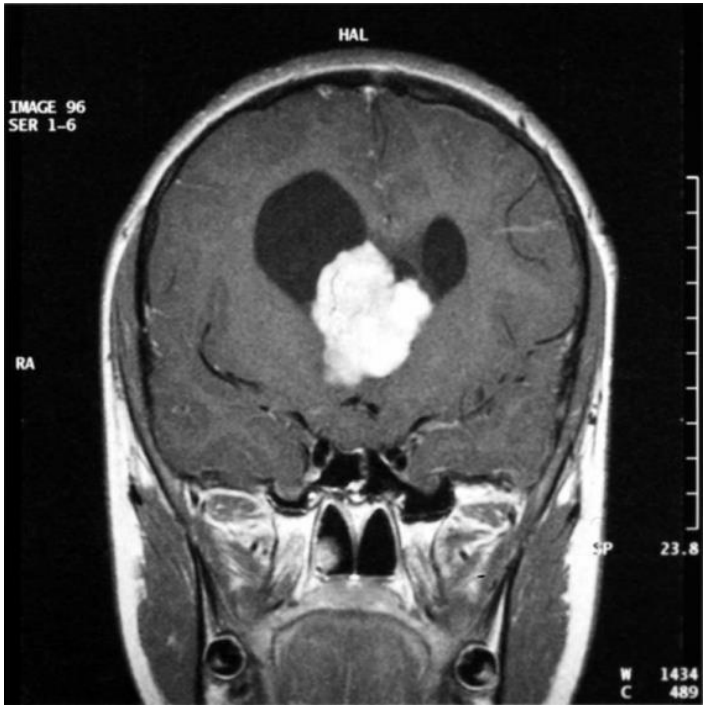
Grupo de trabajo de tumores del SNC

Ana Fernández-Teijeiro Álvarez

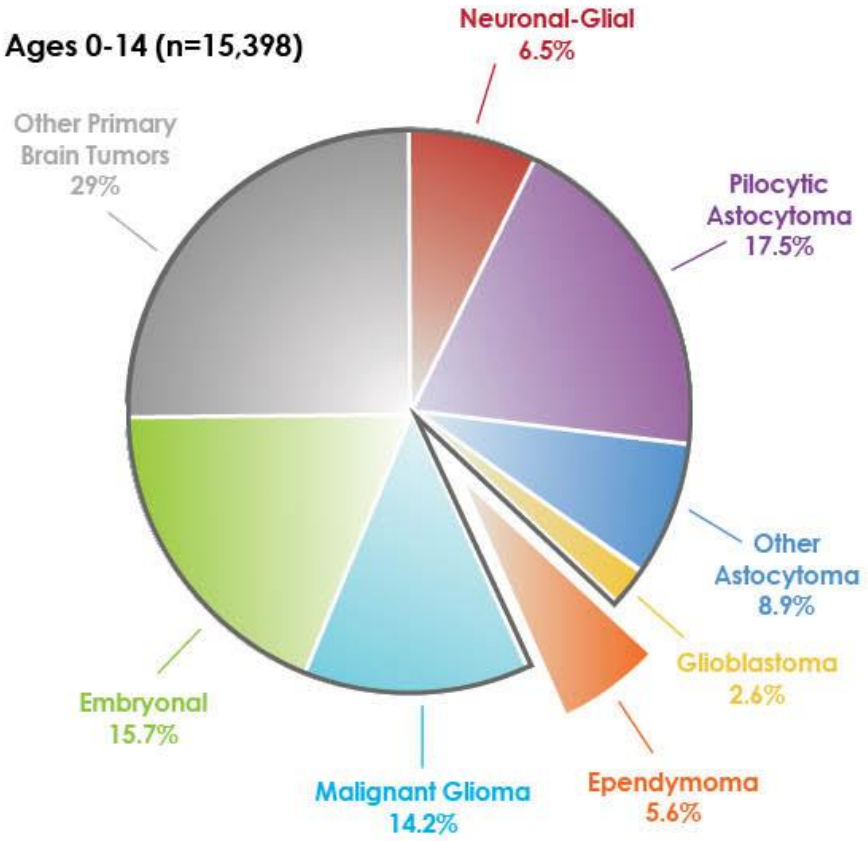
EPENDIMOMA

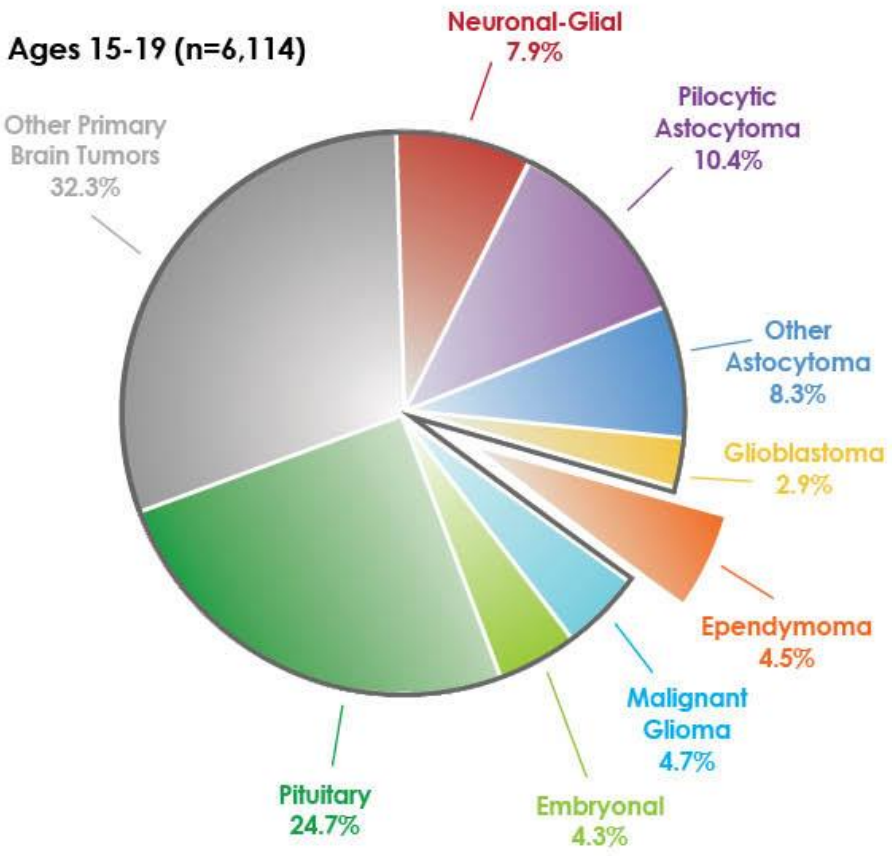
SEHOP
SOCIEDAD ESPAÑOLA
DE HEMATOLOGÍA Y ONCOLOGÍA
PEDIÁTRICAS



Ependimoma

Distribution of Childhood Primary Brain / CNS Tumors



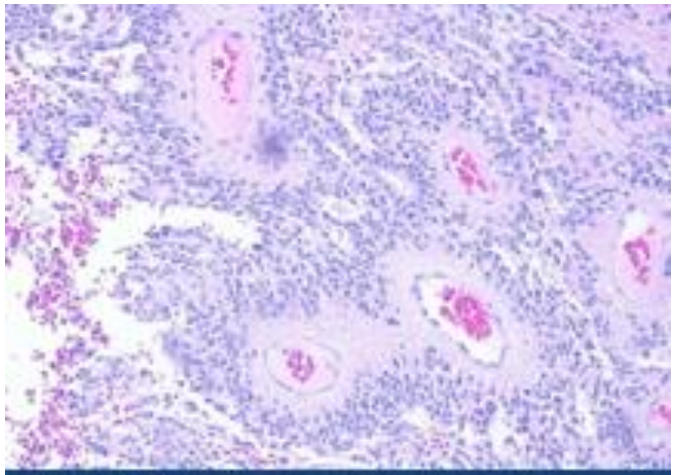


CBTRUS Statistical Report: NPCR and SEER Data from 2006-2010

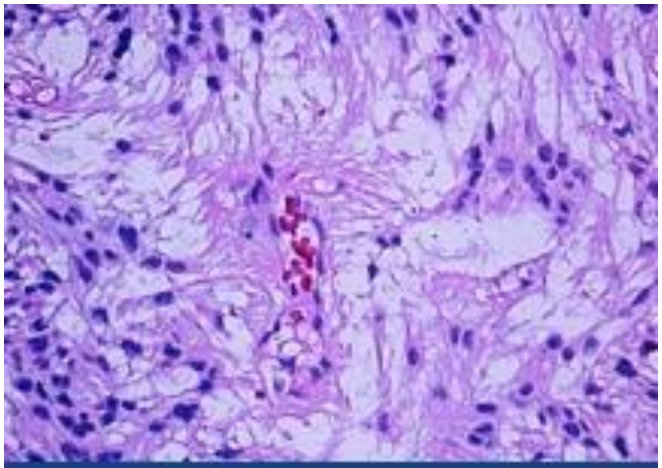
Ependimoma

Edad	• <7 años (25-51% en < 3 años) • Segundo pico: 30-50 años
Localización	• **90% intracraneal** • **2/3 en fosa posterior** • **espinal**
Edad/localización	• **<3 años: fosa posterior** • **Adolesccentes y adultos: médula (WHO I subependimoma y mixopapilar)**

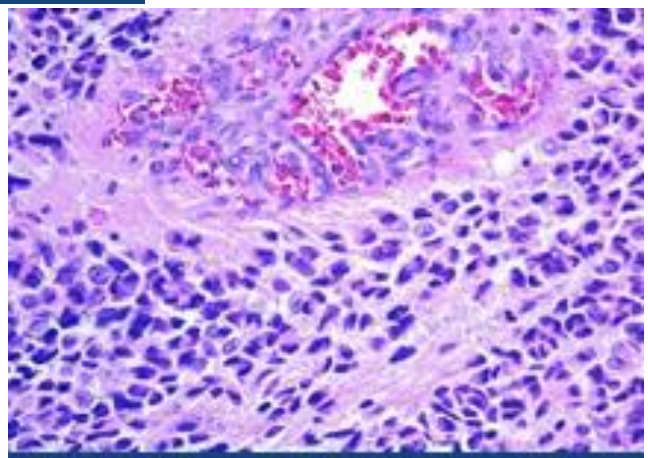
Clasificación WHO 2016



WHO Grade I Ependymoma (Myxopapillary)

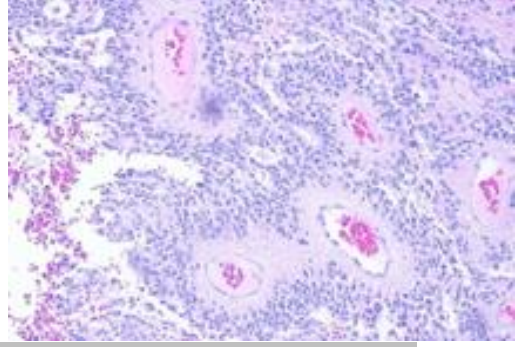


WHO Grade II Ependymoma



WHO Grade III Ependymoma (Anaplastic)

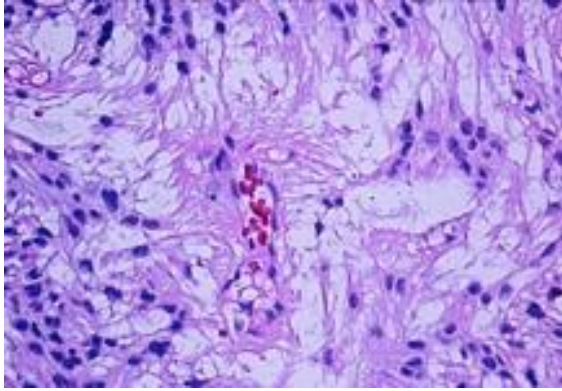
Grade I Ependymoma



- **WHO Grade I – Myxopapillary Ependymoma**
  - Slow growing
  - Commonly occurs in young adults in the spinal cord, sometimes in the bottom of the spinal cord, an area referred to as "cauda equina".
  - Tend to have good long-term survival after surgical resection

- **WHO Grade I – Subependymoma**
  - Slow growing noninvasive tumor
  - Are less cellular masses usually attached to the ventricle wall (cerebrospinal fluid filled cavity in the brain).
  - More common in adults and older men
  - Associated with long-term survival
  - Surgery can be potentially curative

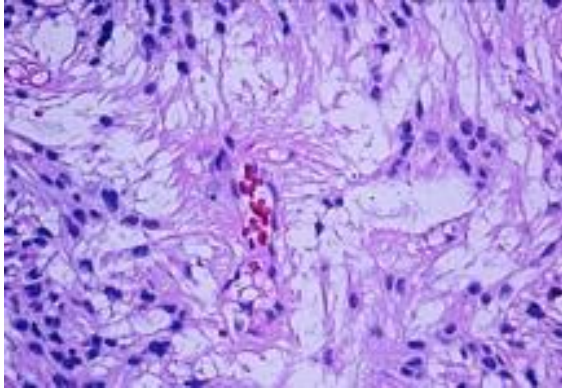
Grade II Ependymoma



- Most common brain tumor in young children
- Most common type of spinal glioma in adults
- Often develop in the ventricles when intracranial
- Several variants exist making diagnosis challenging:
  - Cellular ependymoma
  - Papillary ependymoma
  - Tanycytic ependymoma

Supratentorial ependymomas can be further subclassified as RELA-positive or RELA-negative
Can potentially recur as a higher grade tumor even after treatment

Grade III Ependymoma



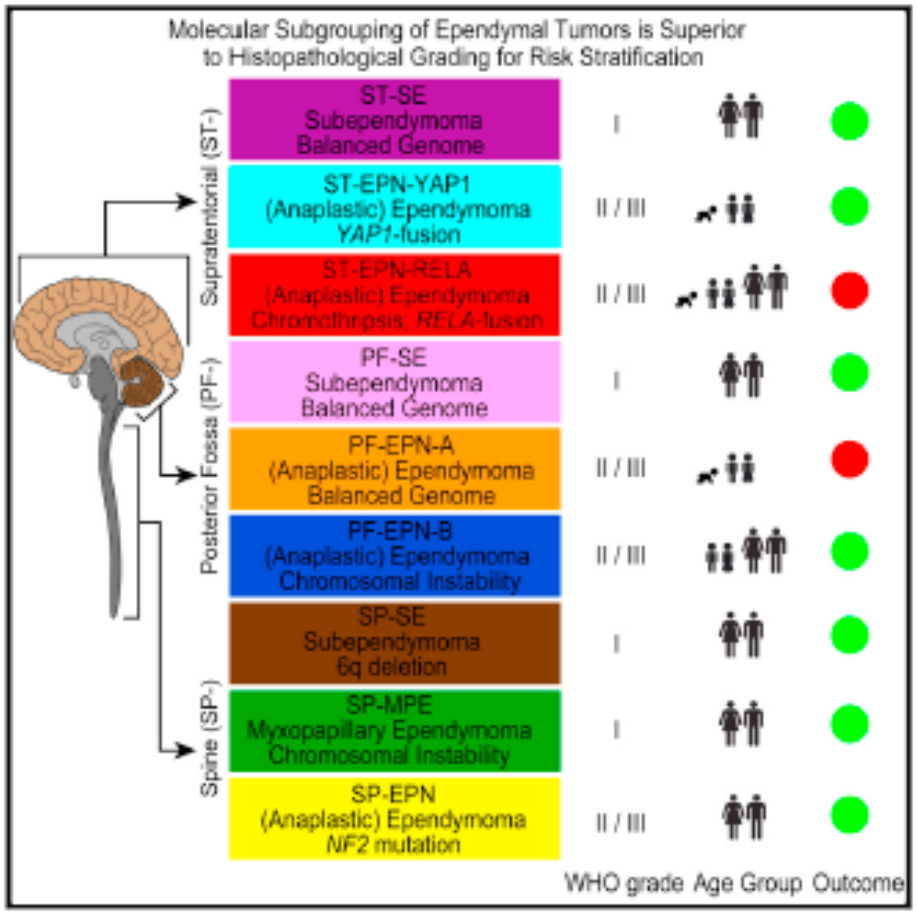
- **Show evidence of increased tumor cell growth compared to conventional ependymoma**
- **Show evidence of new blood vessel formation to support active growth**
- **Exhibit more aggressive behavior than low grade ependymomas**
- **Often require additional treatment after surgery and can recur**

Article

Cancer Cell

Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups

Graphical Abstract



Authors

Kristian W. Pajtler, Hendrik Witt, ..., Marcel Kool, Stefan M. Pfister

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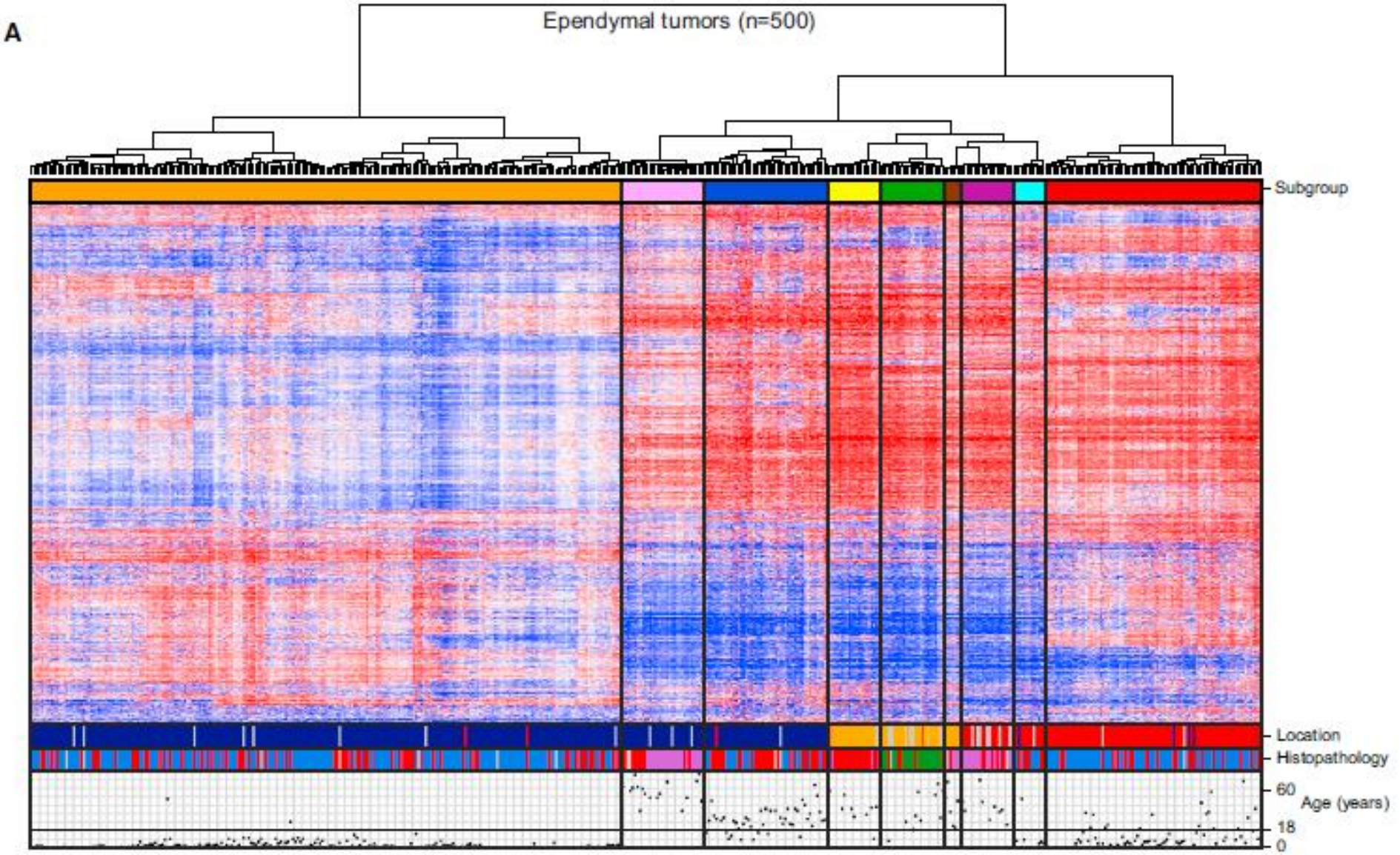
s.pfister@dkfz.de (S.M.P.)

In Brief

Pajtler et al. classify 500 ependymal tumors using DNA methylation profiling into nine molecular subgroups. This molecular classification outperforms the current histopathological grading in the risk stratification of patients.


A
Ependymal tumors (n=500)
Subgroup
Location
Histopathology
60
Age (years)
18
0

Molecular and clinical characteristics of ependymal tumor subgroups

Anatomic compartment	SPINE (SP-)			Posterior fossa (PF-)			Supratentorial (ST-)		
Molecular subgroup	SE	MPE	EPN	SE	EPN-A	EPN-B	SE	EPN-YAP1	EPN-RELA
Histopathology	Subependymoma (WHO I)	Myxopapillary ependymoma (WHO I)	(Anaplastic) ependymoma (WHO II/III)	Subependymoma (WHO I)	(Anaplastic) ependymoma (WHO II/III)	(Anaplastic) ependymoma (WHO II/III)	Subependymoma (WHO I)	(Anaplastic) ependymoma (WHO II/III)	(Anaplastic) ependymoma (WHO II/III)
Genetics	6q deletion	CIN	CIN; *NF2* mutation	Balanced	Balanced	CIN	Balanced	Focal aberrations Chr. 11q; YAP1-fusion	Aberrations Chr. 11; chromothripsis; *RELA*-fusion
Age distribution	A	C A	C A	A	I C A	C A	A	I C A	I C A
Gender ratio	M F	M F	M F	M F	M F	M F	M F	M F	M F
Prognosis	Good	Good	Good	Good	Poor	Intermediate	Good	Good	Poor

Kun-Wei Liu et al., Sci. Signal. 2017;10:eaaf7593

Current therapy and the evolving molecular landscape of paediatric ependymoma

Soumen Khatua [a,*], Vijay Ramaswamy [b], Eric Bouffet [b]

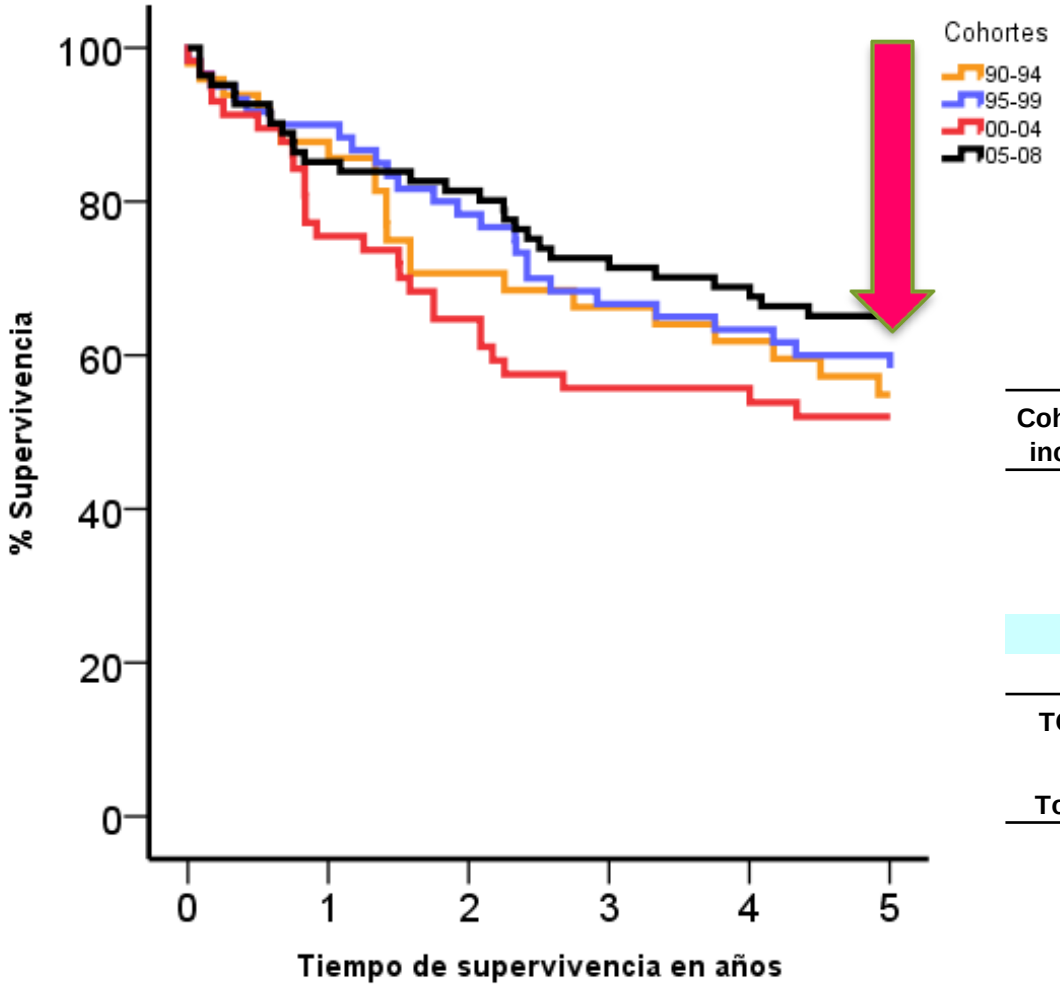
European Journal of Cancer 70 (2017) 34–41

Table 2
Molecular classification of ependymal tumours across CNS compartments based on genome-wide DNA methylation patterns.

Anatomical compartment	Supratentorial (ST)			Posterior Fossa (PF)			Spinal (SE)		
Molecular subtypes	RELA	YAP1	SE	Group A	Group B	SE	MPE	EPN	SE
Pathology WHO grade	II/III	II/III	I	II/III	II/III	I	I	II/III	I
Genetics	NFkB Signalling	Notch signalling	Balanced genome	Silent genome CIMP + ve	6q, 22q loss; 9q, 15q, 18q gain; CIMP−ve	Balanced genome	HIF-1α, HK2, PDK1 over-expressed	NF2 mutations	6q deletion
Age	Preschool children	Younger children	Adult	Younger children	Older children/adults	Older children/ adults	Mainly adults	Mainly adults	Older children/adults
Survival outcome	Inferior	Superior	Superior	Inferior	Superior	Superior	Superior	Superior	Good outcome with surgery

RELA, fusion of *C11orf95-RELA*; YAP1, fusion of *MAMLD1-YAP1 or FAM118B-YAP1*; SE, subependymoma; MPE, Myxopapillary ependymoma; CIMP, CpG island methylator phenotype; NF2, Neurofibromatosis type 2.

Supervivencia ependimoma RETI



Mortalidad 35-45%

Cohortes de incidencia	n	% supervivencia 3 años	% supervivencia 5 años
90-94	49	66(53-80)	55(40-69)
95-99	60	67(55-79)	58(46-71)
00-04	59	56(43-69)	52(39-65)
05-08	83	71(62-81)	64(53-74)
05-09	106	72(63-80)	
TOTAL 90-08	**251**		
Total 90-09	**274**		

EFS 23-57%
OS 50-71%

Tratamiento actual ependimoma

VOLUME 22 · NUMBER 15 · AUGUST 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Preliminary Results From a Phase II Trial of Conformal Radiation Therapy and Evaluation of Radiation-Related CNS Effects for Pediatric Patients With Localized Ependymoma

Thomas E. Merchant, Raymond K. Mulhern, Matthew J. Krasin, Larry E. Kun, Tani Williams, Chenghong Li, Xiaoping Xiong, Raja B. Khan, Robert H. Lustig, Frederick A. Boop, and Robert A. Sanford

International Journal of Radiation Oncology * Biology * Physics

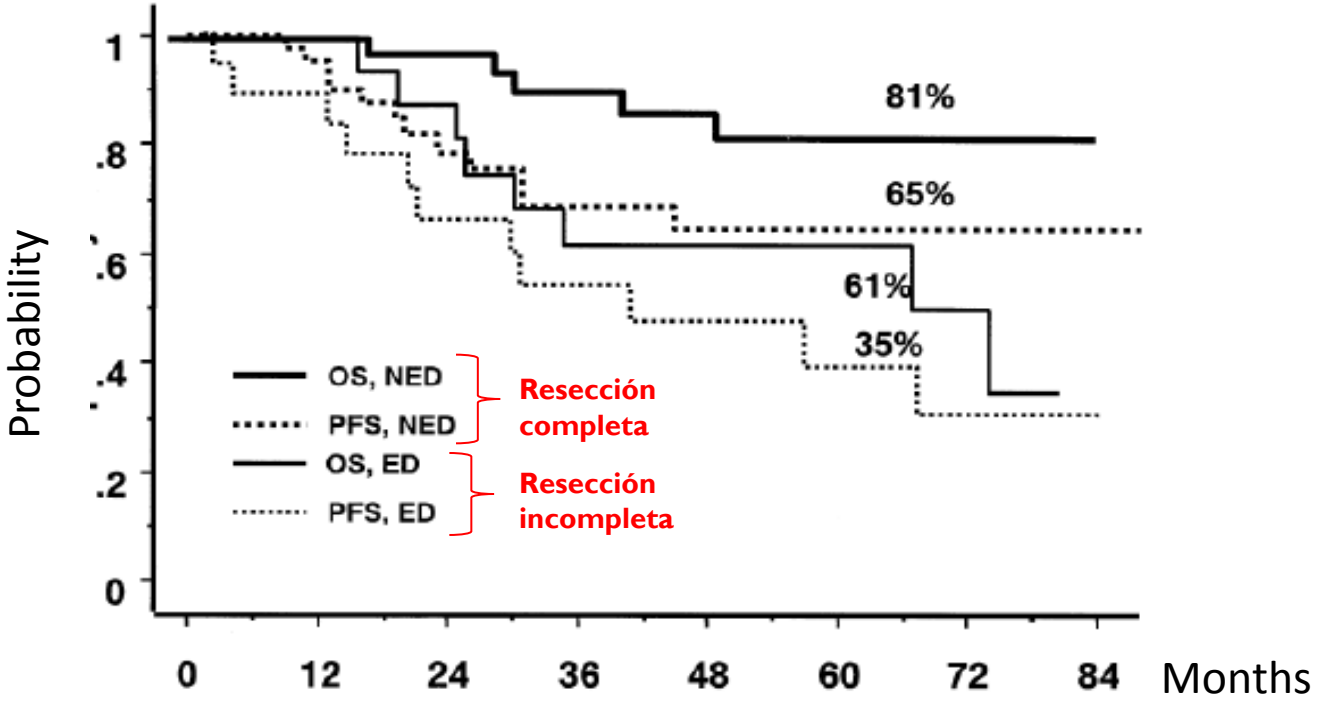
Volume 85, Issue 4 , Pages e193-e199, 15 March 2013

Supratentorial Ependymoma: Disease Control, Complications, and Functional Outcomes After Irradiation

•Efrat Landau, MD,
•Frederick A. Boop, MD,
•Heather M. Conklin, PhD,
•Shengjie Wu, MS,
•Xiaoping Xiong, PhD,
•Thomas E. Merchant, DO, PhD

Received 25 September 2012; received in revised form 18 October 2012; accepted 19 October 2012. published online 12 December 2012.

Justificación de la cirugía



OS and PFS improvement
when resection is complete in children > 3 years old

Massimino et al. IJROBP 2004

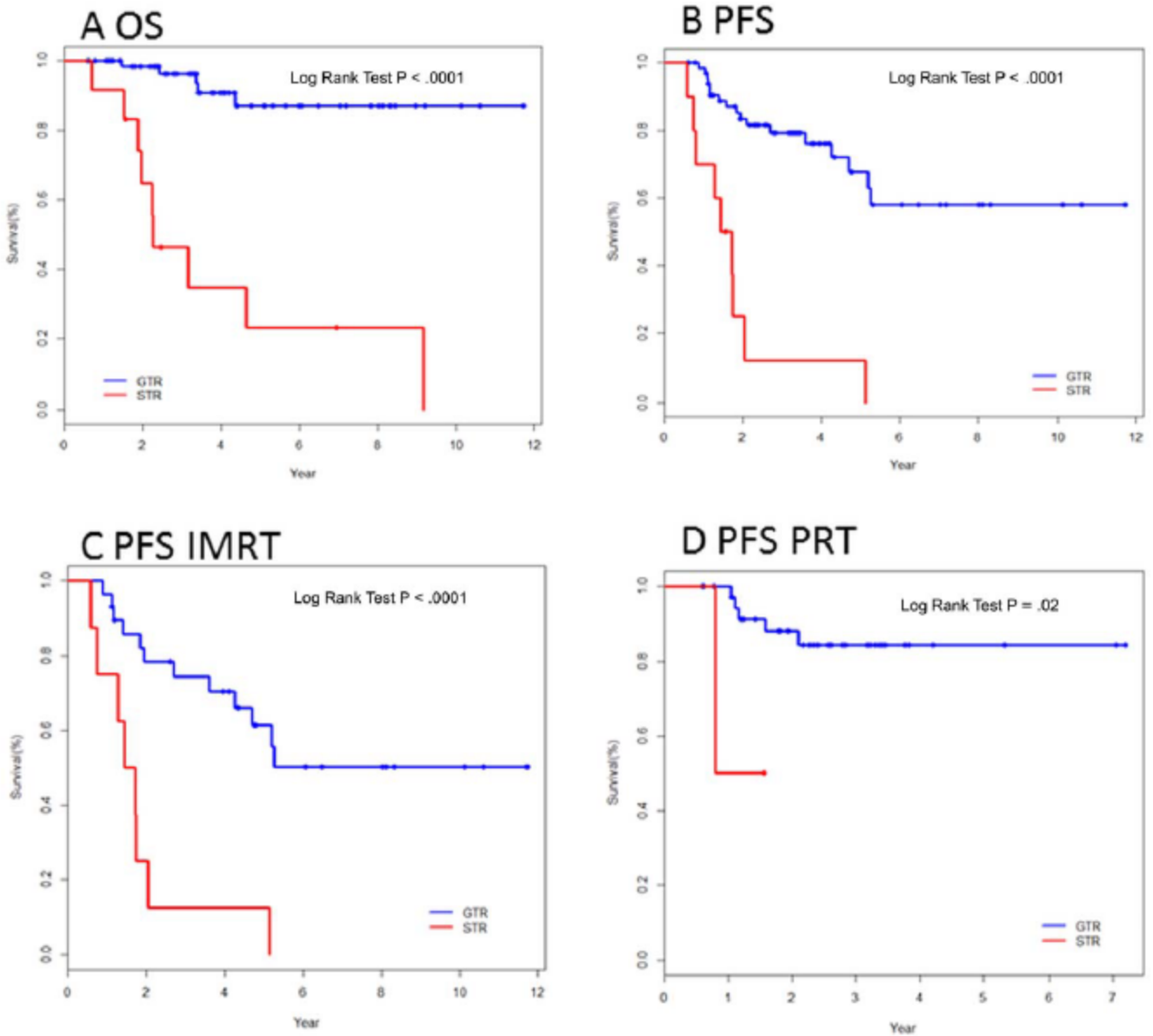


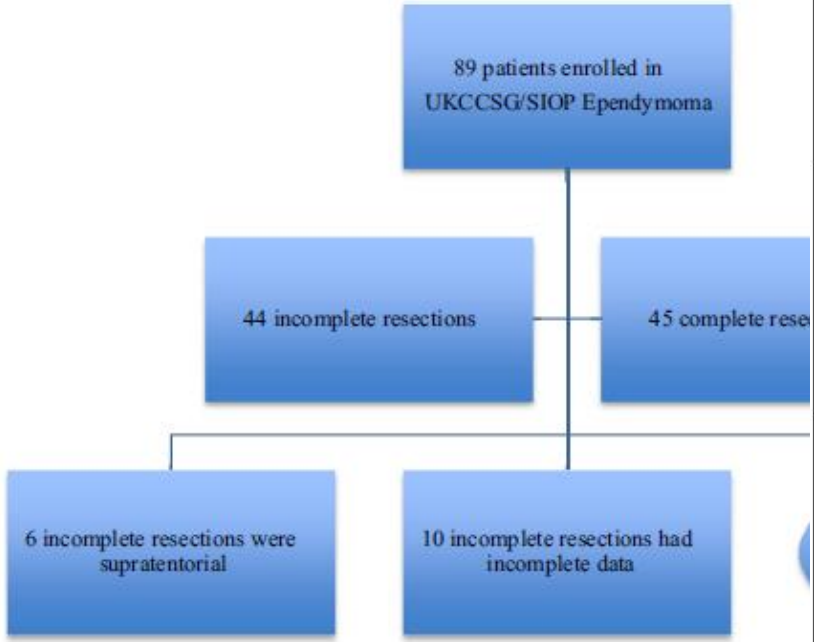
Figure 3. Survival curves showing that GTR is associated with better PFS and OS, regardless of the radiation therapy modality. GTR indicates gross total resection; IMRT, intensity-modulated radiation therapy; OS, overall survival; PFS, progression-free survival; PRT, proton-beam radiation therapy; STR, subtotal resection.

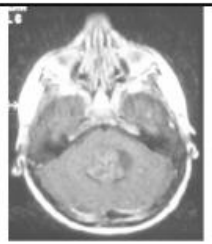
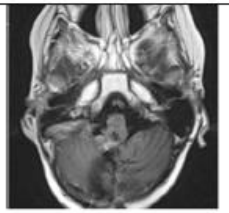
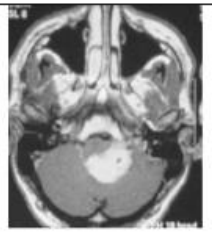
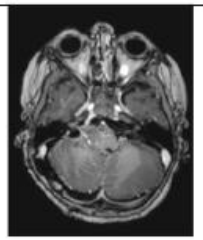
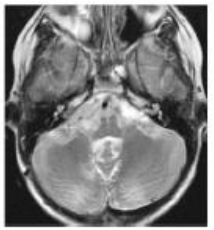
Childs Nerv Syst (2016) 32:2189–2196
DOI 10.1007/s00381-016-3225-9

ORIGINAL PAPER

Assessing 'second-look' tumou
posterior fossa ependymoma—
panel and staging tool for futu

Christopher P. Millward[1] · Conor Mallucci[1] · Tim Jas
Richard Heyward[3] · Tim Cox[3] · Kung Chong[3] · Richa



Classification Stage	Classification Description	Illustrative example
I	Tumour is confined to the midline, within the fourth ventricle only with no progression beyond this boundary.	
II	Tumour has progressed laterally through the foramina of Luschka and/or Magendie either unilaterally or bilaterally.	
III	Tumour has progressed beyond the foramina of Luschka and/or Magendie to enter the cerebellopontine angle either unilaterally or bilaterally.	
IV	Tumour has progressed through the cerebellopontine angle anterior to the brainstem either unilaterally or bilaterally.	
V	Tumour has progressed to encase the basilar artery and/or is multifocal in nature.	

Childs Nerv Syst (2016) 32:2189–2196
DOI 10.1007/s00381-016-3225-9

ORIGINAL PAPER

Assessing 'second-look' tumour resectability in childhood posterior fossa ependymoma—a centralised review panel and staging tool for future studies

Christopher P. Millward[1] · Conor Mallucci[1] · Tim Jaspan[2] · Donald Macarthur[2] · Richard Heyward[3] · Tim Cox[3] · Kung Chong[3] · Richard G. Grundy[2]

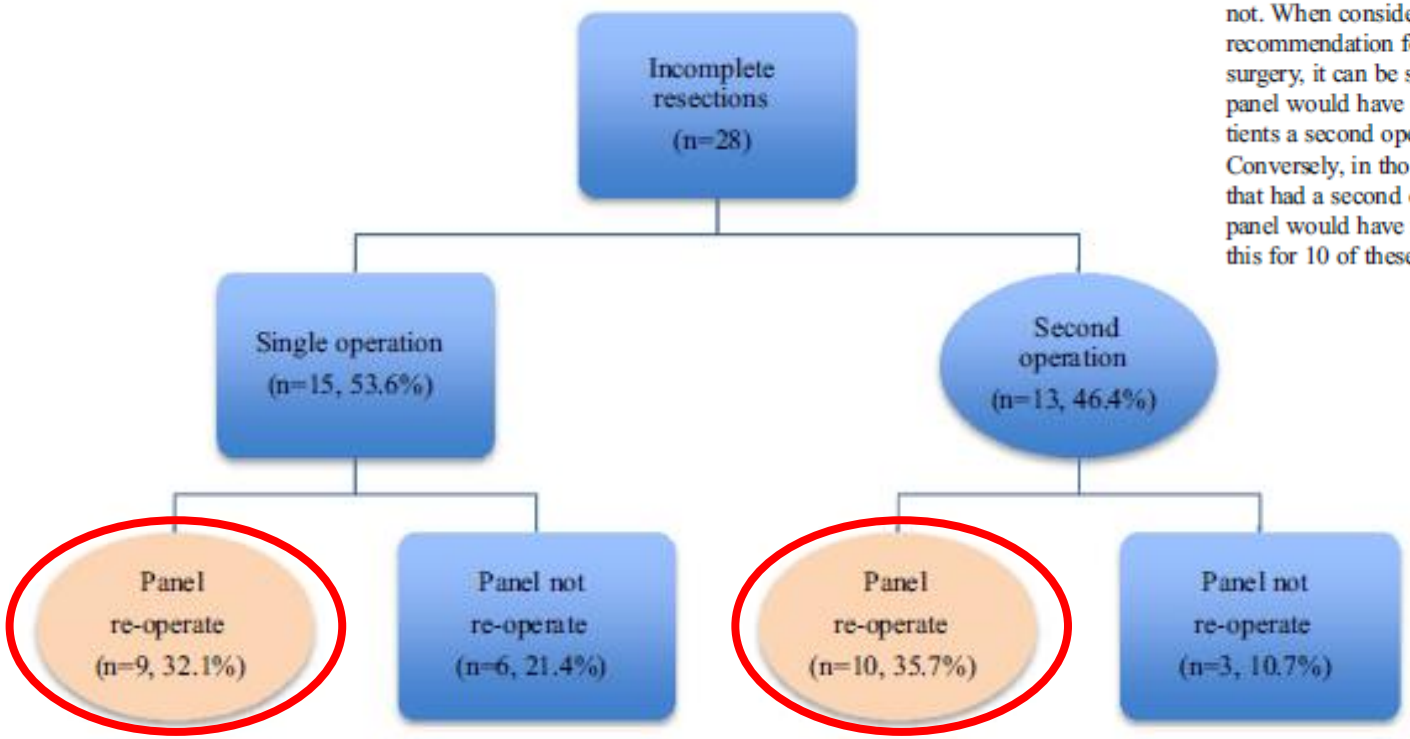
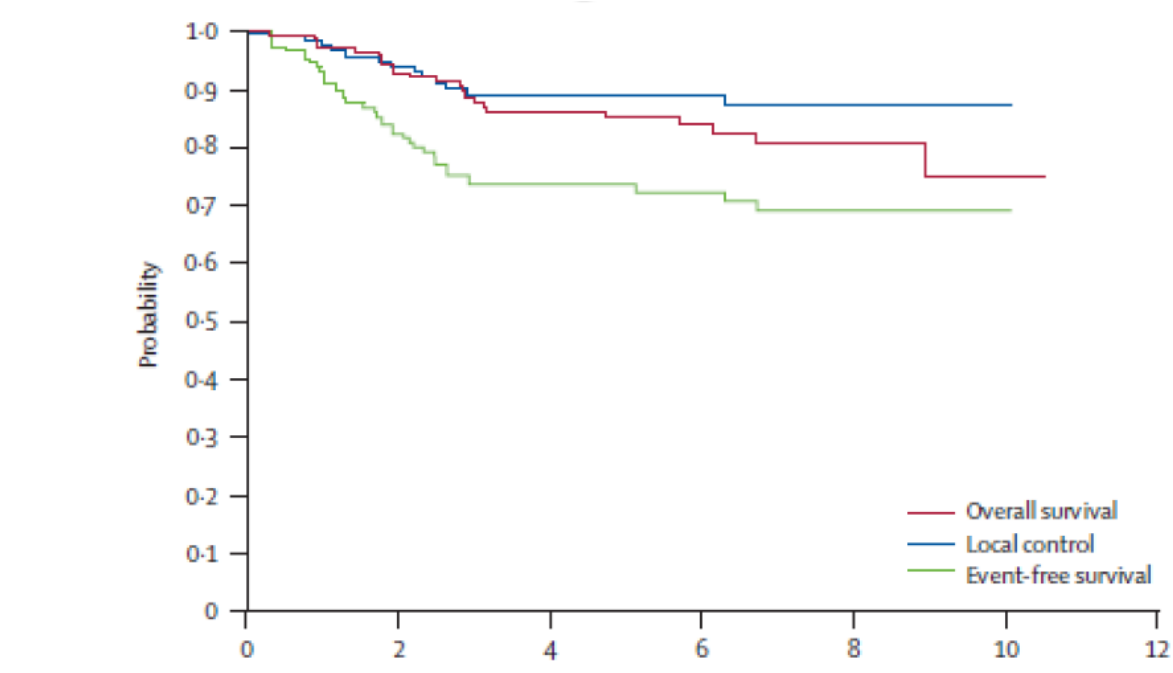


Fig. 3 Schematic summary of panel recommendation for second-look surgery when compared to actual outcome in the original study. Thirteen patients had further surgery, whilst 15 did not. When considering the panel recommendation for second-look surgery, it can be seen that the panel would have offered 9 patients a second operation. Conversely, in those 13 patients that had a second operation, the panel would have recommended this for 10 of these

Justificación de la radioterapia

Background: St Jude's Children Research Hospital

- Control local con mejoría de EFS y SG con **59.4 Gy en 33 fracciones**
- Ausencia de incremento aparente de efectos neurocoginitivos tardíos tras 5 años de seguimiento.



Number at risk						
Overall survival	153	141	101	79	47	13
Local control	153	134	85	66	38	7
Event-free survival	153	134	85	66	38	7

Merchant Childs Nerv Syst 2009

VOLUME 22 · NUMBER 15 · AUGUST 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prelir
Radia
CNS I
Locali

Thomas E.
Chenghsu
and Rober

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 5, pp. 1336–1345, 2004

0360-3016/04/$–see front matter

doi:10.1016/j.ijrobp.2003.08.030

CLINICAL INVESTIGATION Brain

HYPERFRACTIONATED RADIOTHERAPY AND CHEMOTHERAPY FOR CHILDHOOD EPENDYMOMA: FINAL RESULTS OF THE FIRST PROSPECTIVE AIEOP (ASSOCIAZIONE ITALIANA DI EMATOLOGIA-ONCOLOGIA PEDIATRICA) STUDY

MAURA MASSIMINO, M.D.,* LORENZA GANDOLA, M.D.,† FELICE GIANGASPERO, M.D.,‡ ALESSANDRO SANDRI, M.D.,§ PINUCCIA VALAGUSSA, B.S.,‖ GIORGIO PERILONGO, M.D.,** MARIA LUISA GARRÈ, M.D.,# UMBERTO RICARDI, M.D.,¶ MARCO FORNI, M.D.,†† LORENZO GENITORI, M.D.,‡‡ GIOVANNI SCARZELLO, M.D.,§§ FILIPPO SPREAFICO, M.D.,* SALVINA BARRA, M.D.,¶¶ MAURIZIO MASCARIN, M.D.,*** BIANCA POLLO, M.D.,††† MARTINA GARDIMAN, M.D.,‡‡‡ ARMANDO CAMA, M.D.,# PIERINA NAVARRIA, M.D.,†

International Journal of Radiation Oncology * Biology * Physics
Volume 85, Issue 4 , Pages e193-e199, 15 March 2013

Supratentorial Ependymoma: Disease Control, Complications, and Functional Outcomes After Irradiation

•Efrat Landau, MD,
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•Shengjie Wu, MS,
•Xiaoping Xiong, PhD,
•Thomas E. Merchant, DO, PhD

Received 25 September 2012; received in revised form 18 October 2012; accepted 19 October 2012. published online 12 December 2012.

Effect of Cerebellum Radiation Dosimetry on Cognitive Outcomes in Children With Infratentorial Ependymoma

Thomas E. Merchant, DO, PhD _ Shelly Sharma, MD, Xiaoping Xiong, PhD

Shengjie Wu, MS, Heather Conklin, PhD

,

Received: December 21, 2013; Received in revised form: March 28, 2014; Accepted: June 18, 2014;
Published Online:August 20, 2014,

Int J Radiat Oncol Biol Phys. 2014 Mar 15;88(4):814-21. doi: 10.1016/j.ijrobp.2013.12.006. Epub 2014 Jan 22.

Emotional and behavioral functioning after conformal radiation therapy for pediatricependymoma.

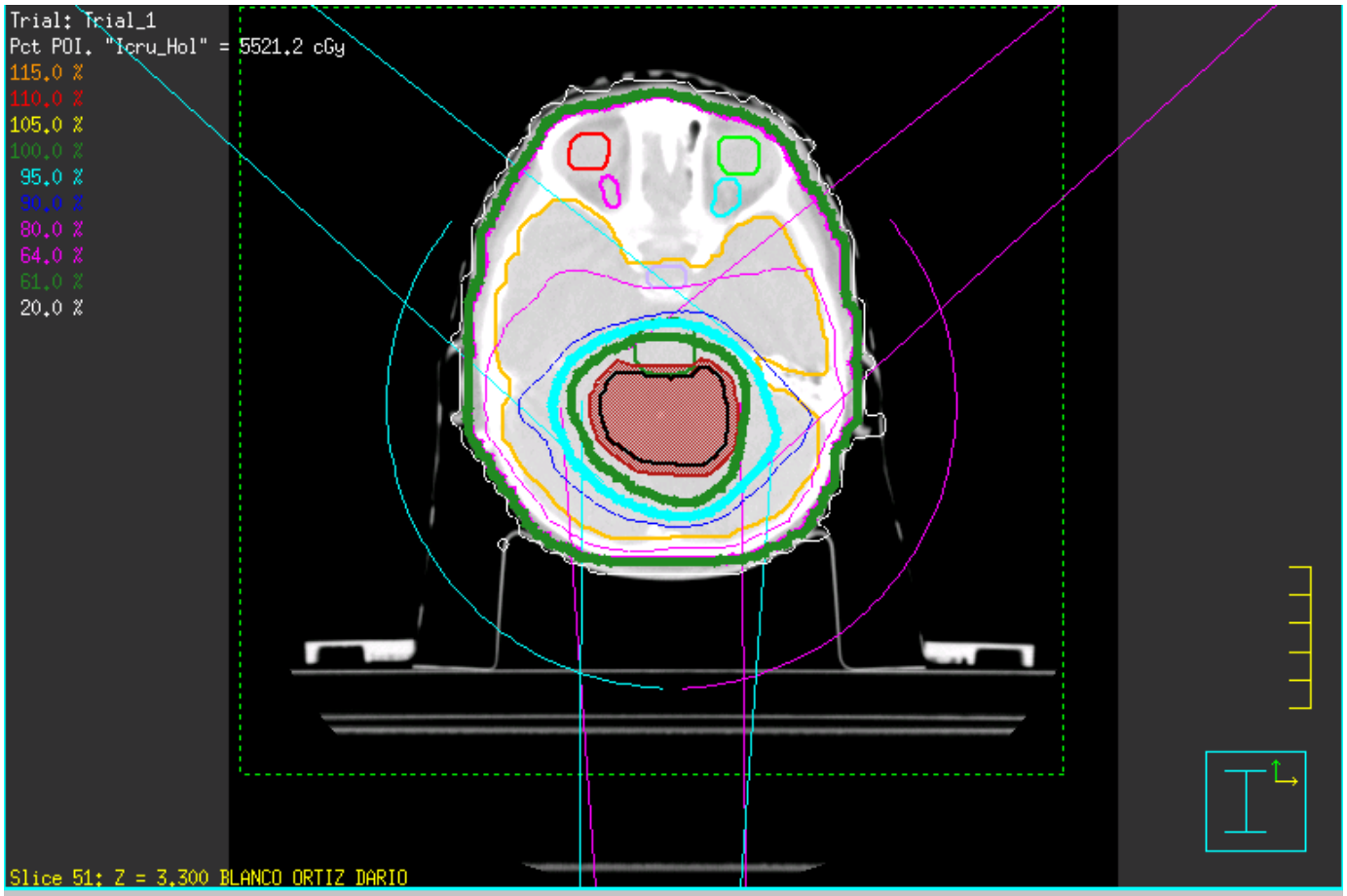
Willard VW[1], Conklin HM[1], Boop FA[2], Wu S[3], Merchant TE[4].

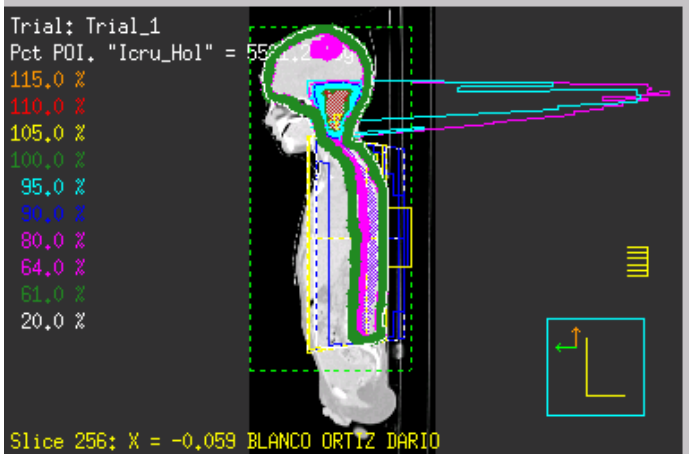
Int J Radiat Oncol Biol Phys. 2012 Sep 1;84(1):217-223.e1. doi: 10.1016/j.ijrobp.2011.10.043. Epub 2012 Apr 27.

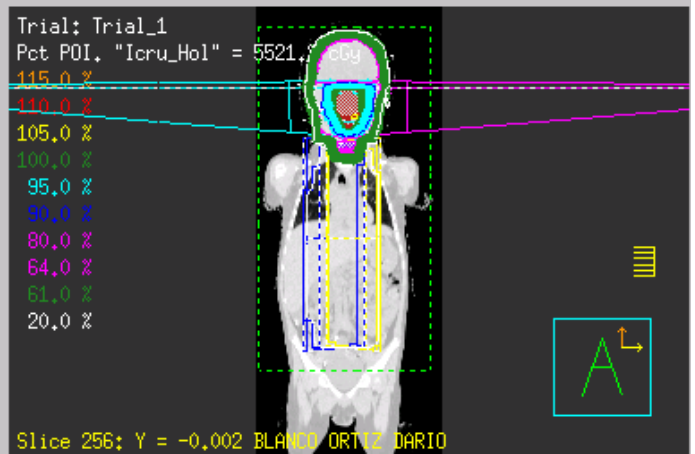
A 5-year investigation of children's adaptive functioning following conformal radiation therapy for localized ependymoma.

Netson KL[1], Conklin HM, Wu S, Xiong X, Merchant TE.

Journal of Neuro-Oncology
December 2011, Volume 105, Issue 3, pp 583-590
Date: 03 Jun 2011
Post-operative radiation improves survival in children younger than 3 years with intracranial ependymoma
Matthew Koshy, Shayna Rich, Thomas E. Merchant, Usama Mahmood, William F. Regine, Young Kwok

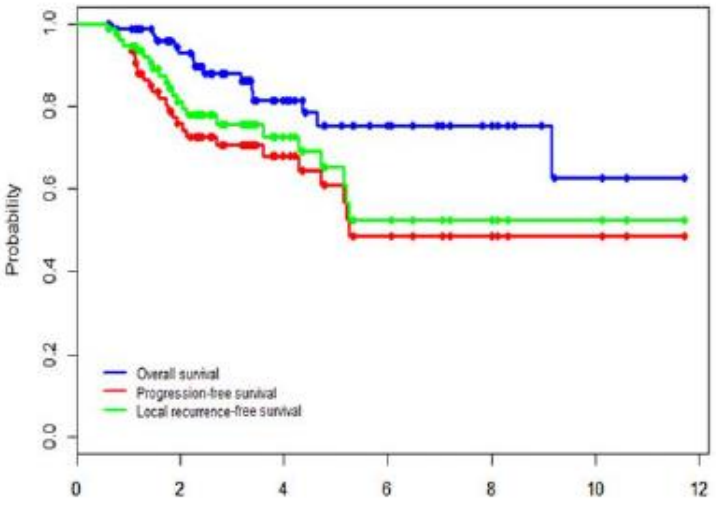

Trial: Trial_1
Pct POI. "Icru_Hol" = 5521.2 cGy
115.0 %
110.0 %
105.0 %
100.0 %
95.0 %
90.0 %
80.0 %
64.0 %
61.0 %
20.0 %
Slice 51: Z = 3.300 BLANCO ORTIZ DARIO


Trial: Trial_1
Pct POI. "Icru_Hol" =
115.0 %
110.0 %
105.0 %
100.0 %
95.0 %
90.0 %
80.0 %
64.0 %
61.0 %
20.0 %
Slice 256: X = -0.059 BLANCO ORTIZ DARIO


Trial: Trial_1
Pct POI. "Icru_Hol" = 5521.2 cGy
115.0 %
110.0 %
105.0 %
100.0 %
95.0 %
90.0 %
80.0 %
64.0 %
61.0 %
20.0 %
Slice 256: Y = -0.002 BLANCO ORTIZ DARIO

Progression-Free Survival of Children With Localized Ependymoma Treated With Intensity-Modulated Radiation Therapy or Proton-Beam Radiation Therapy

Mariko Sato, MD, PhD[1]; Jillian R. Gunther, MD, PhD[2]; Anita Mahajan, MD[2]; Eunji Jo, MS[3]; Arnold C. Paulino, MD[2]; Adekunle M. Adesina, MD[4]; Jeremy Y. Jones, MD[4]; Leena M. Ketonen, MD, PhD[2]; Jack M. Su, MD[4]; M. Fatih Okcu, MD, MPH[4]; Soumen Khatua, MD[2]; Robert C. Dauser, MD[4]; William E. Whitehead, MD, MPH[4]; Jeffrey Weinberg, MD[2]; and Murali M. Chintagumpala, MD[4]



Number at risk							
Overal survival	79	61	37	25	25	6	6
Progression-free survival	77	49	26	13	13	13	13
Local recurrence-free survival	77	51	26	13	13	13	13

Figure 1. Kaplan-Meier estimates of overall survival, progression-free survival, and local recurrence-free survival for 79 children with localized ependymomas.

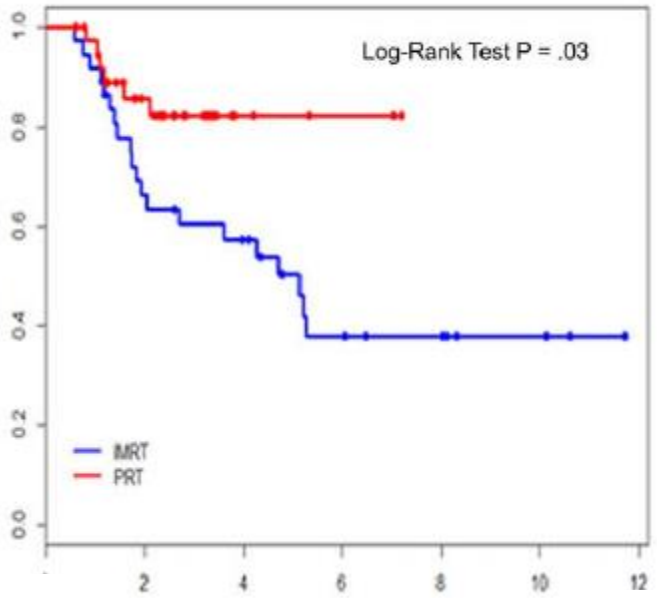
Progression-F Ependymoma T Therapy

h Localized ated Radiation herapy

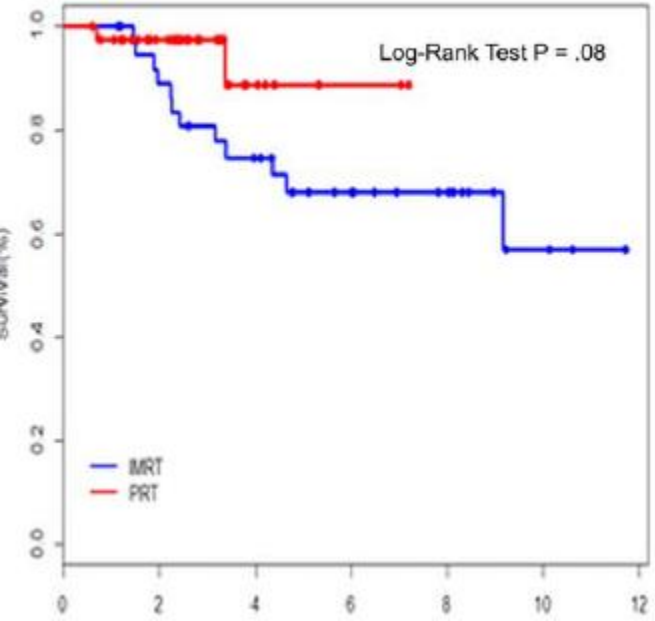
Mariko Sato, MD, PhD[1]; Jillian
Adekunle M. Adesina, M
M. Fatih Okcu, MD, MPH[4]; S
Jef

[3]; Arnold C. Paulino, MD[2];
[2]; Jack M. Su, MD[4];
. Whitehead, MD, MPH[4];

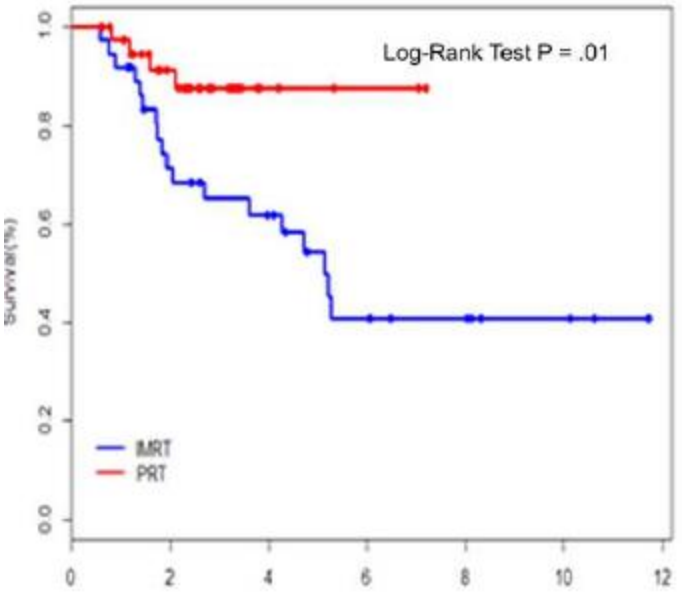
A: Progression-free survival



B: Overall survival



C: Local recurrence-free survival



Current therapy and the evolving molecular landscape of paediatric ependymoma

European Journal of Cancer 70 (2017) 34–41

Soumen Khatua [a,*], Vijay Ramaswamy [b], Eric Bouffet [c]

Table 1
Clinical trials in paediatrics.

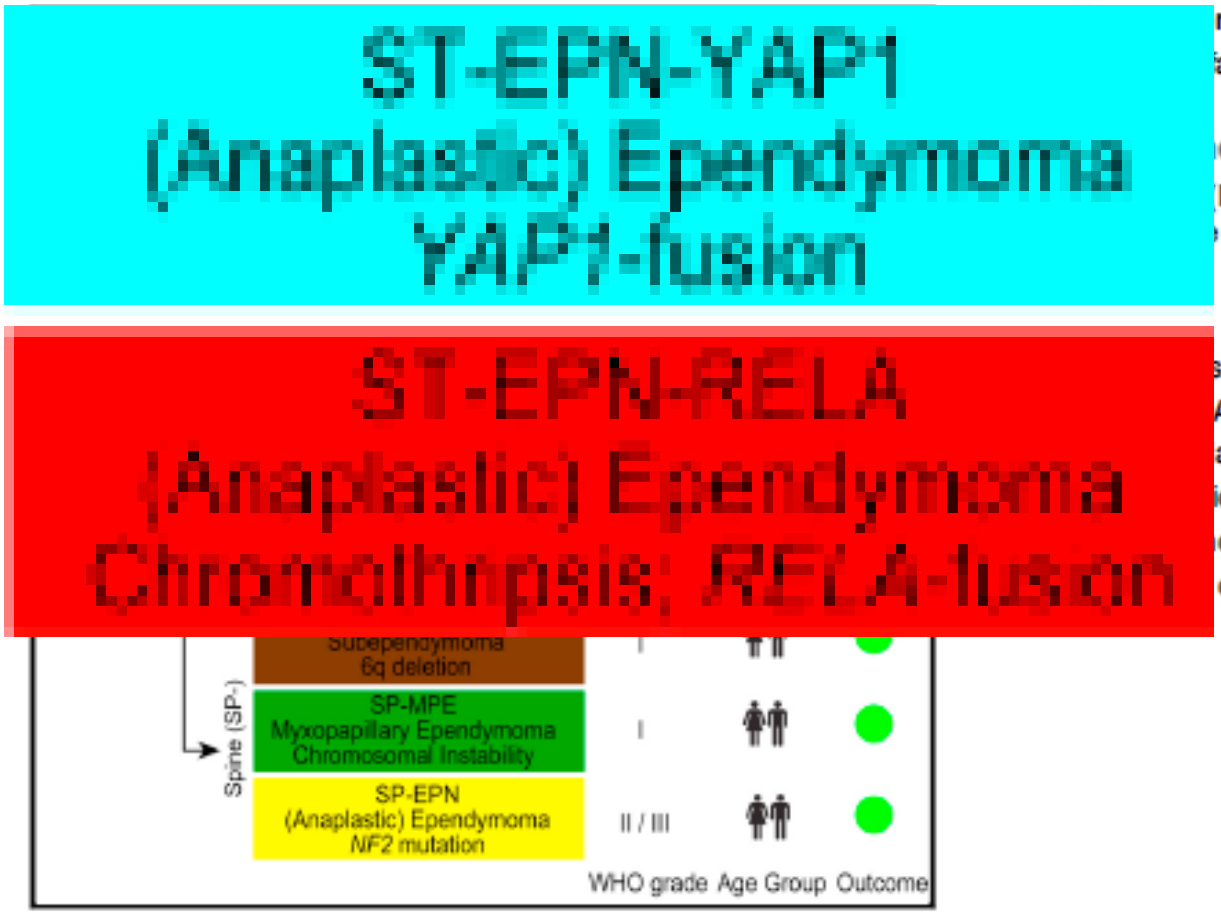
Clinical trial	Patients (number)	Chemotherapy	PFS (years)	OS (years)
CCG 942 [34]	36, 22 received combined therapy, 14 only RT	CCNU, VCR, Pred	36% at 10	39% at 10
CCG 921 [35]	32, following surgery and radiation received CT: 14 (arm A); 18 (arm B)	(Arm A) CCNU, VCR, Pred (Arm B) 8 in 1 drug regimen	50± 10% at 5	64± 9% at 5 No difference in arm A or B
UKCCSG/SIOP [36]	89 less than 3 years, 80 were non-metastatic	Carboplatin, VCR, MTX, CDDP	41.8% at 5	63.4% at 5 (5 year OS was 76% in those who received higher dose chemotherapy)
SFOP [37]	72 (82%) anaplastic	Procarbazine, Carboplatin, VP16, CDDP, VCR, CPM	22% at 4	59% at 4
POG 9233 [38]	48 less than 3 years	Surgery then chemo, arm A: CPM, VCR, CDDP, VP16; Arm B: CPM, VCR and dose-intensified CDDP, VP16	23% at 2 27% at 2	54% at 2 40% at 2
Head Start III [39]	19	Five induction chemotherapy cycles followed by one consolidation cycle of myeloablative chemotherapy and ASCR	86% at 3	100% at 3
Foreman *et al.* [40]	5 with 4th ventricular ependymoma	Chemotherapy followed by second look surgery in 4 patients		
CCG 9942 [41]	84 with 41 having residual tumour	Patients with residual tumour received: VCR, CTX, VP16, CDDP	57% ± 6% at 5	71 ± 6% at 5
Phase I trial using lapatinib [42]	16 with ependymoma	MTD was 900mg/m2 orally twice daily		No objective response seen
Phase I trial with 5FU [45]	23 eligible, 6/23 were located in ST region	5FU given IV bolus dose weekly for 4 weeks and rest for 1 week: 1 cycle		5 patients had a partial response (duration 6–54 weeks). 4 patients had stable disease (duration 6–67 weeks)

RT, radiotherapy; CT, chemotherapy; CCNU, lomustine; VCR, vincristine; Pred, prednisone; MTX, methotrexate; CDDP, cisplatin, CPM, cyclophosphamide; VP16, etoposide; ASCR, autologous stem cell rescue; MTD, maximum tolerated dose; IV, intravenous; OS, overall survival; POG, Pediatric Oncology Group.

Cancer Cell

Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups

Graphical Abstract



Authors

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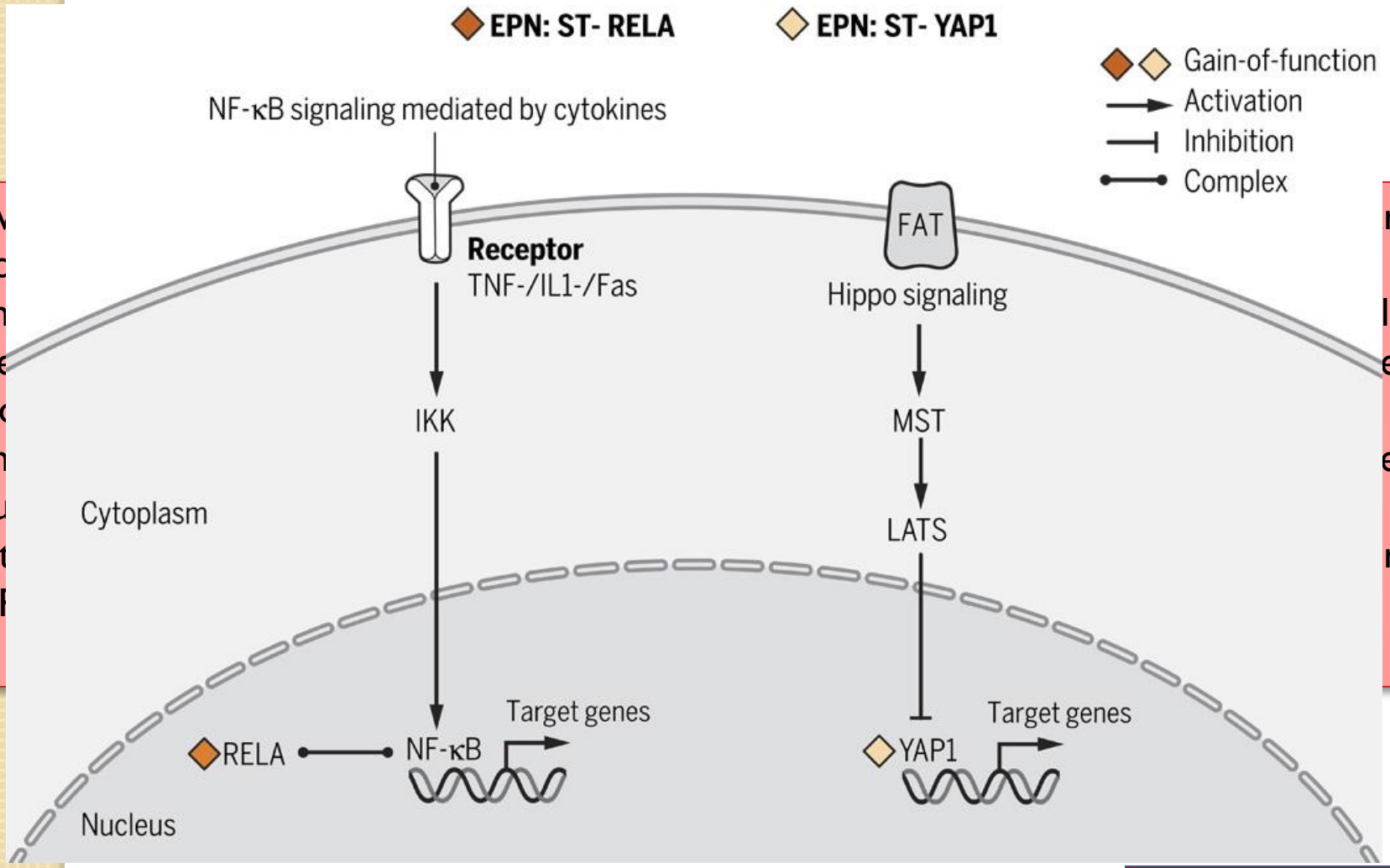
Synopsis of signaling pathway alterations and potential drug targets in molecular subgroups of pediatric EPN.



Kun-Wei Liu et al., Sci. Signal. 2017;10:eaaf7593

Science Signaling
AAAS

Acta Neuropathol (2017) 133:5–12
DOI 10.1007/s00401-016-1643-0

CONSENSUS PAPER

The current co
ependymoma :

Kristian W. Pajtler[1,2,3]
Amy Smith[8] · Jordan R
Yonehiro Kanemura[14] ·
Katherine E. Warren[17]
Andreas von Deimling[2]
Amar Gajjar[11] · Andre
Kenneth D. Aldape[30] · T

General Consensus Statements

1. Outside of clinical trials, treatment decisions should not be based on grading (II vs III)
2. ST and PF ependymomas are different diseases although the impact on therapy is still evolving
3. Central radiological and histological review should be a principal component of future clinical trials
4. Molecular subgrouping should be part of all clinical trials henceforth
5. Submission of fresh-frozen tumor samples as well as of blood samples will be mandatory in future clinical trials

Subgroup Consensus Statements

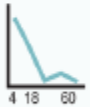
Molecular subgroup	Tumor Location	Genetics	Age Distribution (yrs)	Gender Distribution	Survival (OS;months)	Subgroup-specific consensus
ST-EPN-RELA		 Aberrant 11q Chromothripsis	 4 18 60	 ♂ > ♀	 120	There is not enough evidence to recommend distinct treatment approaches. Outcome should be further validated in prospective and retrospective studies.
ST-EPN-YAP1		 Aberrant 11q	 4 18 60	 ♂ < ♀	 120	It should be rapidly determined whether the YAP1 subgroup is associated with favorable clinical outcome.
PF-EPN-A		 Balanced	 4 18 60	 ♂ > ♀	 120	Outside of clinical trials, in patients > 12 months of age, maximal safe resection and focal radiotherapy is the standard of care.
PF-EPN-B		 Chromosomal Instability	 4 18 60	 ♂ < ♀	 120	An observation only clinical trial will be implemented to determine the opportunity of de-escalating therapy.

Fig. 1 General and molecular subgroup specific consensus statements on the clinical management of intracranial ependymoma

Labón et al. SpringerPlus (2016) 5:879
DOI 10.1186/s40064-016-2562-1

SpringerPlus

RESEARCH Open Access

Re-irradiation of recurrent pediatric ependymoma: modalities and outcomes:

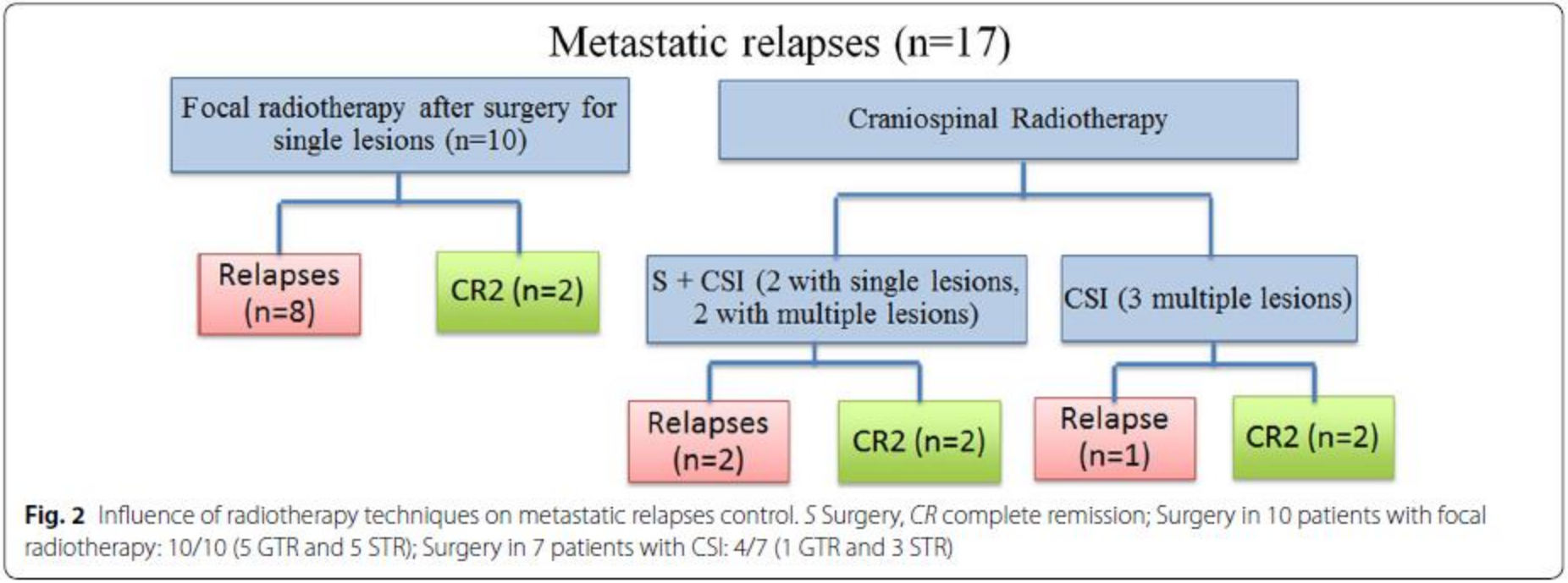


Fig. 2 Influence of radiotherapy techniques on metastatic relapses control. *S* Surgery, *CR* complete remission; Surgery in 10 patients with focal radiotherapy: 10/10 (5 GTR and 5 STR); Surgery in 7 patients with CSI: 4/7 (1 GTR and 3 STR)

Patient 11 died at the beginning of RT2 due to rapid tumor progression.

FFRT). Four experienced distant and 1 local relapse after RT3. Only two are alive with a follow up of 6 and 20 months.

J Neurooncol (2014) 116:107–111
DOI 10.1007/s11060-013-1259-3

CLINICAL STUDY

Fractionated stereotactic radiosurgery for recurrent ependymoma in children

Lindsey M. Hoffman · S. Reed Plimpton · Nicholas K. Foreman · Nicholas V. Stence · Todd C. Hankinson · Michael H. Handler · Molly S. Hemenway · Rajeev Vibhakar · Arthur K. Liu

Complicaciones de reirradiación

- Radionecrosis
- Secuelas endocrinas
- Secuelas neurocognitivas
- Segundos tumores

Manejo actual

Quimioterapia

Quimioterapia VEC

VEC	
Week 0 **Day 1**	D1: Vincristine (VCR): 1.5 mg/m² (maximal dose 2 mg) i.v. bolus D1-D3 Etoposide (VP16): 100 mg/m² infused over 60 minutes. D1 cyclophosphamide: 3000 mg/m² in 3 divided infusions (1000 mg/m²/infusion) infused over 60 minutes.
Week 3 **Day 22**	D22: Vincristine (VCR): 1.5 mg/m² (maximal dose 2 mg) i.v. bolus D22-D24: Etoposide (VP16): 100 mg/m² infused over 60 minutes. D22: cyclophosphamide: 3000 mg/m² in 3 divided infusions (1000 mg/m²/infusion) infused over 60 minutes.
Week 6 **Day 43**	D43: Vincristine (VCR): 1.5 mg/m² (maximal dose 2 mg) i.v. bolus D43-D45: Etoposide (VP16): 100 mg/m² infused over 60 minutes. D43: cyclophosphamide: 3000 mg/m² in 3 divided infusions (1000 mg/m²/infusion) infused over 60 minutes.

Pediatr Blood Cancer 2014;61:636–642

A Phase II Trial of a Multi-Agent Oral Antiangiogenic (Metronomic) Regimen in Children With Recurrent or Progressive Cancer

Nathan J. Robison, MD,[1,2†] Federico Campigotto, MS,[3] Susan N. Chi, MD,[1,2] Peter E. Manley, MD,[1,2] Christopher D. Turner, MD,[1,2†] Mary Ann Zimmerman, RN, MSN,[1,2] Christine A. Chordas, RN, MSN,[1,2] Annette M. Werger, RN, MSN,[1,2] Jeffrey C. Allen, MD,[4] Stewart Goldman, MD,[5] Joshua B. Rubin, MD, PhD,[6] Michael S. Isakoff, MD,[7] Wilbur J. Pan, MD, PhD,[8] Ziad A. Khatib, MD,[9] Melanie A. Comito, MD,[10] Anne E. Bendel, MD,[11] Jay B. Pietrantonio, BS,[1,2†] Laura Kondrat, RN, MSN,[1,2†] Shannon M. Hubbs, BA,[1,2†] Donna S. Neuberg, ScD,[3] and Mark W. Kieran, MD, PhD[1,2*]

TABLE I. 5-Drug Oral Regimen: Dosing Schedule

Medication	Dosing schedule
Continuous	
Thalidomide	Start at 3 mg/kg (rounded to nearest 50 mg) daily Increase dose weekly by 50 mg as tolerated to 24 mg/kg (max 1,000 mg) daily
Celecoxib	<20 kg: 100 mg twice daily 20–50 kg: 200 mg twice daily >50 kg: 400 mg twice daily
Fenofibrate	90 mg/m^2 (max 200 mg) daily
Alternating 21 day cycles	
Etoposide	50 mg/m^2 daily for 21 days
Cyclophosphamide	2.5 mg/kg (max 100 mg) daily for 21 days

Patients with history of significant myelosuppression with prior therapy initiated etoposide at 35 mg/m^2 day and escalated to 50 mg/m^2 as tolerated.

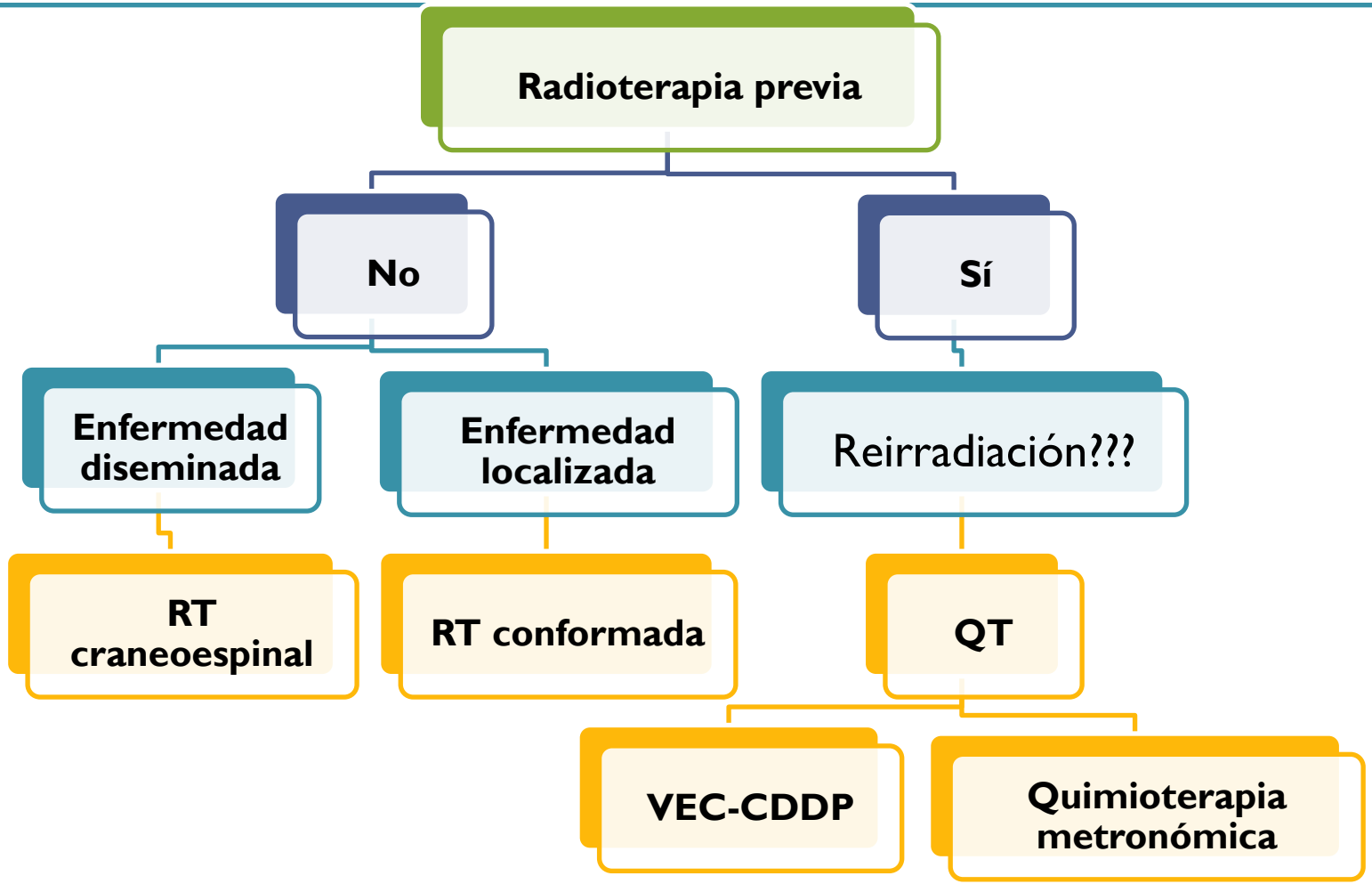
TABLE III. Clinical Outcomes by Disease Strata

Stratum	N	Best response					Completed 27 weeks therapy
		CR	PR	SD	PD	NE	
High grade glioma	21	—	1	7	13	—	1 (5%)
Ependymoma	19	—	2	10	7	—	7 (37%)
Low grade glioma	12	—	4	5	3	—	7 (58%)
Bone tumors	12	—	—	1	10	1	—
Medulloblastoma/PNET	8	1	1	1	5	—	1 (13%)
Leukemia	4	—	—	1	3	—	—
Neuroblastoma	3	—	—	2	1	—	1 (33%)
Miscellaneous	18	—	4	9	5	—	7 (39%)
Miscellaneous CNS Tumors	9	—	3	5	1	—	5(56%)
Miscellaneous non-CNS tumors	9	—	1	4	4	—	2(22%)

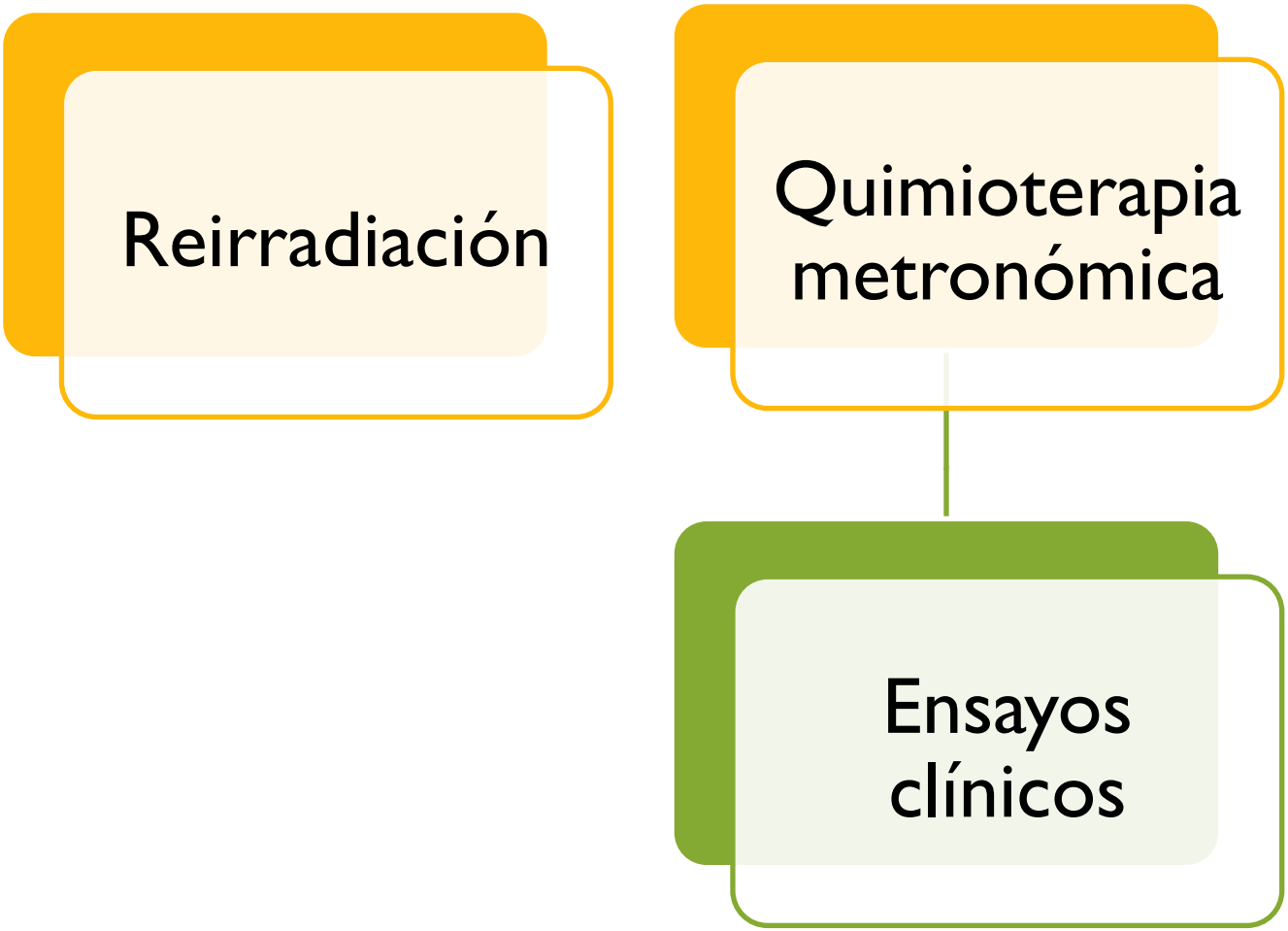
CNS, central nervous system; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable. One patient with anaplastic glioneuronal tumor (miscellaneous CNS tumors strata) and best response SD sustained a CR during continuation therapy.

Nine (47%) ependymoma patients had metastatic disease at time of enrollment. Primary tumor location was supratentorial (N = 3), infratentorial (N = 13), and spinal (N = 3). All had received at least one prior course of radiation, and a median of 1 prior course of chemotherapy. Seven (37% [90% CI 19%, 58%]) completed therapy with SD or better. Two-year PFS and OS for patients with ependymoma were 34% (90% CI 16%, 52%) and 43% (90% CI 23%, 61%) (Fig. 1). Long-term (>3 year) survivors included two with metastatic disease.

No cirugía posible ó enfermedad diseminada



Segunda recaída y sucesivas



Ensayos clínicos

5-Fluoracilo

- Fase I. St. Jude/Royal Masden

Bevacizumab

Lapatinib

- Inhibidor de ERBB1 y ERBB2
- Fase II:CERN. NO respuesta tumoral

Sunitinib

- Inhibidor de torixin-kinasa
- Fase II: COG (ACNS 1021Bien tolerado. No eficaz

Enzastaurin

Cancer Medicine

Open Access

ORIGINAL RESEARCH

Phase II evaluation of sunitinib in the treatment of recurrent or refractory high-grade glioma or ependymoma in children: a children's Oncology Group Study ACNS1021

Cynthia Wetmore[1], Vinay M. Daryani[2], Catherine A. Billups[3], James M. Boyett[3], Sarah Leary[4], Rachel Tanos[1], Kelly C. Goldsmith[1], Clinton F. Stewart[2], Susan M. Blaney[5] & Amar Gajjar[6]

[1]Department of Pediatrics, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta and Emory University School of Medicine, 1760 Haygood Drive NE, Atlanta, Georgia 30322

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[6]Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105

Cancer Medicine 2016; 5(7):1416–1424

Neuro-Oncology

Neuro-Oncology 17(12), 1620–1627, 2015
doi:10.1093/neuonc/nov181

Phase I study of 5-fluorouracil in children and young adults with recurrent ependymoma

Karen D. Wright, Vinay M. Daryani, David C. Turner, Arzu Onar-Thomas, Nidal Boulos, Brent A. Orr, Richard J. Gilbertson, Clinton F. Stewart, and Amar Gajjar

Neuro-Oncology 14(11):1404–1412, 2012.
doi:10.1093/neuonc/nos213
Advance Access publication September 26, 2012

Lack of efficacy of bevacizumab + irinotecan in cases of pediatric recurrent ependymoma—a Pediatric Brain Tumor Consortium study

Sridharan Gururangan, Jason Fangusaro, Tina Young Poussaint, Arzu Onar-Thomas, Richard J. Gilbertson, Sridhar Vajapeyam, Amar Gajjar, Stewart Goldman, Henry S. Friedman, Roger J. Packer, James M. Boyett, and Larry E. Kun

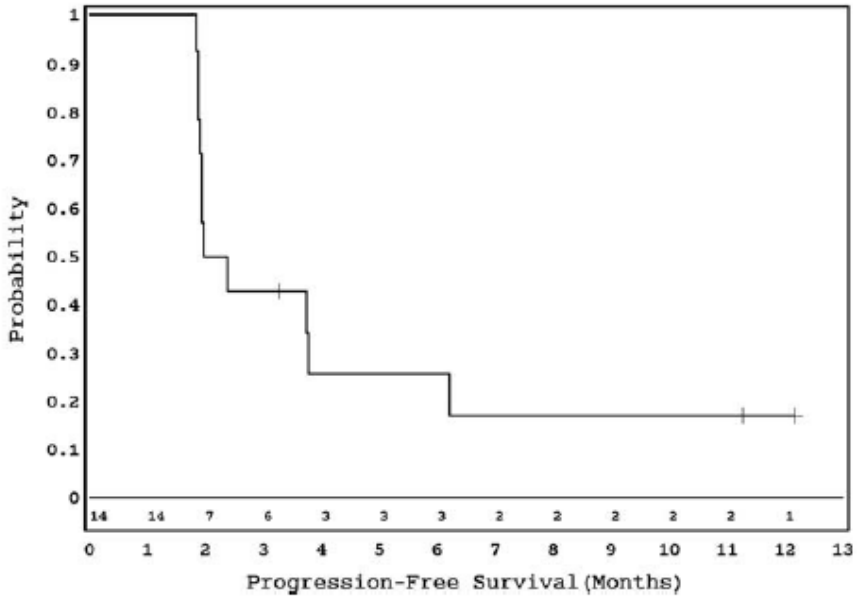

Fig. 1. Kaplan–Meier survival curve showing PFS in 14 eligible patients with recurrent ependymoma.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(11)1073–1079
doi:10.1093/jjco/hyt124
Advance Access Publication 3 September 2013

Phase I Study of Bevacizumab Plus Irinotecan in Pediatric Patients with Recurrent/Refractory Solid Tumors

Keiko Okada*, Kai Yamasaki, Chika Tanaka, Hiroyuki Fujisaki, Yuko Osugi and Junichi Hara

Department of Pediatric Hematology/Oncology, Osaka City General Hospital, Osaka, Japan

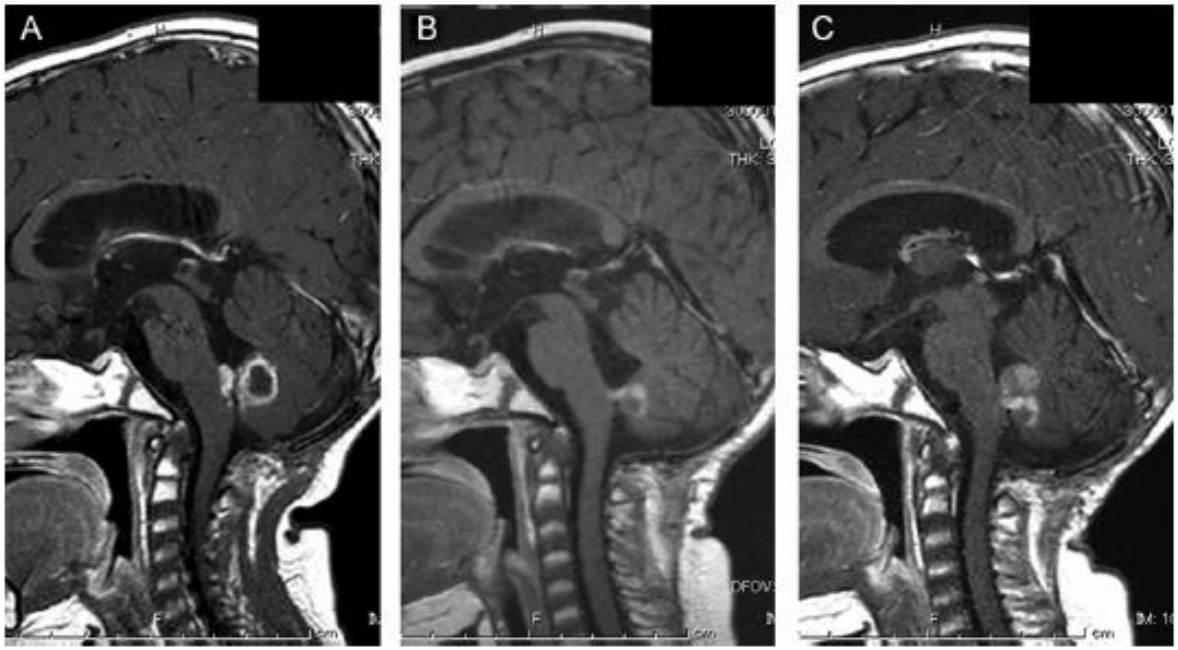

Figure 3. A 3-year-old girl with relapsed ependymoma. Contrast-enhanced sagittal T1 images at the beginning of treatment (A), after six doses (B) and after nine doses (C) of BVZ plus irinotecan.

Futuro

Inmunoterapia: vacunas

Dianas moleculares:

- Problema: falta de modelos preclínicos de ependimoma
- Medicina de precisión


Por Ahora
Necesito una sonrisa...
El resto
Lo arreglamos ¿Después?


¡Gracias!