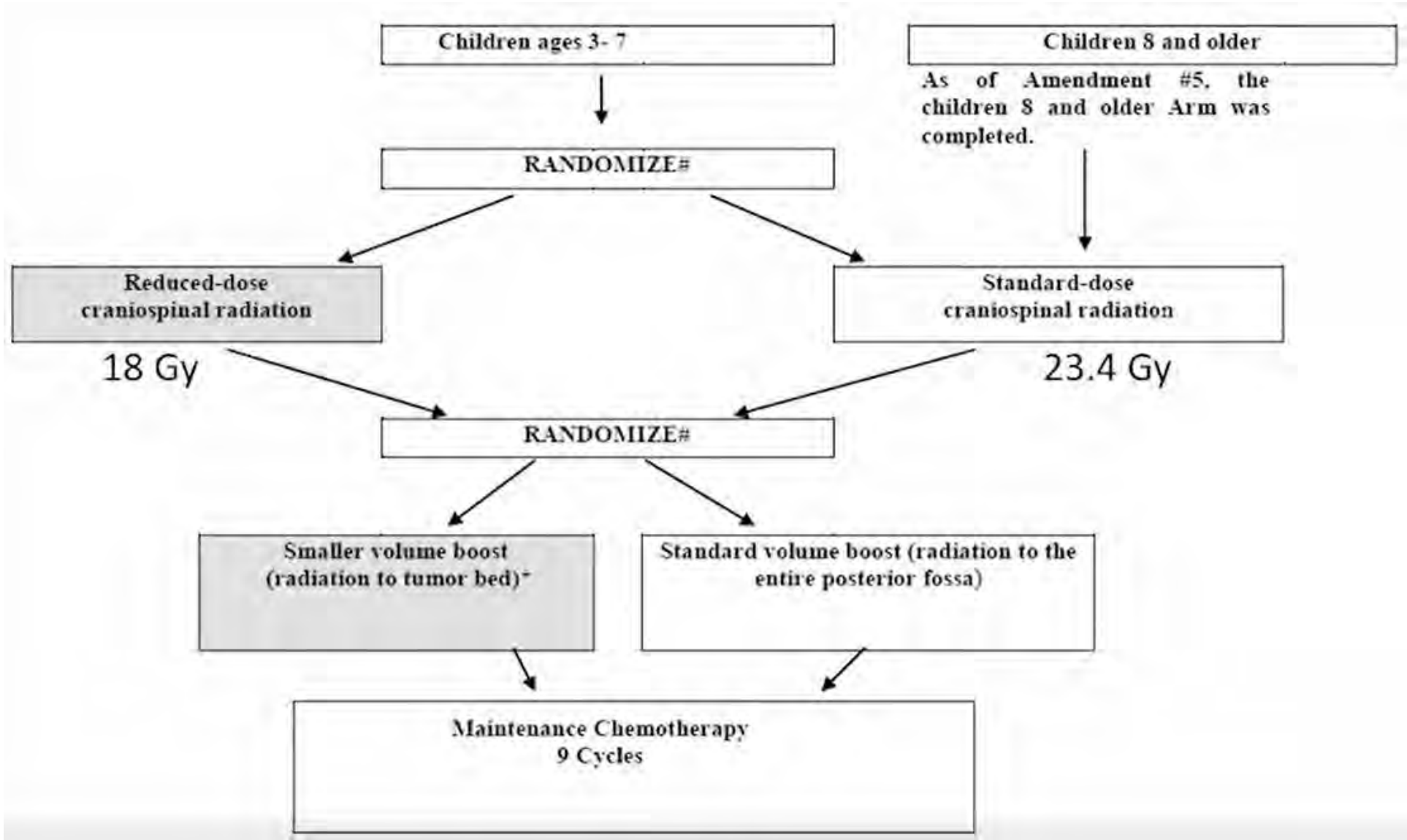
Gajjar et al. JCO 2021 39(7): 822-835

Medulloblastoma – Molecular Based Risk Groups

Risk	5y OS	Characterization
Low	>90%	WNT subgroup and non-metastatic group 4 tumors with whole chromosome 11 loss or whole chromosome 17 gain
Average	75–90%	Non-metastatic SHH TP53wt without MYCN amplification, non-metastatic group 3 without MYCN amplification, non-metastatic group 4 with intact chromosome 11
High	50–75%	Metastatic SHH or group 4 tumors, or MYCN amplified SHH medulloblastoma
Very High	<50%	Group 3 with metastases or SHH with TP53 mutation

Seidel et al. Cancers 2021, 13, 5945

ACNS0331 – Medulloblastoma – Average Risk



ACNS0331 – Medulloblastoma – Average Risk

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

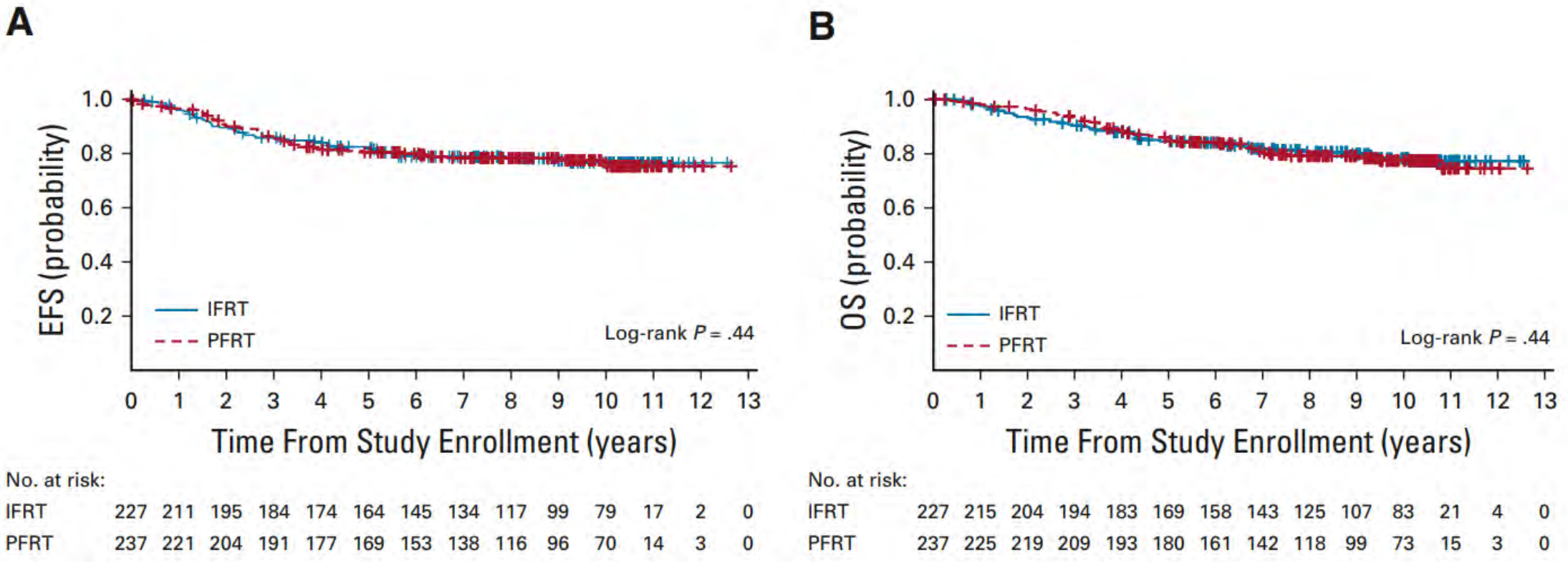
Vincristine (1.5 mg/m^2, maximum dose 2.0 mg) IV push or infusion on Days 1 and 8

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

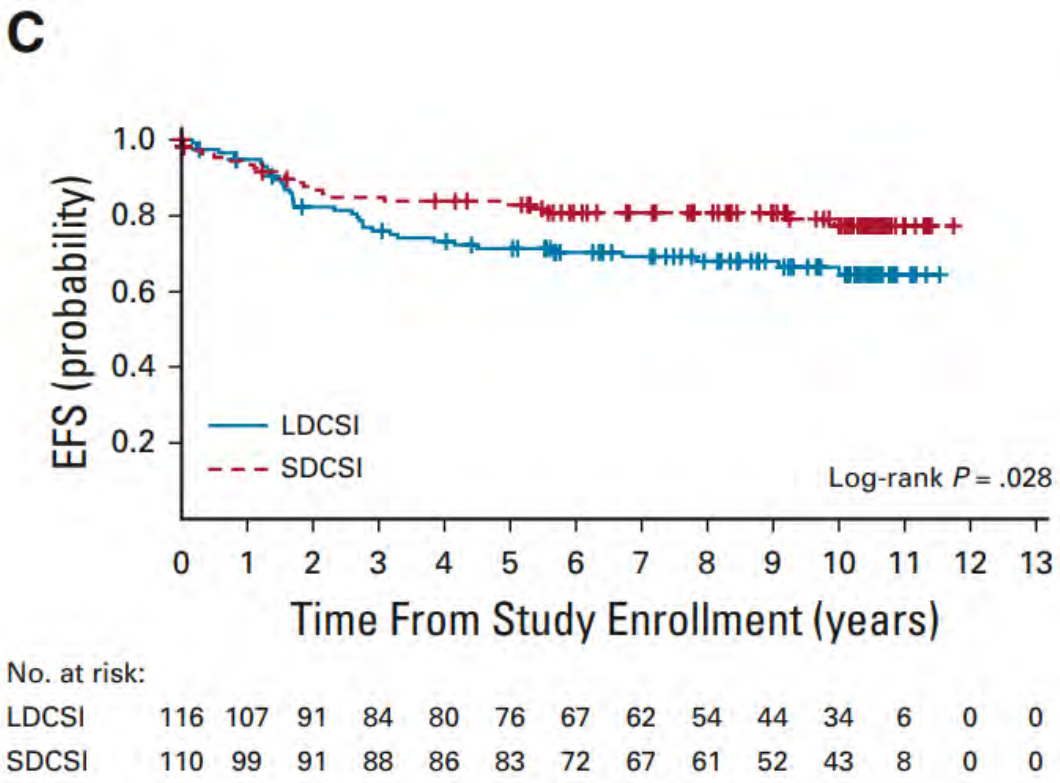
Michalski et al. JCO 2021; 39 (24): 2685

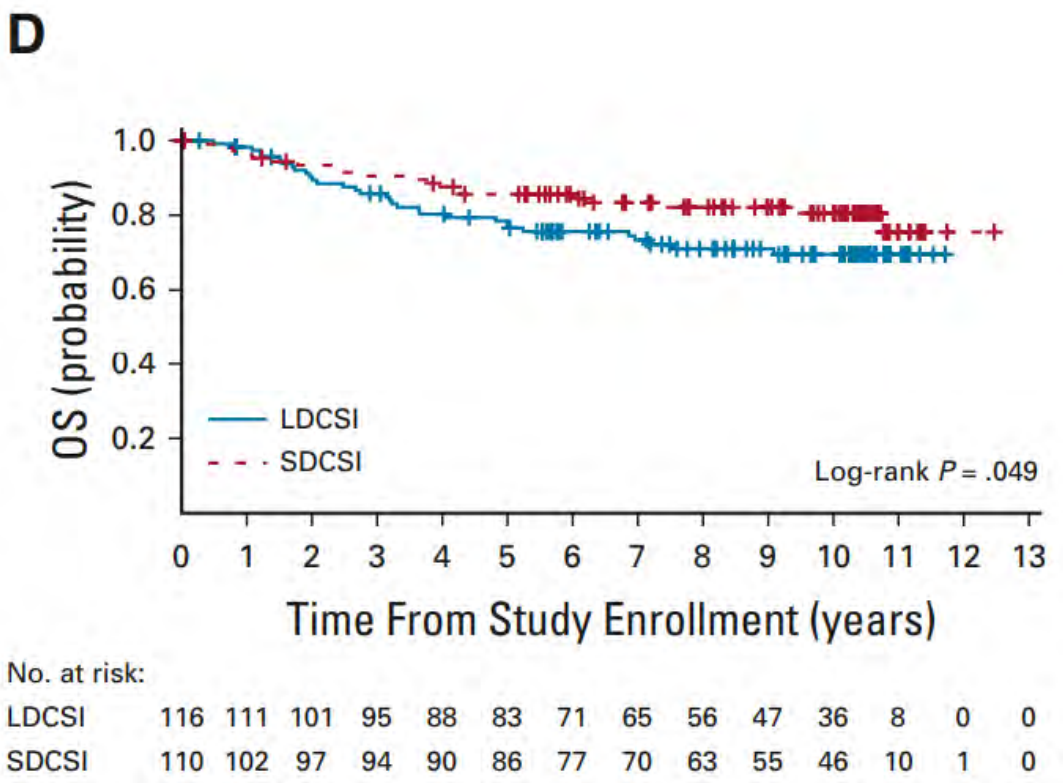
ACNS0331 – Medulloblastoma – Involved field vs posterior fossa RT



Michalski et al. JCO 2021; 39 (24): 2685

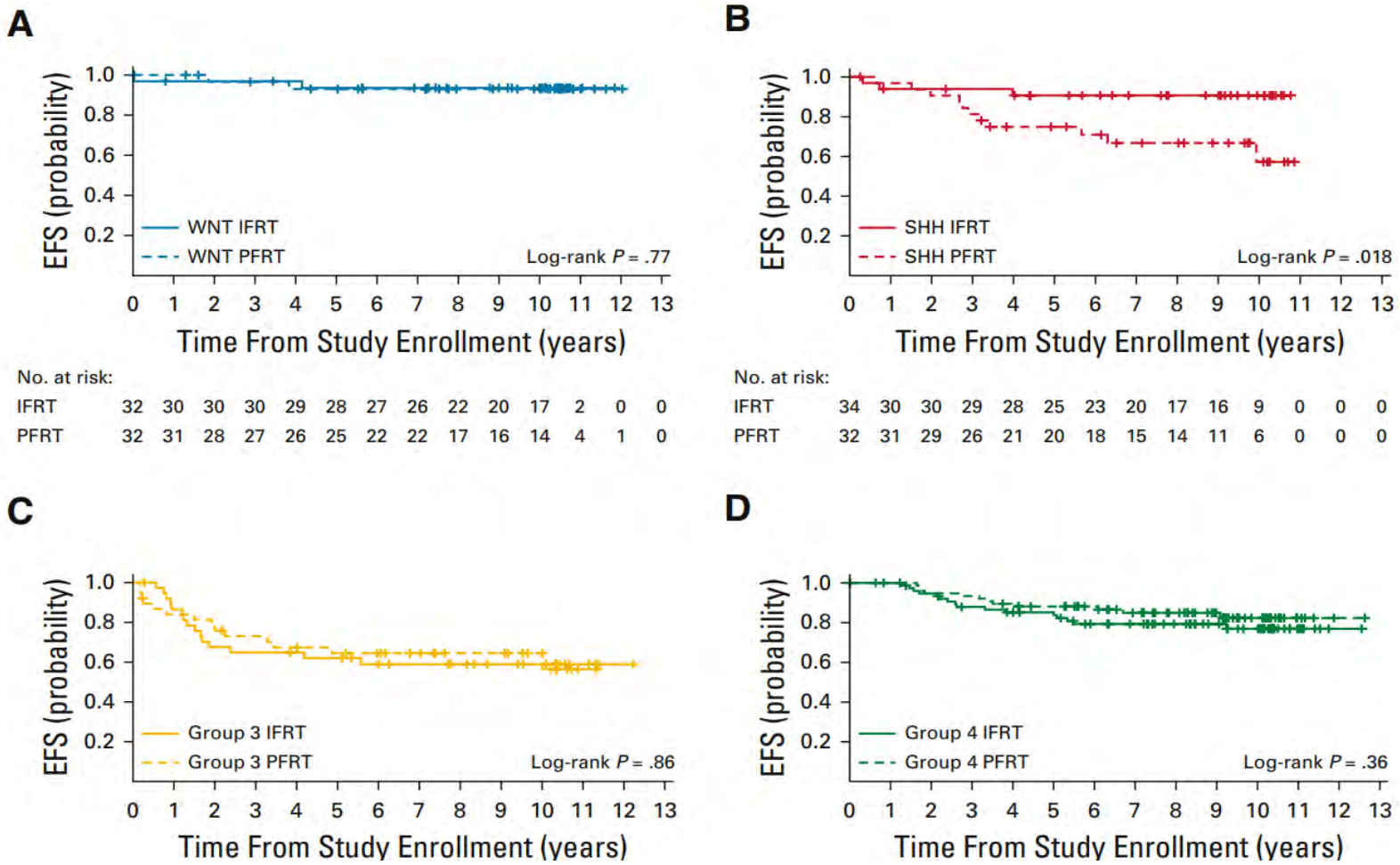
ACNS0331 – Medulloblastoma – low dose vs standard dose CSI





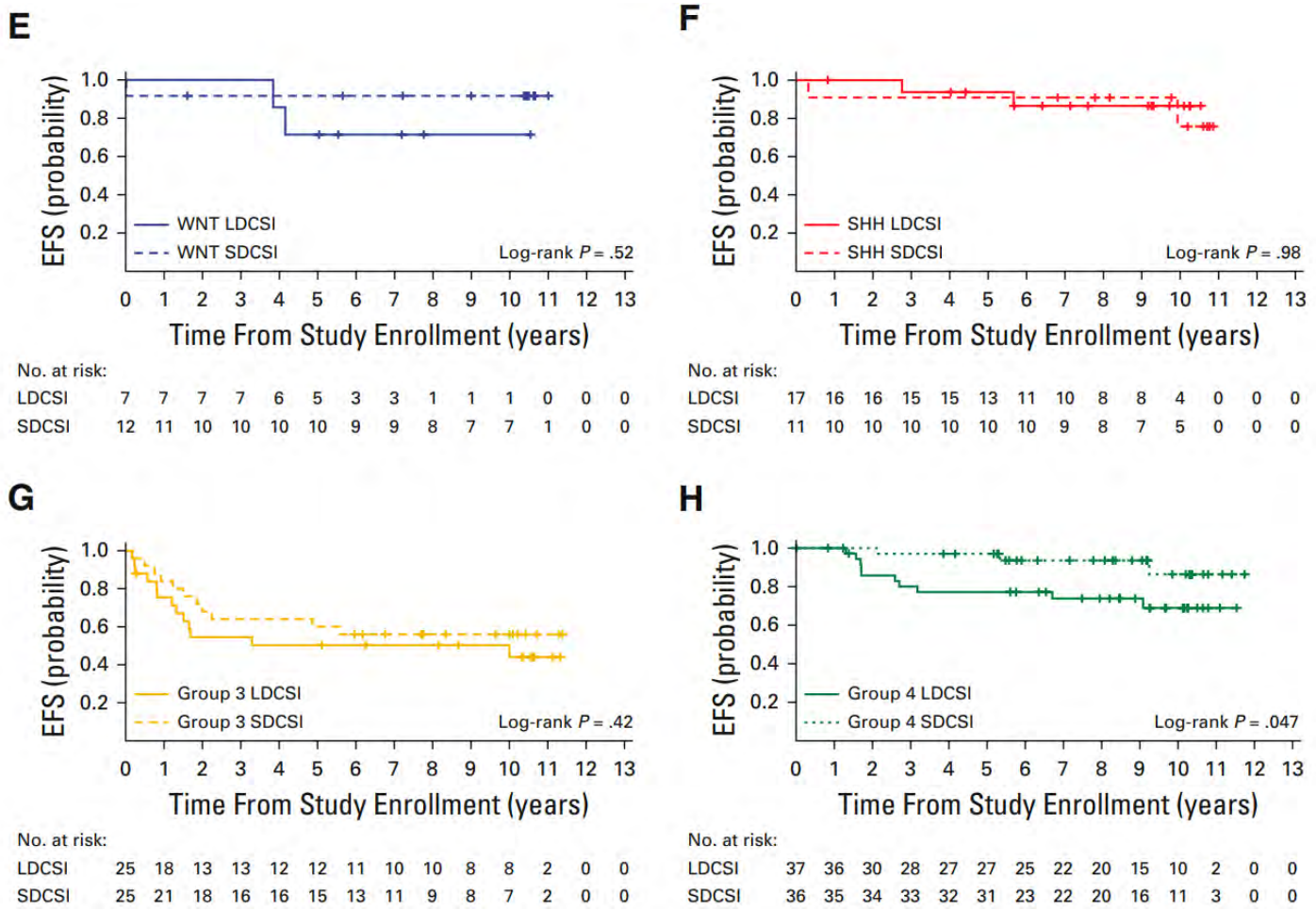
Michalski et al. JCO 2021; 39 (24): 2685

ACNS0331 – Medulloblastoma – EFS for molecular subgroups by RT field



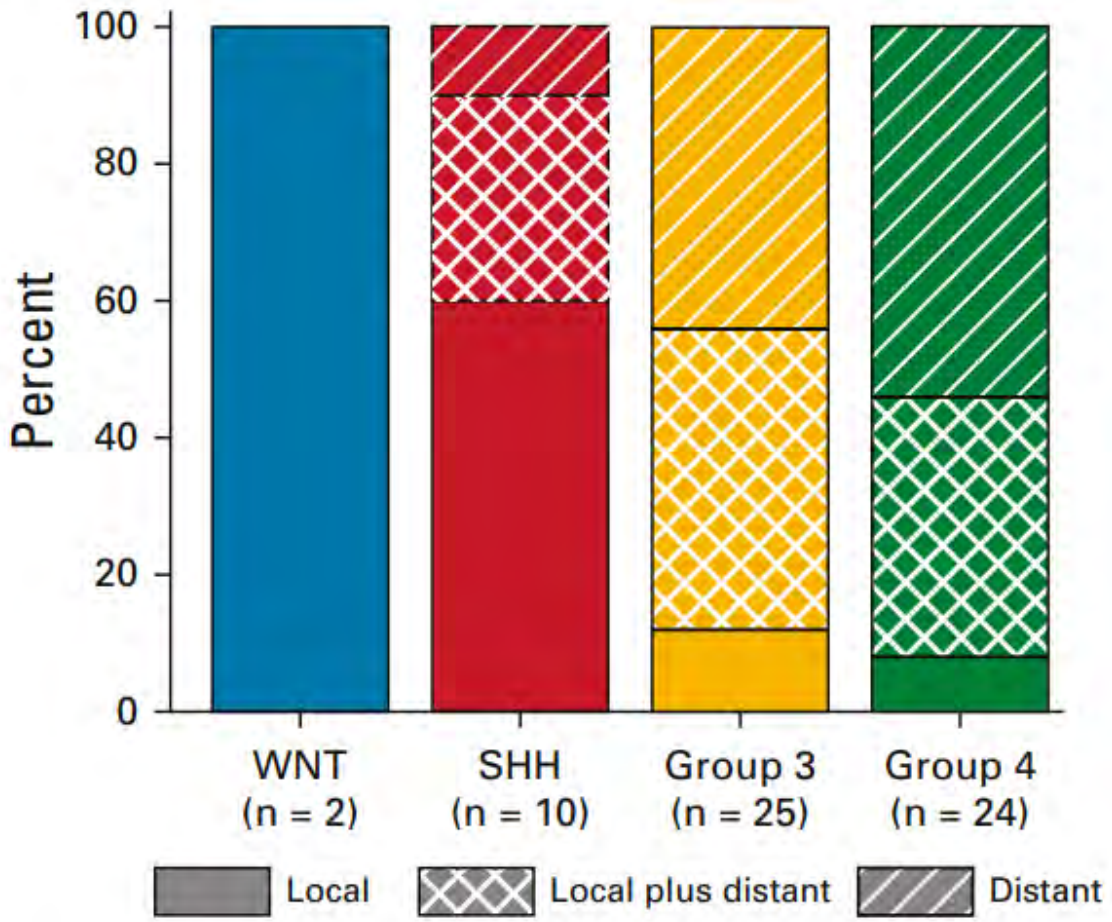
Michalski et al. JCO 2021; 39 (24): 2685

ACNS0331 – Medulloblastoma – EFS for molecular subgroups by CSI dose



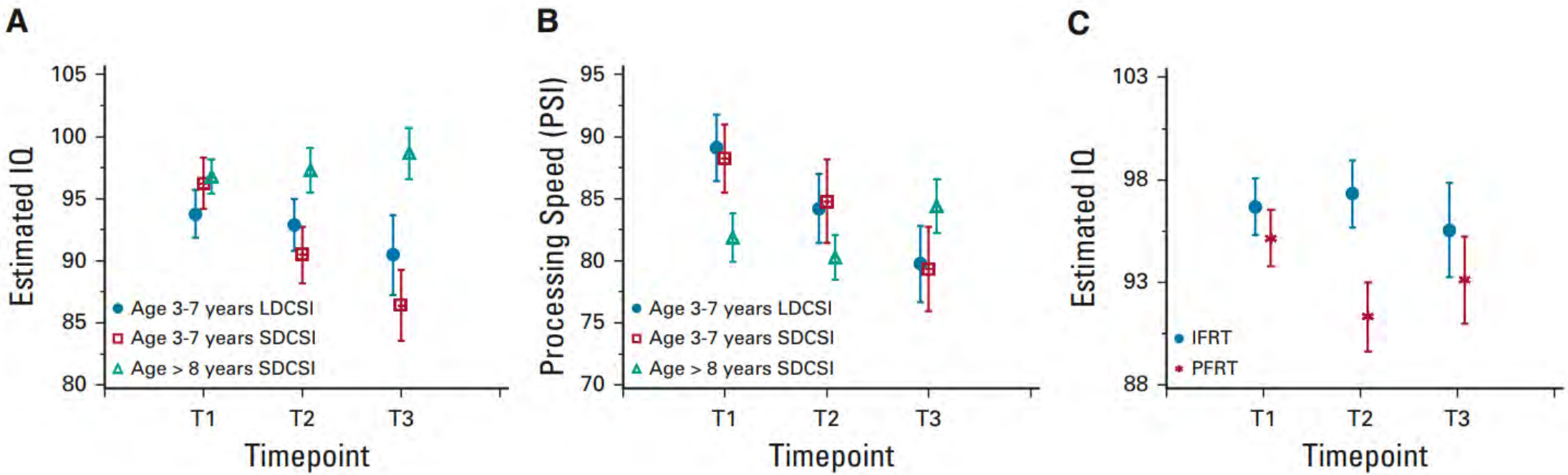
Michalski et al. JCO 2021; 39 (24): 2685

ACNS0331 – Medulloblastoma – Pattern of failure by molecular subgroup



Michalski et al. JCO 2021; 39 (24): 2685

ACNS0331 – Medulloblastoma – Neurocognitive outcomes by trial random assignment



Michalski et al. JCO 2021; 39 (24): 2685

2021 WHO Classification of Tumors of the Central Nervous System, fifth edition

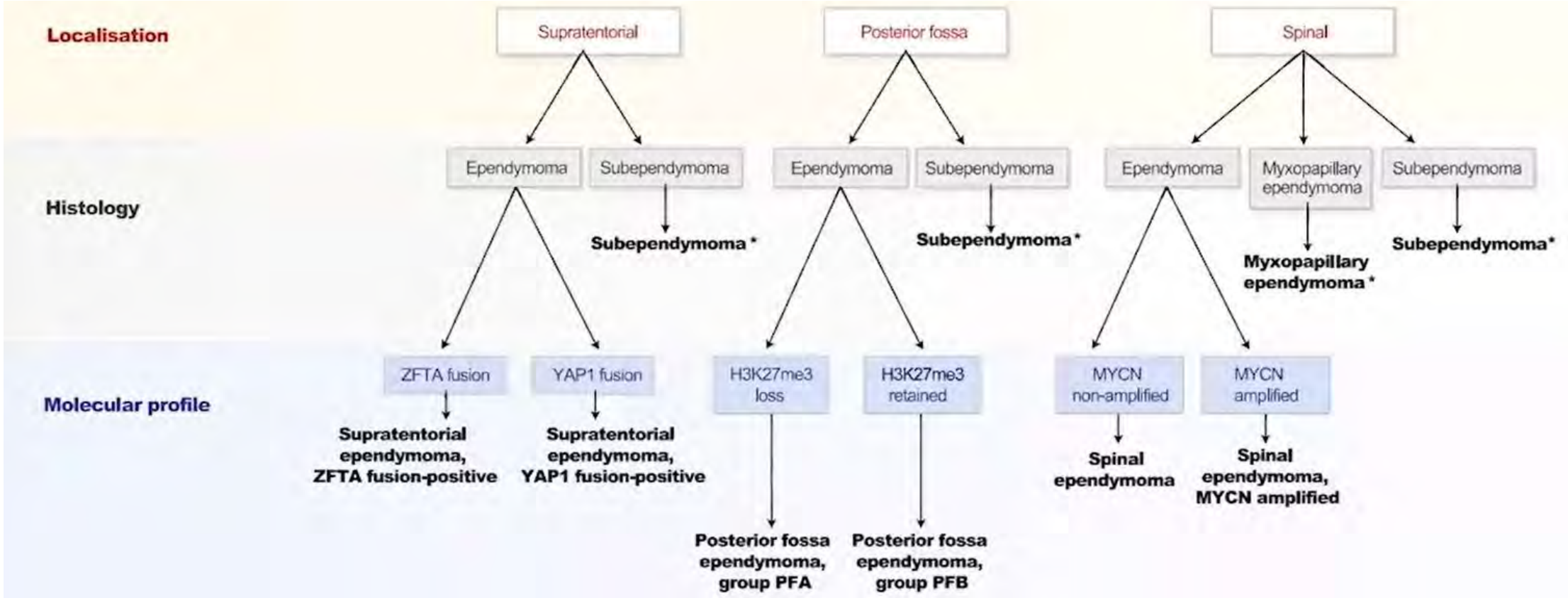
Ependymal tumors
Supratentorial ependymoma
Supratentorial ependymoma, ZFTA fusion-positive
Supratentorial ependymoma, YAP1 fusion-positive
Posterior fossa ependymoma
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma
Spinal ependymoma, MYCN-amplified
Myxopapillary ependymoma
Subependymoma

Louis, et al. Neuro-Oncology, 2021, 23(8), 1231–1251

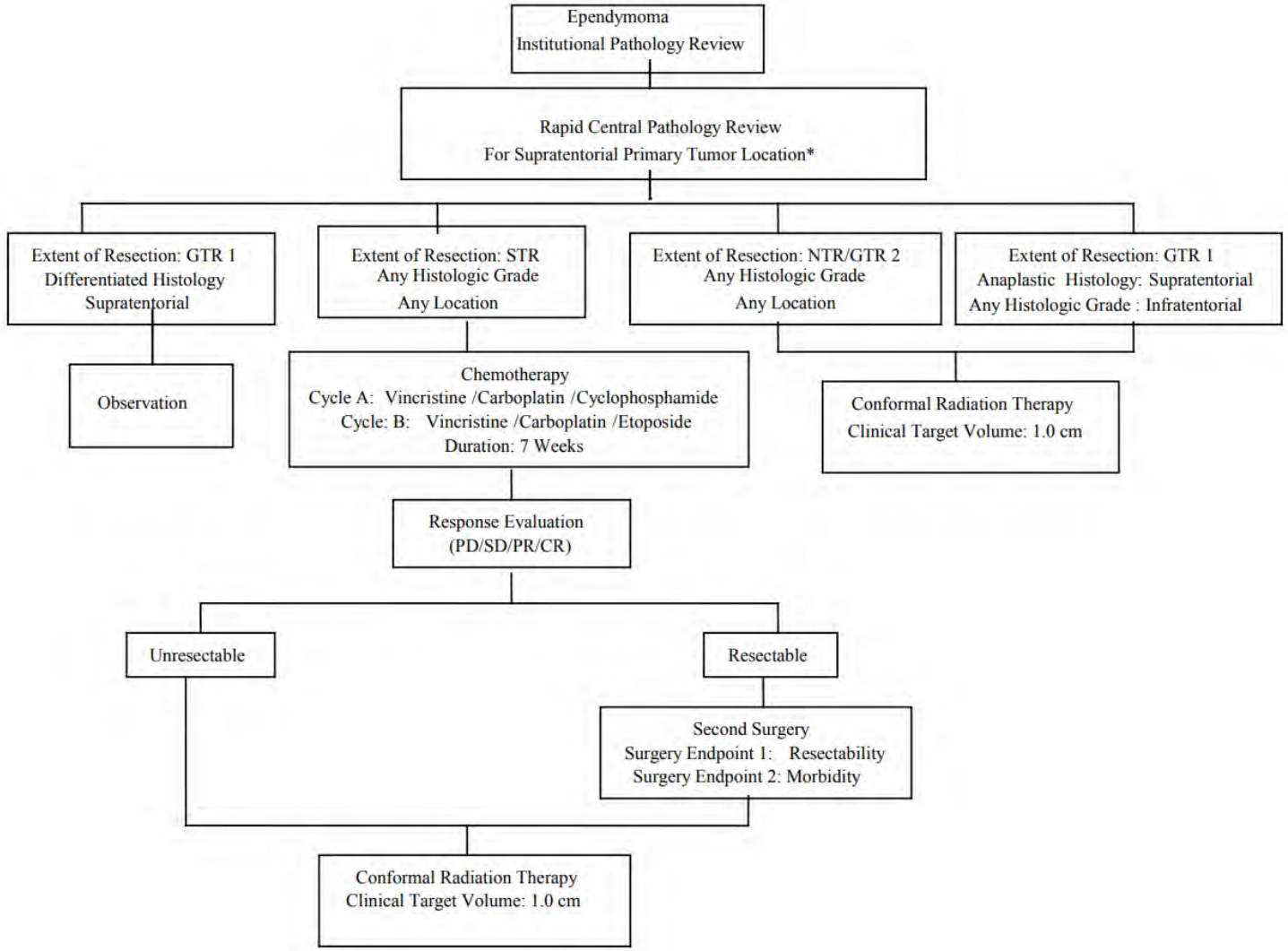
Ependymoma

- Third most common CNS tumor in children
- Median age ~ 4 years
- May occur anywhere within the CNS
  - Posterior fossa/IVth ventricle (60%), classically tracks out through foramen of Lushka, through foramen magnum
  - Supratentorial (30%)
  - Spinal cord (10%) (usually myxopapillary)

Ependymoma Classification



ACNS 0121 – ependymoma – protocol schema



ACNS 0121 – ependymoma – chemo & RT

		Cycle A			Cycle B			
Week		0	1	2	3	4	5	6
Day		1 2	8		1	8	15	22
Cycle A	Vincristine (1.5 mg/m²/dose IV)	X						
	Carboplatin (375 mg/m²/dose IV)	X						
	Cyclophosphamide (1,000 mg/m²/dose IV)	X X						
	Mesna (200 mg/m²/dose IV)	X X						
	Filgrastim (5 µg/kg/day SC or IV)		Daily until ANC > 1500 µl					
Cycle B	Vincristine (1.5 mg/m²/dose IV)				X	X		
	Carboplatin (375 mg/m²/dose IV)				X			
	Etoposide (50 mg/m² day PO)					Daily days 1-21 (oral)		

GTV: the postoperative tumor bed and residual tumor

CTV: an anatomically defined margin of 1.0 cm surrounding the gross tumor volume

PTV: CTV + 3-5 mm

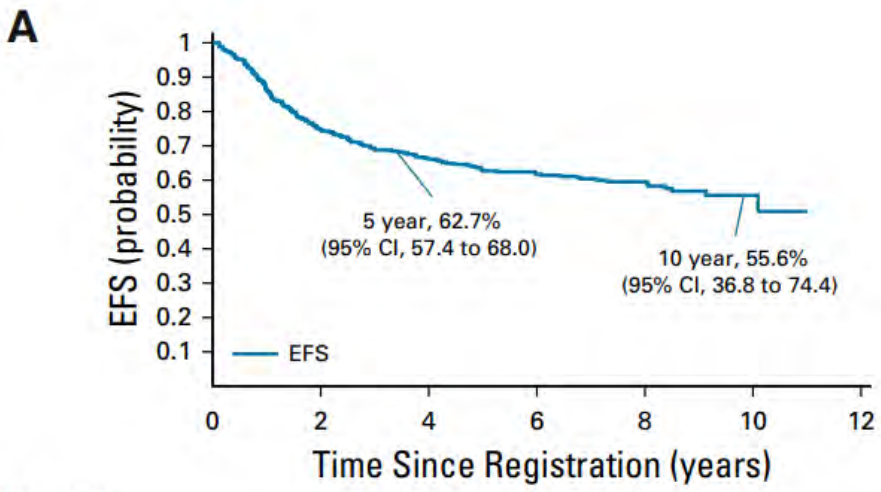
RT dose:
59.4 Gy in 1.8 Gy per fraction

Patients younger than 18 months with GTR 1 or GTR 2 received 54 Gy

Merchant et al. J Clin Oncol 2019; 37:974-983

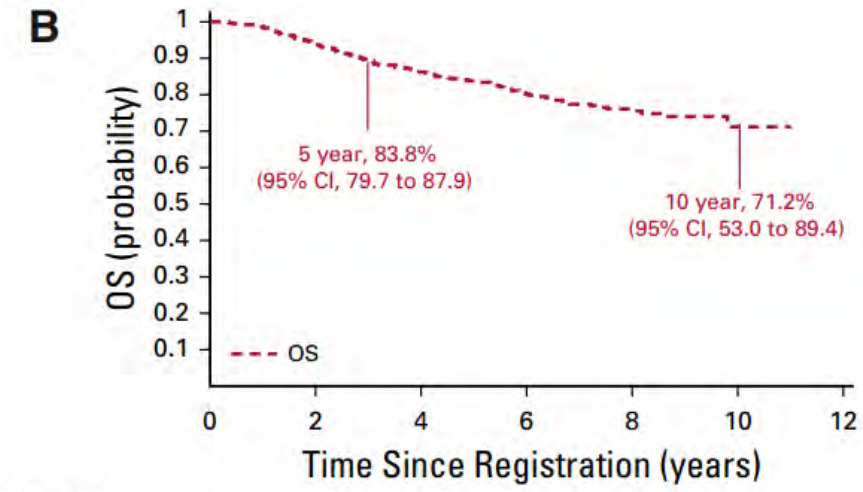
ACNS 0121 – ependymoma – EFS and OS

Merchant et al.
J Clin Oncol 2019;
37:974-983



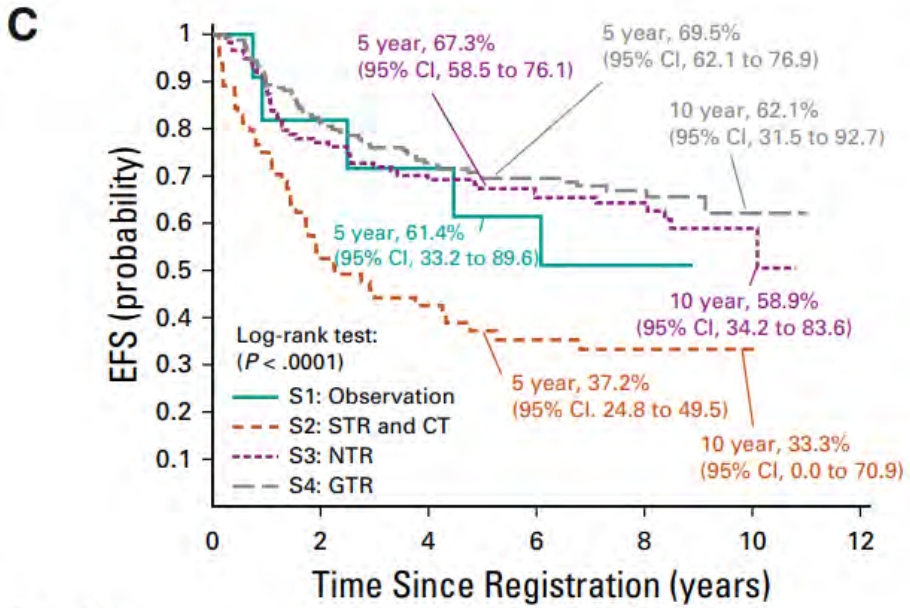
No. at risk

EFS	356	303	235	199	162	56	1



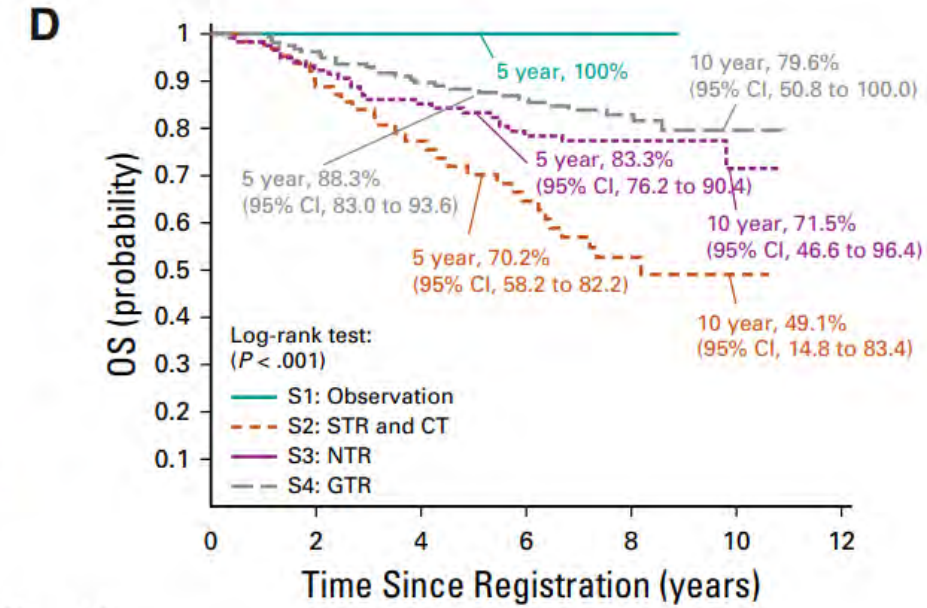
No. at risk

OS	356	346	301	261	206	69	1



No. at risk

S1: Observation	11	9	7	6	3		
S2: STR and CT	64	48	26	21	13	7	
S3: NTR	118	105	82	71	63	24	
S4: GTR	163	141	120	101	83	25	1

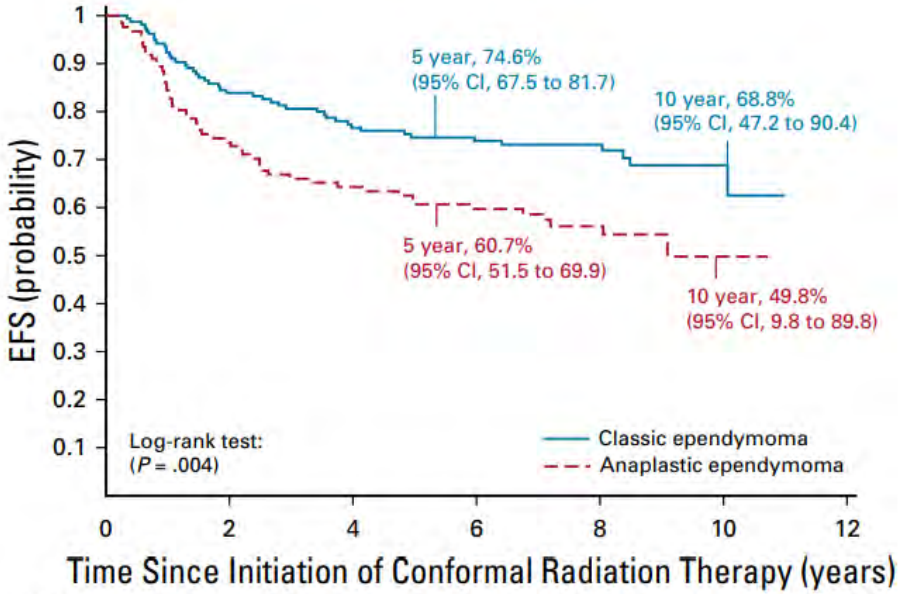


No. at risk

S1: Observation	11	11	10	9	6		
S2: STR and CT	64	63	51	39	26	10	
S3: NTR	118	115	97	86	72	29	
S4: GTR	163	157	143	127	102	30	1

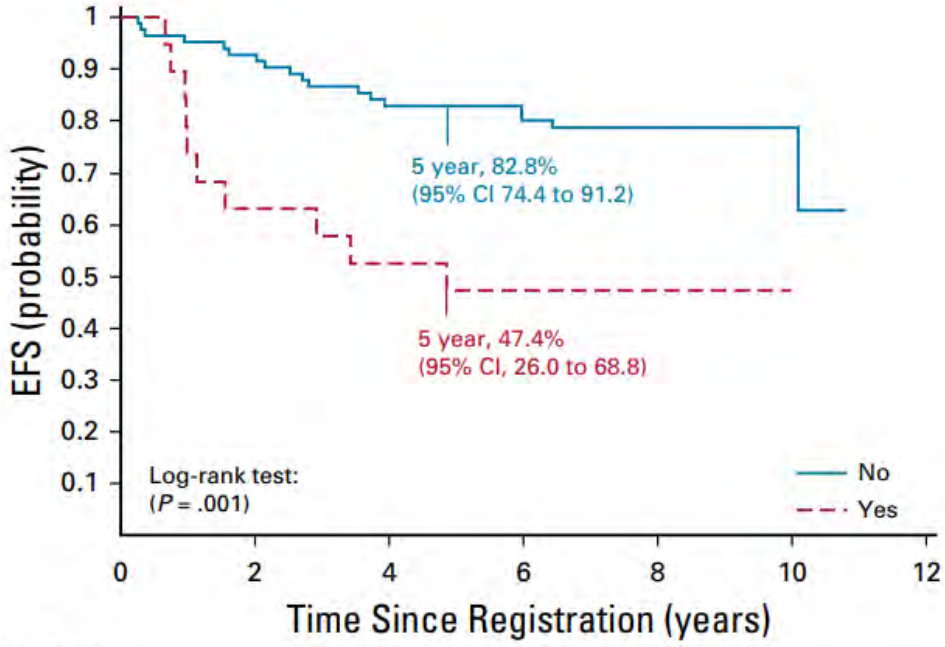
ACNS 0121 – ependymoma – EFS

EFS by pathology subtype



No. at risk						
Classic ependymoma	157	143	124	107	93	33
Anaplastic ependymoma	124	102	78	65	52	16

EFS by 1q gain status



No. at risk					
No	14	10	5	2	2
Yes	5	3	1	1	

Merchant et al. J Clin Oncol 2019; 37:974-983

2021 WHO Classification of Tumors of the Central Nervous System, fifth edition

Germ cell tumors
Mature teratoma
Immature teratoma
Teratoma with somatic-type malignancy
Germinoma
Embryonal carcinoma
Yolk sac tumor
Choriocarcinoma
Mixed germ cell tumor

Louis, et al. Neuro-Oncology, 2021, 23(8), 1231–1251

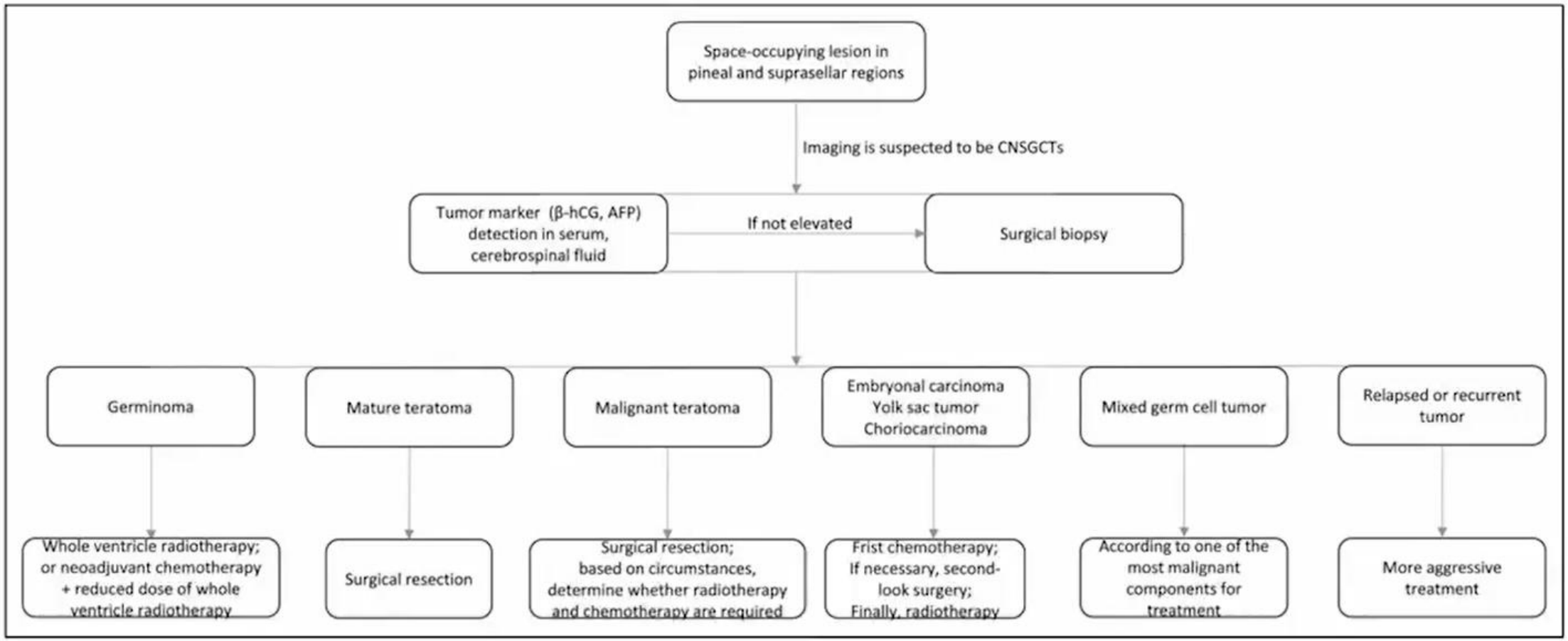
Germ cell tumors

- Relatively rare in US: 2% of pediatric CNS tumors in US but in Japan/Taiwan it is 9% of pediatric brain tumors. (Some controversy over that)

- Germinomas: 60-70%, Germinoma can have mild b-HCG, but positive AFP always indicates NGGCT.

- Usually occurs in either the pineal or suprasellar region (or both) (uncommonly in basal ganglia or thalami)

CNS Germ Cell Tumors

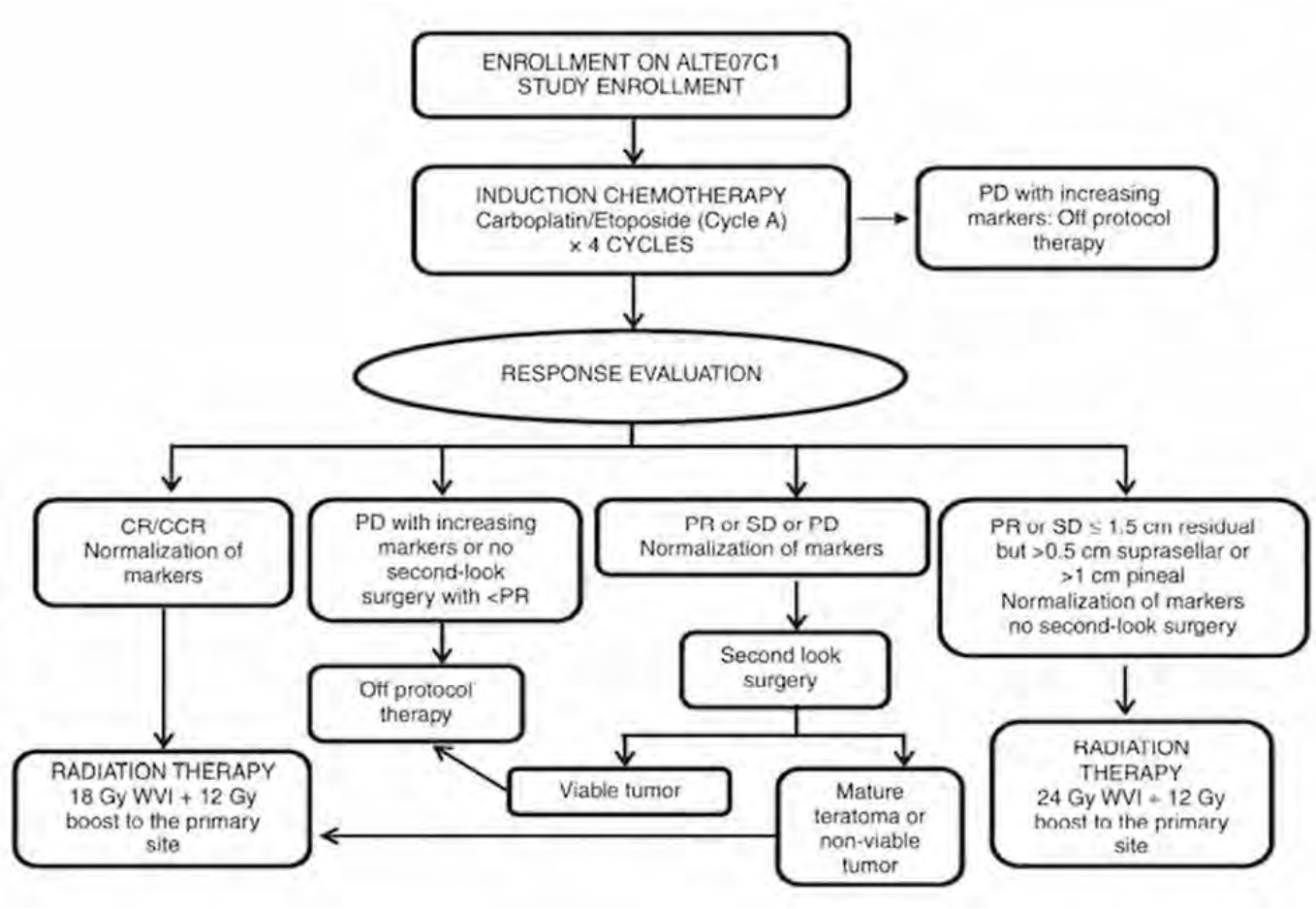


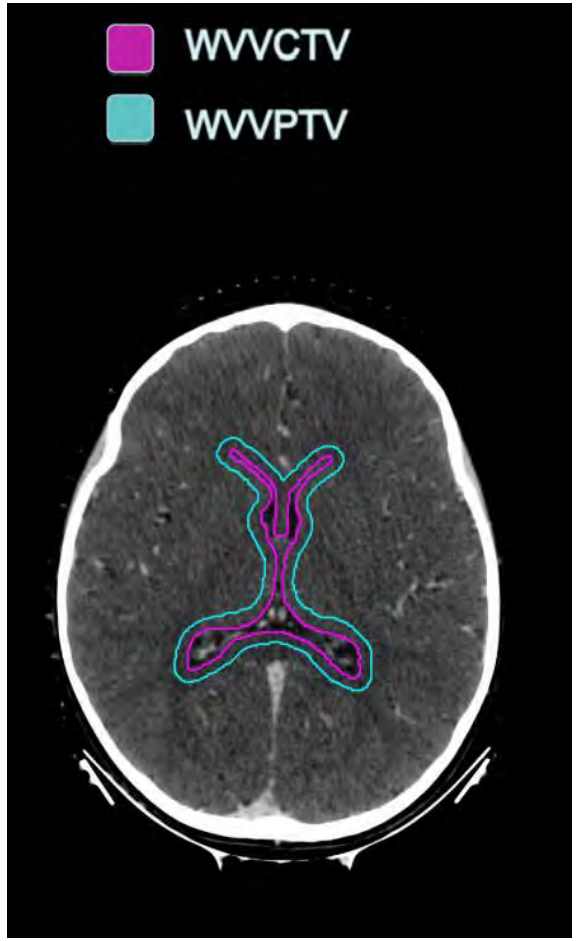
ANCS 1123 NGGCT – Stratum 1

- The NGGCT arm of COG ACNS 1123 CLOSED to due increased failures in the spine. This protocol was evaluating whether we could move from CSI to Whole Ventricle radiation in patients with M0 NGGCT.

- Now both M0 and M+ disease must be treated with CSI (treat per COG closed ANCS 0122); CSI dose is 36 Gy and IF boost to 54 Gy.

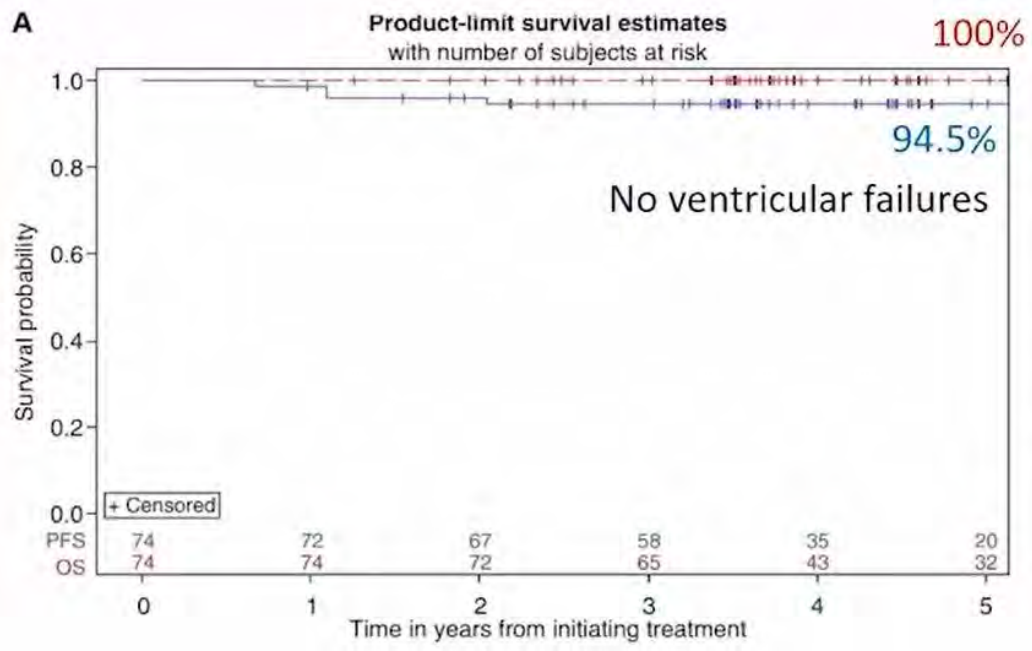
ANCS 1123 – Germinoma (M0) – Stratum 2



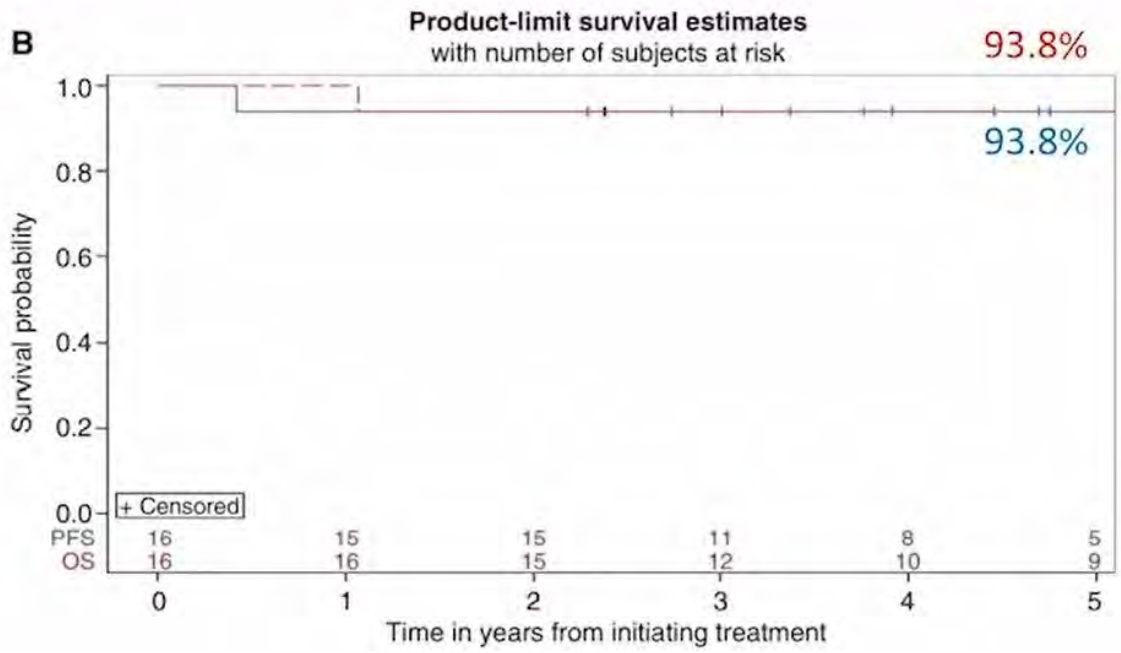


ANCS 1123 Stratum 2 – Outcomes

CR 18 Gy WVI + 12 Gy boost



PR/SD: 24 Gy WVI + 12 Gy boost



Red: OS, Blue: PFS

Bartels et al. Neuro-Oncology 2021; 24 (6): 974

Germ Cell Tumors

	GERMINOMA	NON-GERMINOMA
Tumor markers (serum & CSF)	AFP normal, βHCG normal to mild ↑	↑ AFP or ↑ βHCG possible
Biopsy	Required	Not required if tumor markers elevated but helpful to know histologic subtype
MRI spine and LP	Yes	Yes
Treatment paradigm	Chemo → Sx if incomplete response → RT Alternative: RT alone	Maximal safe resection → chemo → RT
Chemo drugs	Carboplatin & etoposide x 4 cycles Q 3 weeks	Carboplatin, etoposide, ifosfamide x 6 cycles induction, Q 3 weeks
Radiation volume for M0 disease	Whole ventricle + primary site boost	CSI + primary site boost
Radiation dose	PostChemo: 18 or 24 Gy WVV, 12 Gy boost to primary site @ 1.5 Gy/fx RT alone: WVV 25 Gy, 20-25.4 Gy boost	36 Gy CSI, 18 Gy boost to primary site @ 1.8 Gy/fx
Prognosis (5 yr PFS/OS)	88%/93%	60%/68%

What is new in Pediatric CNS tumors?

- 2021 WHO Classification of Tumors of the Central Nervous System, fifth edition

- High grade glioma
  - **ACNS 0423**:
    - Resection → RT + temozolomide + **CCNU**

- Low grade glioma
  - Resection → residual + symptomatic → if not resectable → chemotherapy → RT
  - **ACNS 0221**:
    - conformal RT with CTV 5 mm, 5-year PFS was 71%±6% and OS was 93%±4%
  - Use of molecular markers for prognosis and to direct treatment is increasing

What is new in Pediatric CNS tumors?

- Medulloblastoma
  - Molecular Based Risk Groups
  - **ACNS 0331**:
    - Reducing the radiation boost volume in average-risk MB is safe and does not compromise survival.
    - Reducing CSI dose in young children with average-risk MB results in inferior outcomes, possibly in a subgroup-dependent manner, but is associated with better neurocognitive outcome.

- Ependymoma
  - **ACNS 0121**:
    - The EFS for patients with ependymoma younger than 3 years of age who received immediate postoperative CRT and for older patients is similar.
    - Irradiation should remain the mainstay of care for most subtypes.

What is new in Pediatric CNS tumors?

- Germ cell tumor
  - ACNS 1123:
    - For M0 NGGCT, still need CSI 36 Gy with boost to primary to 54 Gy after chemotherapy due to high spinal recurrence.
    - For M0 germinoma, The Kaplan-Meier based 3-years PFS and OS of 94.5% and 100% for post chemo CR with 18 Gy WVI + 12 Gy boost and 3-years PFS and OS of 94%and 94% for PR/SD with 24 Gy WVI + 12 Gy boost.