Radiotherapy for Infant Brain Tumors

SIOP 2023

INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

OTTAWA, CANADA | OCTOBER 11-14, 2023

55TH CONGRESS OF THE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

OTTAWA, CANADA

OCTOBER 11-14, 2023

#SIOPcongress | Congress Website: SIOP-Congress.org | Society Website: SIOP-Online.org

Disclosure

X	No, nothing to disclose
	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*

Paul Aridgides MD
Associate Professor
SUNY Upstate Medical University
Syracuse, NY USA

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Children's Oncology Group Committees Investigating Impact of Radiotherapy (RT) for Infant Embryonal Tumors / ATRT

- ACNS0334 (PI C Mazewski) Supratentorial PNET/ High Risk MB
- ACNS0334 (PI A Reddy) ATRT
- ACNS2232 (PI L Hoffman) ATRT concept

In conjunction with:
Childhood Cancer International
IPSO
PROS PAEDIATRIC RADIATION ONCOLOGY SOCIETY

UPSTATE MEDICAL UNIVERSITY

CHILDREN'S ONCOLOGY GROUP

Purpose

- Explore RT questions for 3 Infant Brain Tumors
  - Definition: Age <36 months according to COG ACNS0333, ACNS0334
- Medulloblastoma
- Ependymoma
- ATRT

Purpose

- Explore RT questions for 3 Infant Brain Tumors

- Medulloblastoma
  - How should RT be given following a high dose chemotherapy/RT-sparing approach?
- Ependymoma
  - What is the lower age limit for upfront adjuvant RT?
- ATRT
  - Is RT necessary?

Purpose

- Medulloblastoma
  - How should RT be given following a high dose chemotherapy/RT-sparing approach?

WHO 2021 Medulloblastoma

- Medulloblastoma
  - Medulloblastomas, molecularly defined
    - Medulloblastoma, WNT-activated
    - Medulloblastoma, SHH-activated and *TP53*-wildtype
    - Medulloblastoma, SHH-activated and *TP53*-mutant
    - Medulloblastoma, non-WNT/non-SHH → Includes Group 3 and Group 4
  - Medulloblastomas, histologically defined

Infant MB High Dose Chemotherapy RT avoidance: Head Start III

Neuro Oncol 2020

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SURGERY → INDUCTION → SECOND LOOK SURGERY

Cycles 1,3 and 5
Cisplatin
Cyckiphosphamide*
Vincristine
Etoposide IV
HD Methotrexae**
Cycles 2, 4
Cyclophosphamide*
Vincristine
Etoposide (oral)
Temozolomide (oral)

Myeloablative Chemo/AuHCR × 1

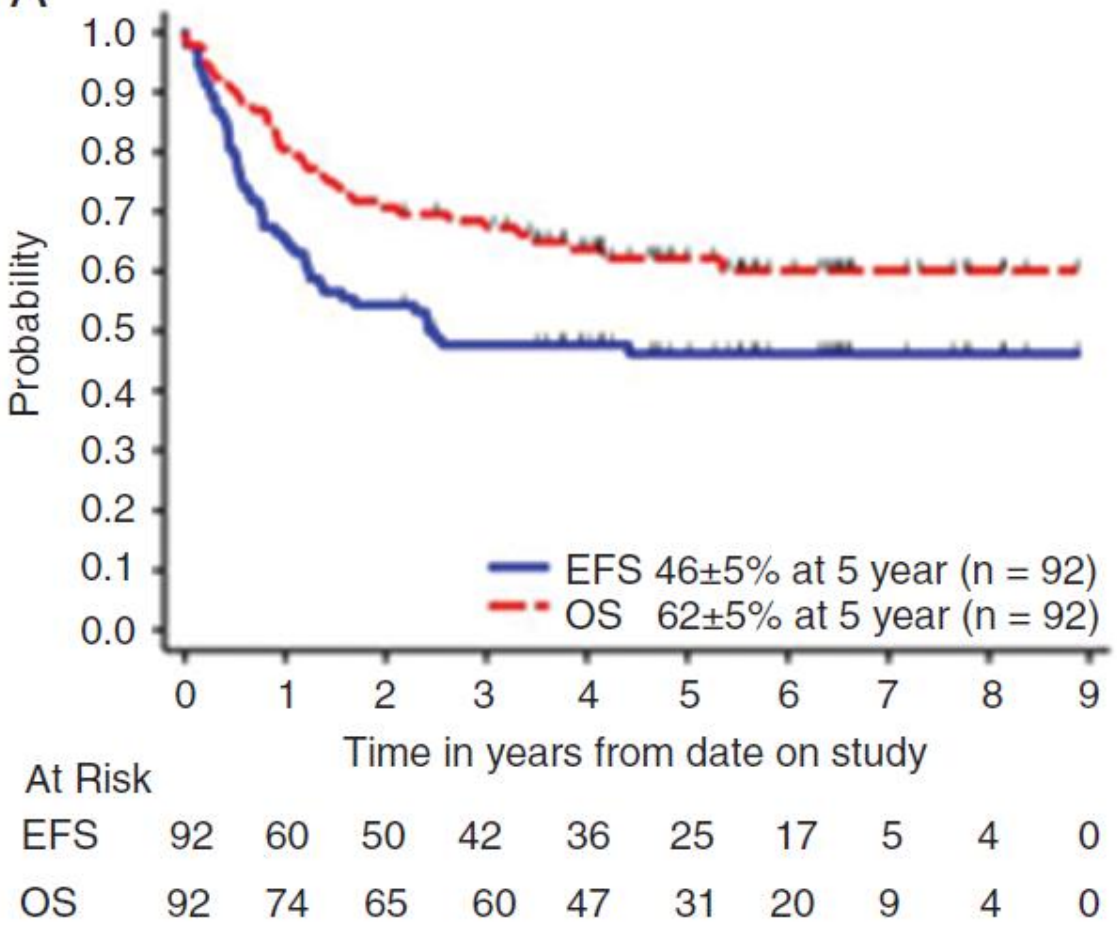
Thiotepa (300mg/m^2/day × 3d)
Etoposide (250mg/m^2/day × 3d)
Carboplatin (AUC of 7/day ×3d)

±RADIATION THERAPY

Histology			
	Classical	**Nodular/Desmoplastic**	**Large Cell/Anaplastic**
Total Cohort (N=92)	52	27	13
Age at Diagnosis (years)			
<3 years	27	24	5

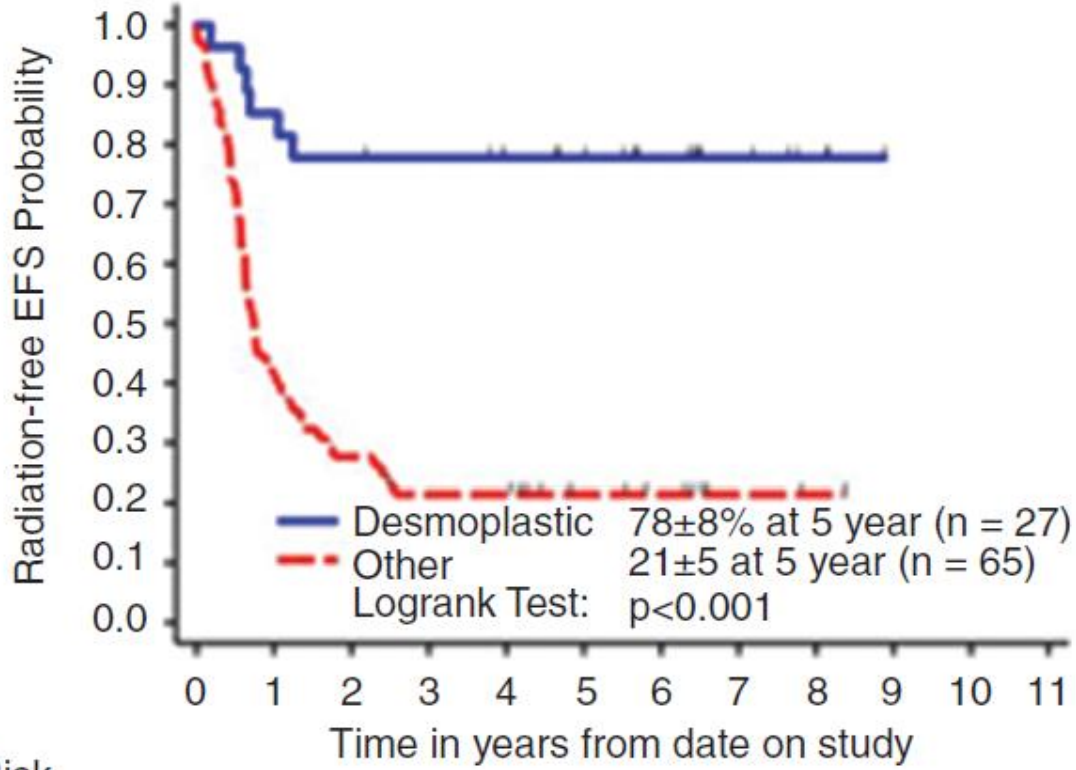
Head Start III: Desmoplastic MB excellent non-irradiated outcomes

A



At Risk										
EFS	92	60	50	42	36	25	17	5	4	0
OS	92	74	65	60	47	31	20	9	4	0

B



At Risk												
Democratic	27	23	21	20	17	14	10	6	3	0	0	0
Other	65	27	15	13	13	8	6	2	1	0	0	

Much Worse Outcomes for RT sparing Classic MB/LCA

- Classic and Large Cell Anaplasia (LCA): 5 yr EFS 30%/OS 50%
  - 22 M0 pts no RT: 11 are alive
  - 32 M+ pts no RT: 12 are alive; only 4 without progression
  - 10 pts received RT: 5 surviving and 5 progressed

Head Start III Radiation Guidelines

Age at Diagnosis (years)	Disease Extent at Diagnosis	Disease Status at Consolidation Start	XRT Dose and Volume
<6	Local or Disseminated	NED	No XRT
<6	Disseminated	Local Residual	18.0Gy CSI + 55.8Gy Tumor Bed Boost
<6	Disseminated	Disseminated Residual ★	23.4Gy CSI + 55.8Gy Tumor Bed Boost
<6	Local	Local Residual	55.8Gy Tumor Bed Boost
6-10	Local or Disseminated	None or Local Residual ★	23.4Gy CSI + 55.8Gy Tumor Bed Boost
6-10	Local or Disseminated	Disseminated Residual	36.0Gy CSI + 55.8Gy Tumor Bed Boost

NED, no evidence of disease; XRT, radiation therapy; CSI, craniospinal irradiation

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CSI:

★ 9 pts 2340cGy

1 pt 3600cGy

<u>No pts reported with:</u>

-1800cGy CSI

-Focal RT primary only

-Focal RT primary plus mets (not in guidelines)

Outcomes Following Radiation Therapy (RT) for Very Young Age CNS Embryonal Tumors on COG ACNS0334 According to Molecular-Confirmed Diagnosis

K. Schumacher[1], P.D. Aridgides[1], J. Gossett[2], G. Kang[2], A. Huang[3], T.E. Merchant[4], and C. Mazewski[5]

[1]SUNY Upstate Medical University, Syracuse, NY, [2]St. Jude Children's Research Hospital, Memphis, TN, [3]Division of Haematology/Oncology, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [4]Division of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, TN, [5]Emory University School of Medicine, Atlanta, GA

ACNS 0334 Treatment
(Randomized +/- MTX)

REGIMEN A INDUCTION (3 CYCLES)
PBSC HARVEST
Vincristine, Etoposide,
Cyclophosphamide, Cisplatin

REGIMEN B INDUCTION (3 CYCLES)
PBSC HARVEST
Vincristine, Etoposide, Cyclophosphamide,
Cisplatin, Methotrexate

Second Look Surgery < CR

CONSOLIDATION (3 CYCLES)
(Thiotepa, Carboplatin)
PBSC RESCUE

RT OPTIONAL post consolidation

ACNS0334 Outcomes According to Molecular Diagnosis for MB without RT details

- MB: 38 patients molecular subtype (11 SHH, 25 Group 3, 2 Group 4)
  - 5 year OS SHH no difference according to MTX
  - 5 year OS 80% for 10 Group 3 with MTX, 40% for 15 Group 3 without MTX (p=0.025)
  - RT given to 6/14 survivors

Mazewski et al 2020

MB Group 3 receiving RT Upfront or RT Relapse

Age at RT (years)	Upfront vs relapse	Pre-RT Stage	CSI Dose (Gy)	Primary Dose (Gy)	Metastatic Dose (Gy)	MTX	Status
2.8	Upfront	R0, M3	18	54	45	YES	Alive
3.5	Upfront	R+, M3	23.4	54	54/50.4/45	YES	DOD
3.4	Upfront	R+, M3	36	36	0	YES	Alive
3.5	Upfront	R0, M3	18	54	0	N	DOD
3.3	Upfront	R0, M3	23.4	54	0	N	DOD
2.8	Upfront	R0, M3	0	50	44	N	Alive
3.6	Relapse	R+, M3	39.6	55.8	0	YES	Alive
5.8	Relapse	R0, M3	36	54	50.4/46.8	N	Alive

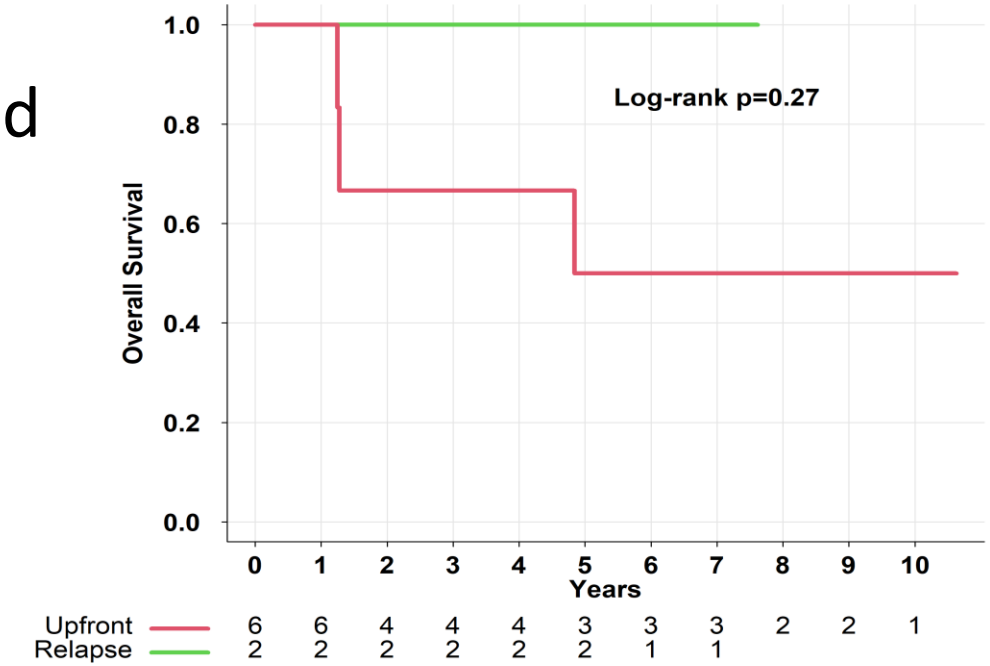
*Full dose CSI $\geq$ 36 Gy:

Relapsed RT Gr 3 MB received higher dose CSI (p=0.013) than Upfront RT

ACNS 0334 RT Molecular Diagnosis Conclusions

- RT cohort for Gr 3 MB on ACNS0334 exhibited long-term survival both for both upfront and relapse RT.
  - Relapsed Gr 3 MB received higher dose CSI (p=0.013)

- **Unknown** Upfront RT Impact on ACNS0334:
  - MB Gr3 with CR to chemotherapy (no pts)
  - Further study of either focal RT or low dose CSI, given very young patient age, would be required



ACNS0334 Gr3 MB
Upfront RT or Relapse RT

Outcomes of Infants and Young Children With Relapsed Medulloblastoma After Initial Craniospinal Irradiation–Sparing Approaches: An International Cohort Study

Craig Erker, MD, MS[1]; Martin Mynarek, MD[2,3]; Simon Bailey, MBChB, PhD[4]; Claire M. Mazewski, MD[5]; Lorena Baroni, MD[6]; Maura Massimino, MD[7]; Juliette Hukin, MB[8]; Dolly Aguilera, MD[5]; Andrea M. Cappellano, MD[9]; Vijay Ramaswamy, MD, PhD[10]; Alvaro Lassaletta, MD[11]; Sébastien Perreault, MD[12]; Cassie N. Kline, MD, MAS[13]; Revathi Rajagopal, MD[14]; George Michaiel, MD[15]; Michal Zapotocky, MD, PhD[16]; Vicente Santa-Maria Lopez, MD[17]; Andres Morales La Madrid, MD[17]; Chantel Cacciotti, MD[18,19]; Eric S. Sandler, MD[20]; Lindsey M. Hoffman, DO[21]; Darren Klawinski, MD[20]; Sara Khan, MD, PhD[22,23]; Ralph Salloum, MD[10]; Anna L. Hoppmann, MD, MPH[24]; Valérie Larouche, MD[25]; Kathleen Dorris, MD[26]; Helen Toledano, MD[27]; Stephen W. Gilheeney, MD, MMS[28]; Mohamed S. Abdelbaki, MD[29,30]; Beverly Wilson, MD[31]; Derek S. Tsang, MD, MSc[32]; Jeffrey Knipstein, MD[33]; Michal Yalon Oren, MD, PhD[34]; Shafqat Shah, MD[35]; Jeffrey C. Murray, MD[36]; Kevin F. Ginn, MD[37]; Zhihong J. Wang, MD[38]; Gudrun Fleischhack, MD[39]; Denise Obrecht, MD[2]; Svenja Tonn[2]; Virginia L. Harrod, MD, PhD[40]; Kara Matheson, MSc[41]; Bruce Crooks, MB ChB[42]; Douglas R. Strother, MD[43]; Kenneth J. Cohen, MD, MBA[44]; Jordan R. Hansford, MBBS, MSc[45]; Sabine Mueller, MD, PhD[46]; Ashley Margol, MD, MS[47]; Amar Gajjar, MD[48]; Girish Dhall, MD[23]; Jonathan L. Finlay, MD[28]; Paul A. Northcott, MD, PhD[49]; Stefan Rutkowski, MD[2]; Steven C. Clifford, PhD[4]; Giles Robinson, MD[48]; Eric Bouffet, MD[10]; and Lucie Lafay-Cousin, MD, MSc[43]

JCO 2023

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380pts

Survival improved:

- SHH
- Localized relapse
- Older age initial
- Use of Salvage CSI

In conjunction with:

Childhood Cancer International

IPSO

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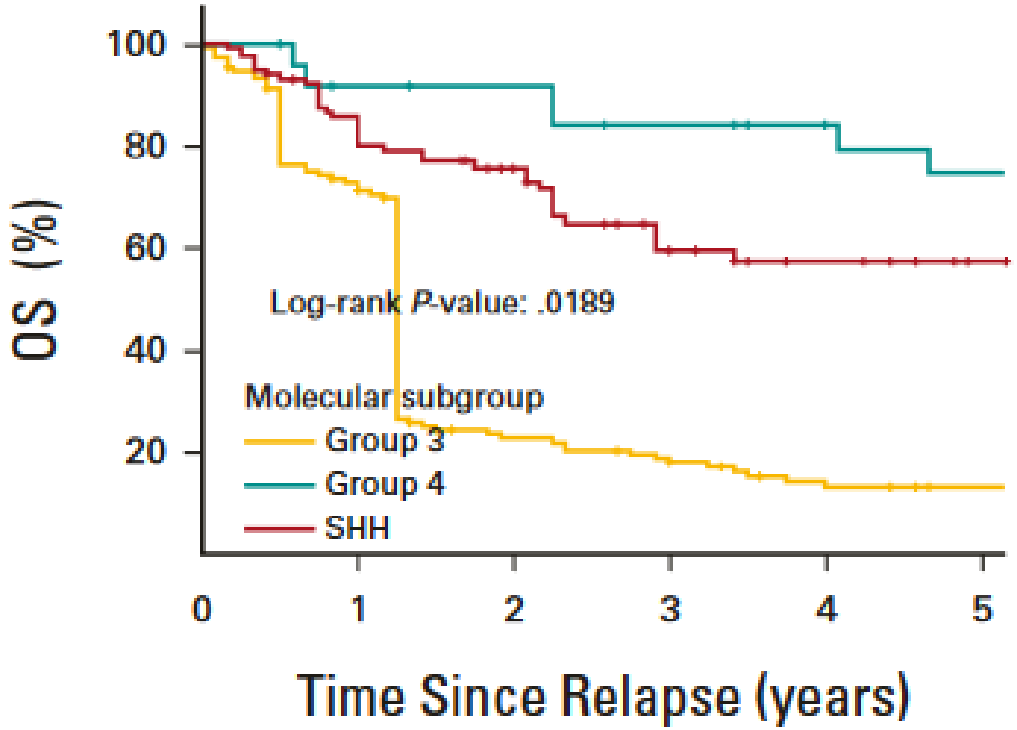
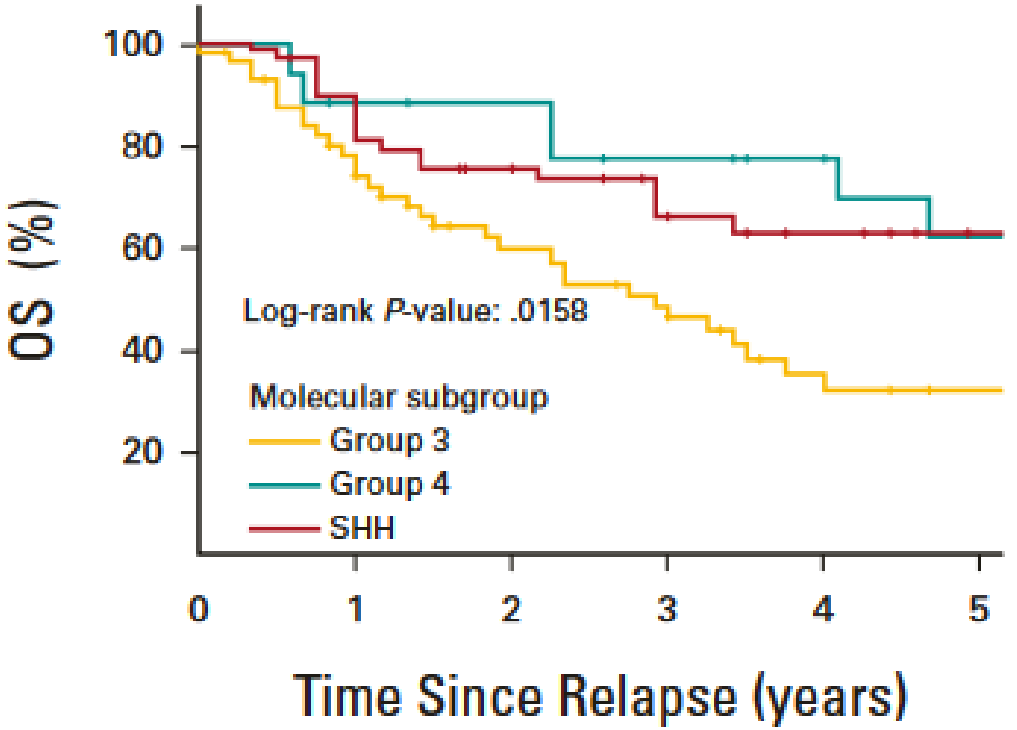
Survival Relapsed MB no initial CSI (iCSI): Salvage CSI biggest impact Gr3

B curative molecular defined



No. at risk:						
Group 3	62	41	26	20	12	8
Group 4	22	18	17	14	12	9
SHH	66	51	40	29	21	15

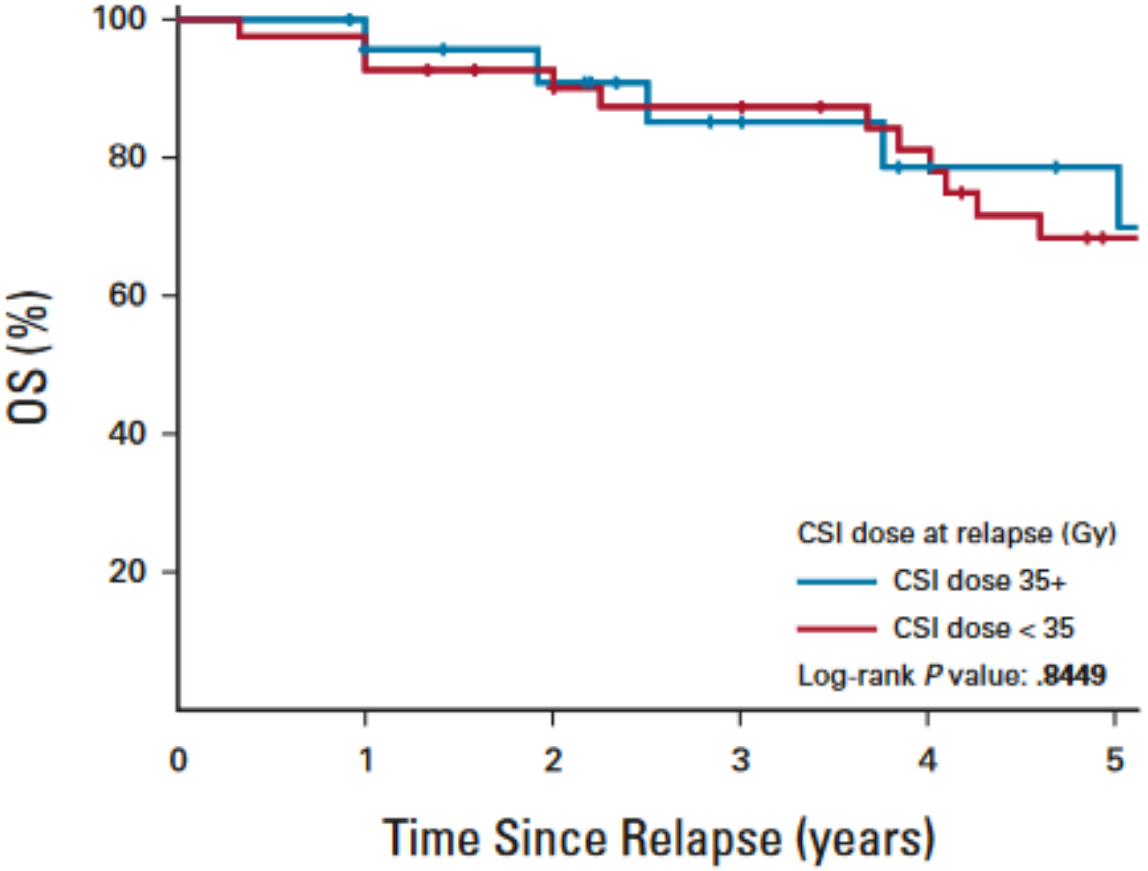
C + CSI



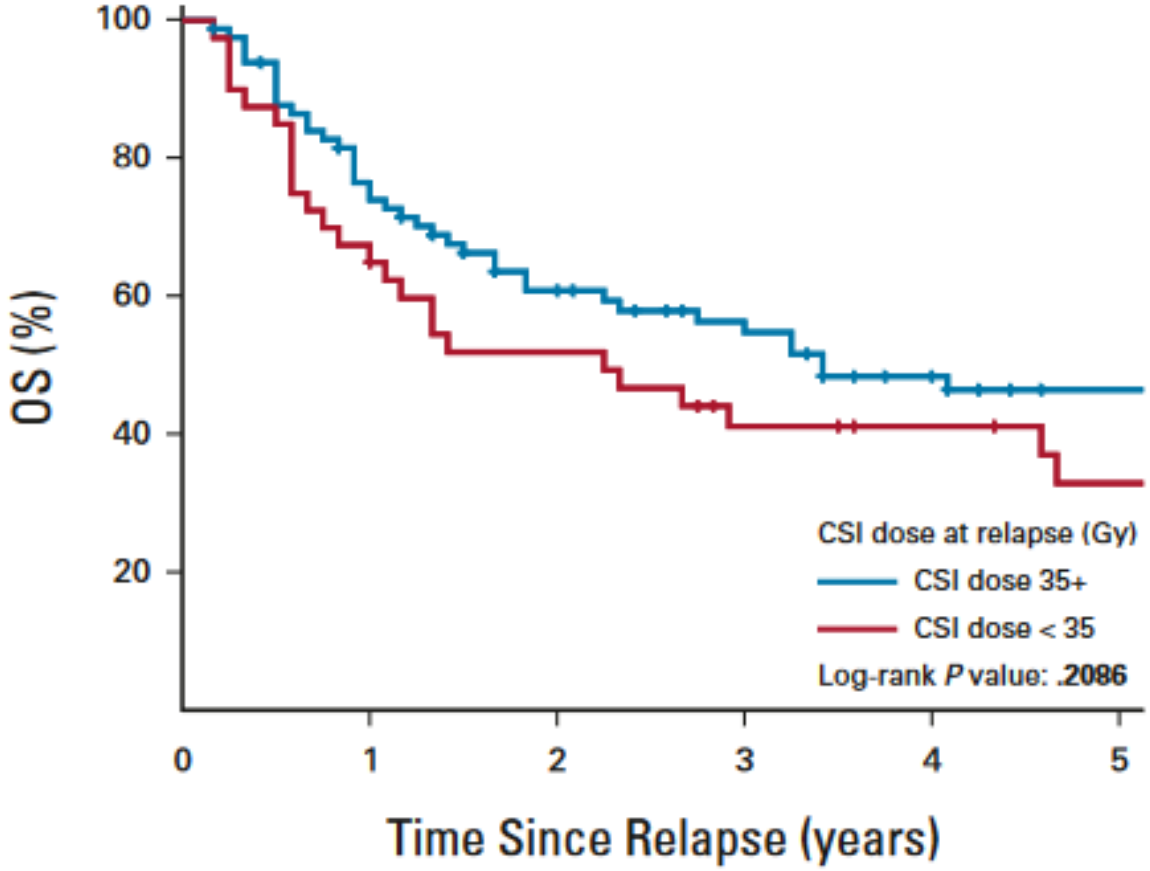
No. at risk:						
Group 3	54	39	25	19	11	8
Group 4	19	16	15	12	10	7
SHH	37	33	27	22	17	12

Relapse CSI dose curves seem to separate (non-sig) for disseminated disease

Localized only relapse



Disseminated relapse



Medulloblastoma

- How should RT be given following a high dose chemotherapy /RT-sparing approach?

Frontline RT for PR (Gr3 0334, classic/LCA HSIII), low dose CSI/focal RT helpful?

-unknown if low dose CSI/focal RT helpful 50% survival 0334 (very few pts)

Frontline RT for CR is generally not used, MORE study for Gr3 (non-desm/non-SHH)

-Desmoplastic / usually SHH no RT (HSIII, 0334)

-Gr3 (+MTX,0334) 80% survival overall, HSIII classic/LCA (HSIII) 50% survival

Relapse RT (especially if disseminated) full dose 35-36Gy CSI

-0334 / multi-institutional cohort

Purpose

- Ependymoma
  - What is the lower age limit for upfront adjuvant RT?

WHO 2021 Ependymoma

Ependymal tumors

- Supratentorial ependymoma
- Supratentorial ependymoma, *ZFTA* fusion-positive — Formerly RELA
- ★ Supratentorial ependymoma, *YAP1* fusion-positive — Median age 1.4yrs- excellent prognosis
- Posterior fossa ependymoma
- ★ Posterior fossa ependymoma, group PFA — Median age 3yrs 25% 1q gain: poor prognosis
- Posterior fossa ependymoma, group PFB

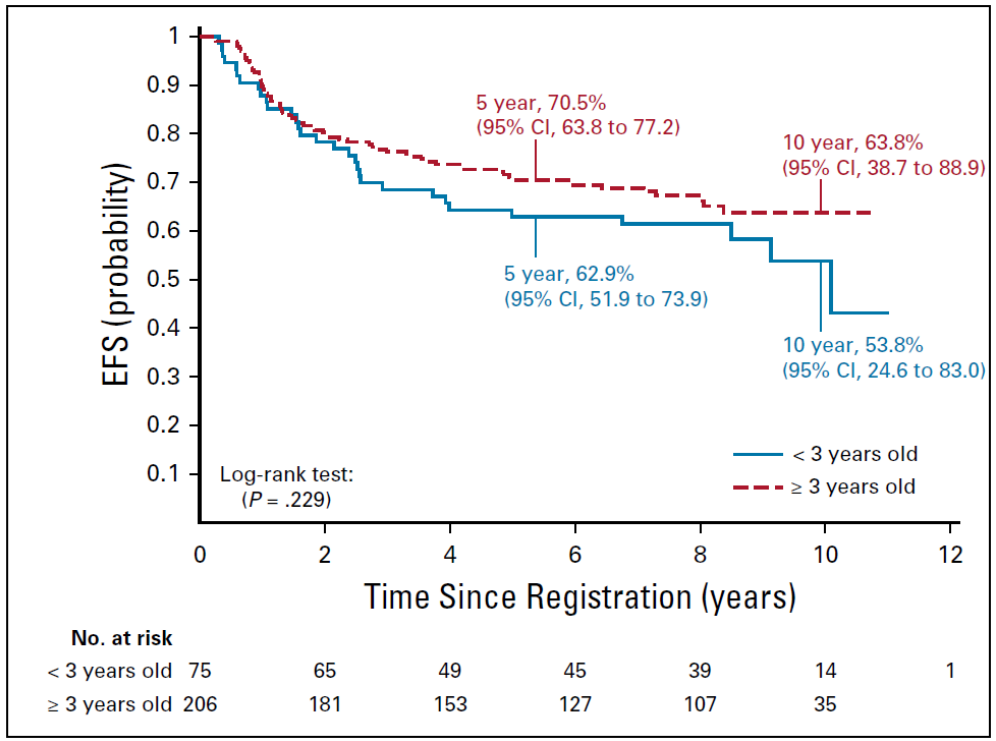
AIEOP Ependymoma Inferior OS age < 3years

-45pts (28%) age < 3
-RT 54Gy (12-18mo) or 59.4Gy

	PFS		OS	
	5-y Estimate (CI)	*P* (log-rank)	5-y Estimate (CI)	*P* (log-rank)
Age		.164		.035
<3 y	57.6% (43.1%–77.2%)		70.3% (56.3%–87.8%)	
≥3 y	67.9% (59.3%–77.8%)		84.8% (77.9%–92.3%)	

Younger age more Gr3 tumors
more infratentorial

COG Ependymoma ACNS0121: non-sig difference age < 3 years old



Median age 5.6 years (1.01 to 21.01)

Strata 3 and 4 (immediate postop RT):

- 5 yr OS Younger than 3: 87.4%, Age >3: 85.8%
- 5 yr EFS 62.9%, 70.5%

In conjunction with:

ACNS0121 and ACNS0831 enrollment ≥ 12 mos

Proton Ependymoma UF MGH 2021

Proton Therapy for Pediatric Ependymoma: Mature Results From a Bicentric Study

Daniel J. Indelicato, MD,* Myrsini Ioakeim-Ioannidou, MD,†
Julie A. Bradley, MD,* Raymond B. Mailhot-Vega, MD, MPH,*
Christopher G. Morris, MS,* Nancy J. Tarbell, MD,† Torunn Yock, MD,†
and Shannon M. MacDonald, MD†

Table 1 Patient, tumor, and treatment characteristics (N = 386)

Characteristic	No. of patients or other value	Local control	Progression-free survival
Median age at RT (range), y	3.8 (0.7-21.3)		
Patients ≤3 y old at RT	200	80%	69%
>3 y old	186	78%	67%

<18 months Ependymoma Delay RT

Childs Nerv 2020

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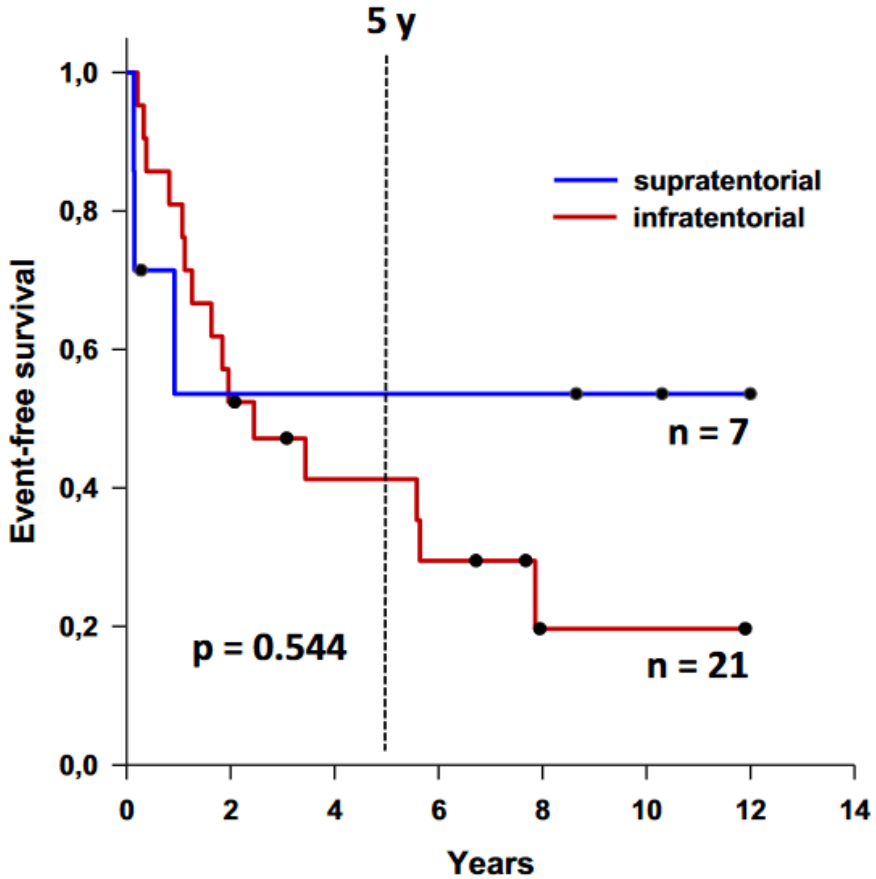
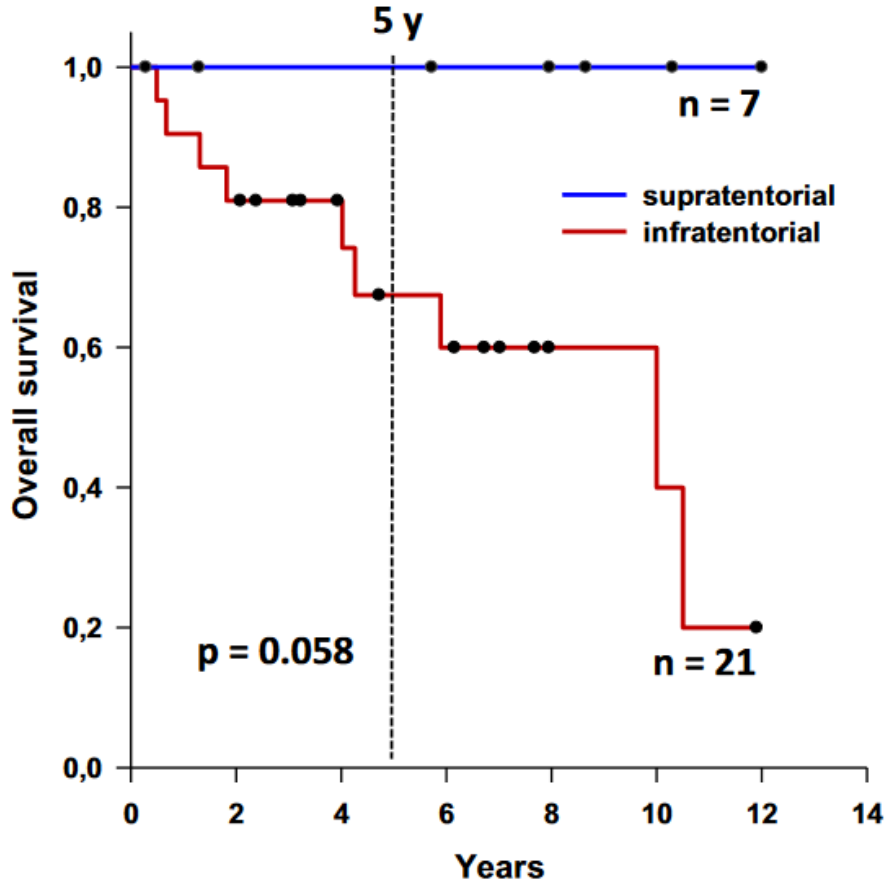
Ependymomas in infancy: underlying genetic alterations, histological features, and clinical outcome

Stephanie T. Jünger[1,2] · Felipe Andreiuolo[1] · Martin Mynarek[3] · Evelyn Dörner[1] · Anja zur Mühlen[1] · Stefan Rutkowski[3] · Andre O. von Bueren[3,4] · Torsten Pietsch[1]





- 28pts <18 months dx HIT2000-E protocols
- postpone RT age 18mos
- All PF: PFA, absent 1q gain
  - Still poor prog
- ST: RELA or YAP

SJCY07 Ependymoma Delay RT

Molecular grouping and outcomes of young children with newly diagnosed ependymoma treated on the multi-institutional SJYC07 trial

Neuro Oncol 2019

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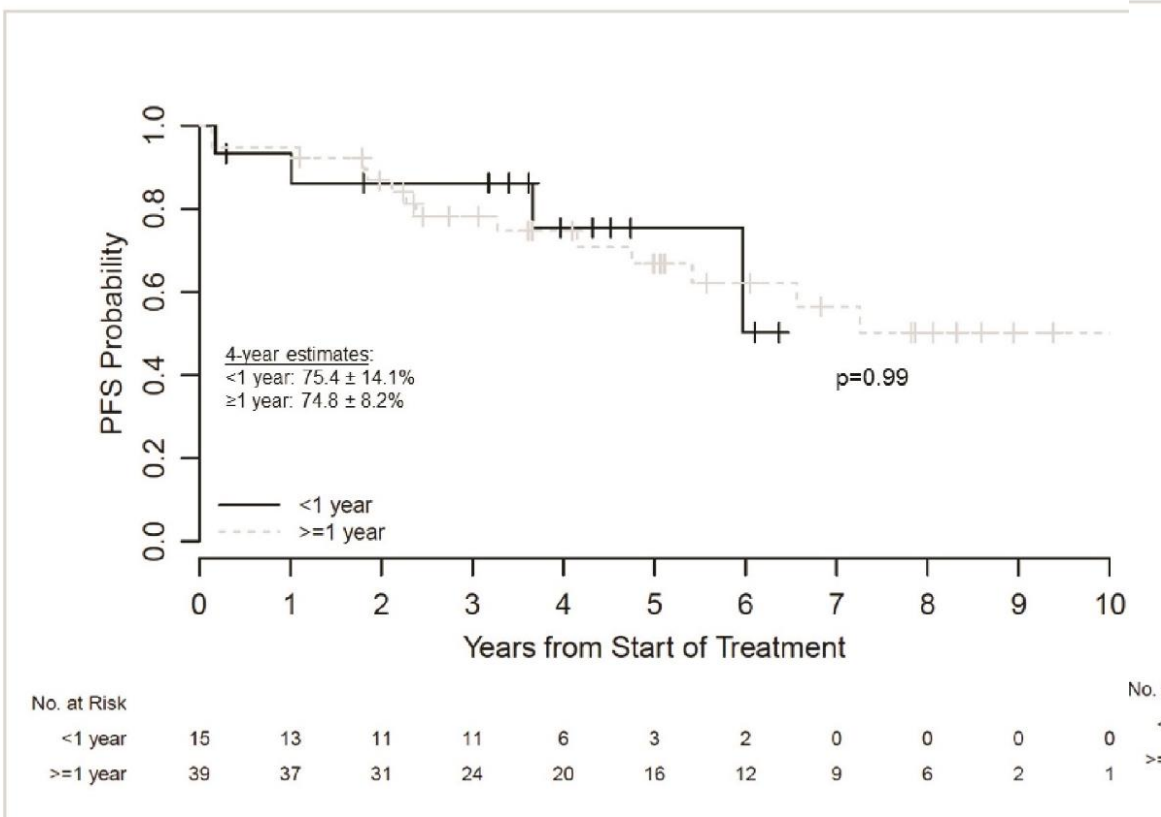
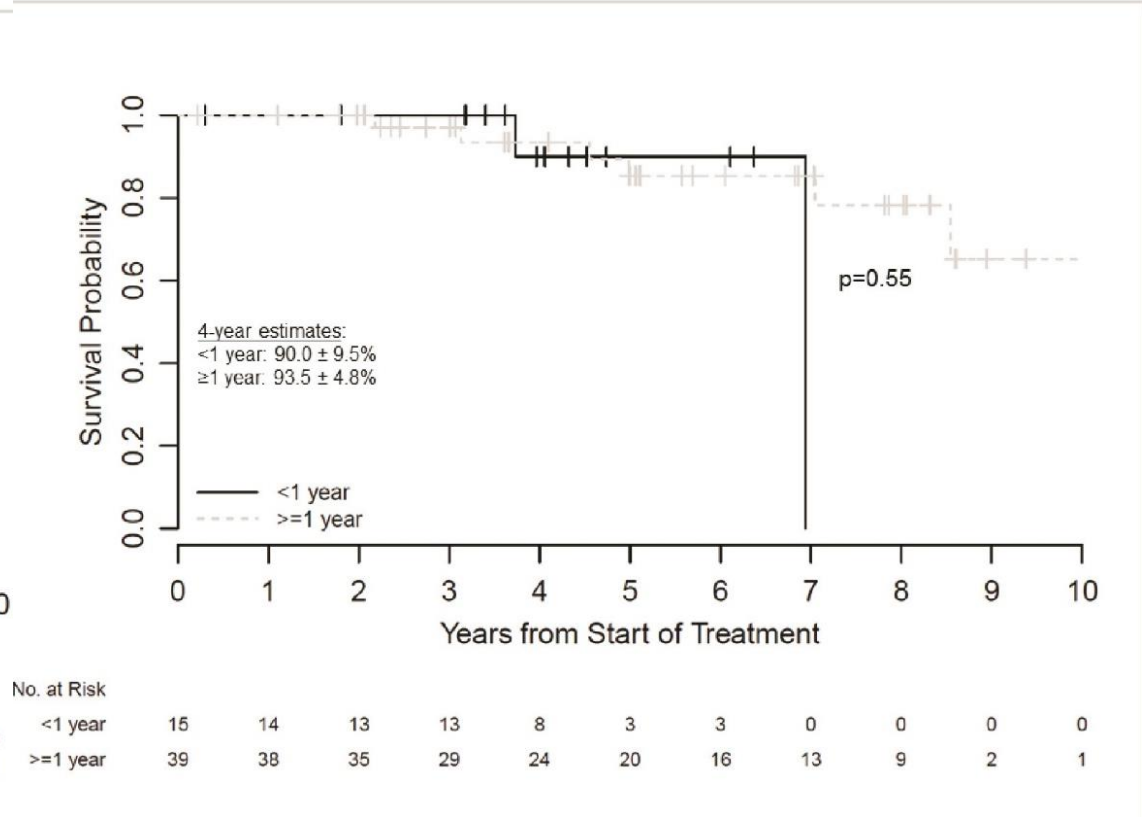
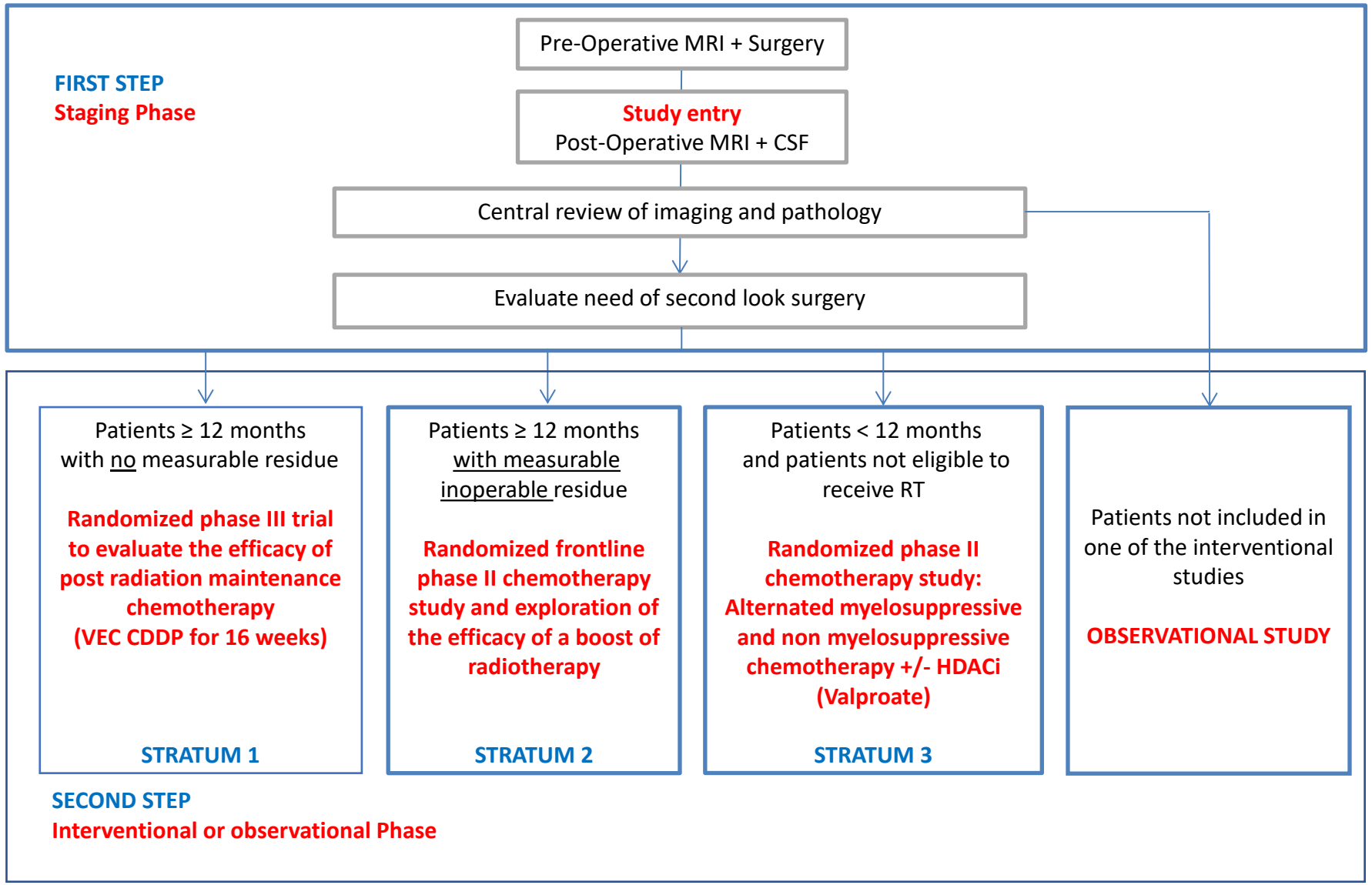
Worse PFS:
PFA-EPN-A, 1q gain
STR

15 pts age <12 mo (13 RT upfront): 4 progressed, 2 died





Ependymoma SIOPE II Study design



RT questions:

Boost RT 8Gy/2fx following 59.4Gy (Stratum 2)

No RT (age <12 months)

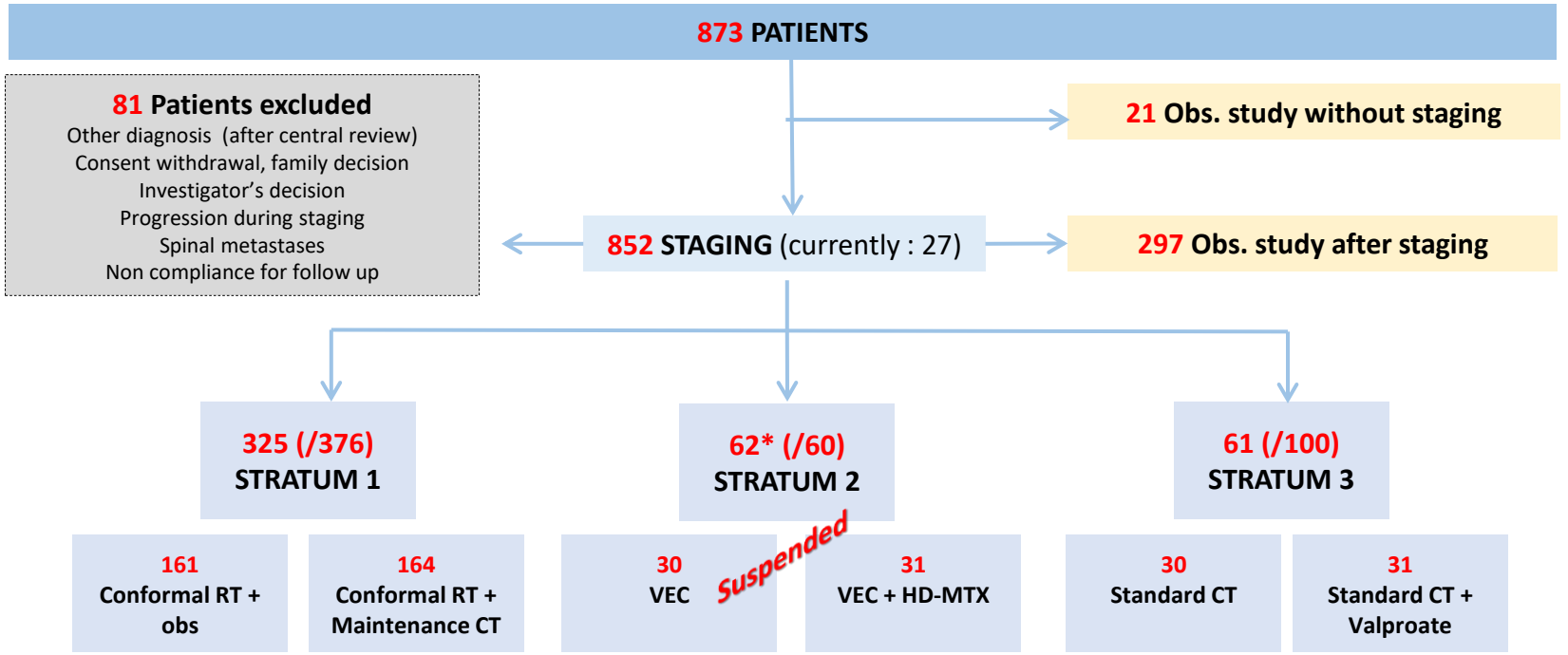
Post RT +/- chemotherapy for GTR

Overall recruitment

observational arm may include:
- who refused inclusion
- spinal ependymomas
- possible relapses
-patients who have a contraindication, as the inability to receive radiotherapy.

August 22nd, 2023

EUROPE



treatment by
by investigator choice

***60 evaluable patients**
COMPLETED ACCRUAL

Courtesy of Pierre Leblond

- Ependymoma

What is the lower age limit for upfront adjuvant RT?

Age < 3 (generally age 1-3) mixed results for worse prognosis with RT
-worse (AIEOP), non-sig worse (ACNS0121), similar (UF/MGH)

Postponing or avoiding RT with systemic therapy requires MORE study
-HIT RT at 18mo poorly for PFA, well for ST (RELA or YAP)
-SHYCO7 age <12 mo, poorly for PFA/1q gain, well for ST RELA

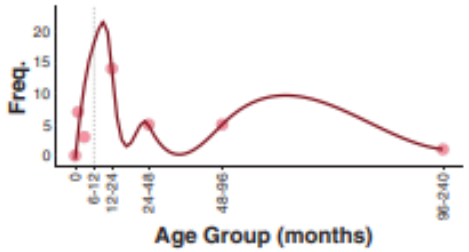
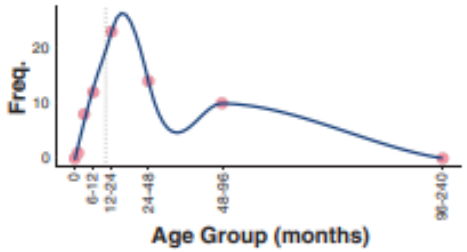
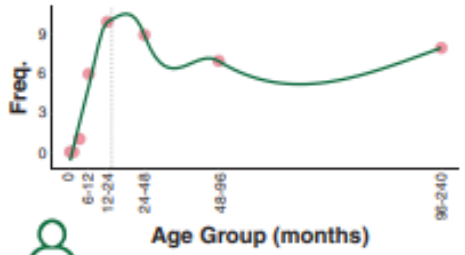
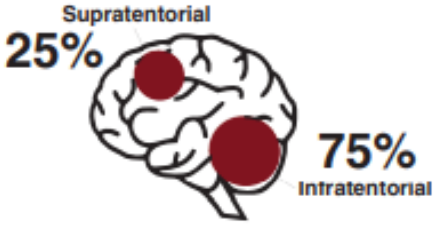
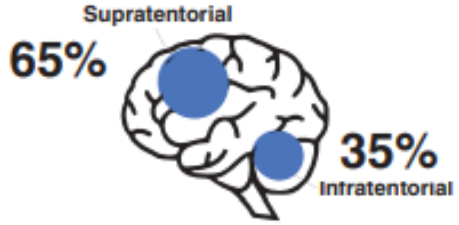
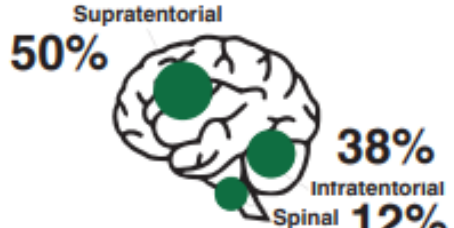
SIOPE II Stratum 3 (open to accrual) chemo +/- HDACi < 1year old

Purpose

- ATRT
  - Is RT necessary?

WHO 2021 ATRT

- Embryonal tumors
  - Other CNS embryonal tumors
    - Atypical teratoid/rhabdoid tumor

Molecular subgroup	ATRT-TYR	ATRT-SHH	ATRT-MYC
Torchia et. al., 2015 Torchia et. al., 2016 Han et. al., 2016 Johann et. al., 2016	Group2 Group2A hIC1 ATRT-TYR	Group1 Group1 hIC2 ATRT-SHH	Group2 Group2B hIC3 ATRT-MYC
Age and Gender Distribution	 Infant, 0-1 Year Median age: 12 Months 57% M 43% F	 Toddler, 2-5 Years Median age: 20 Months 55% M 45% F	 Older patients, >3 Years Median age: 27 Months 52% M 48% F
Tumor Location			

TYR ? Best prognosis

SHH ? Mets

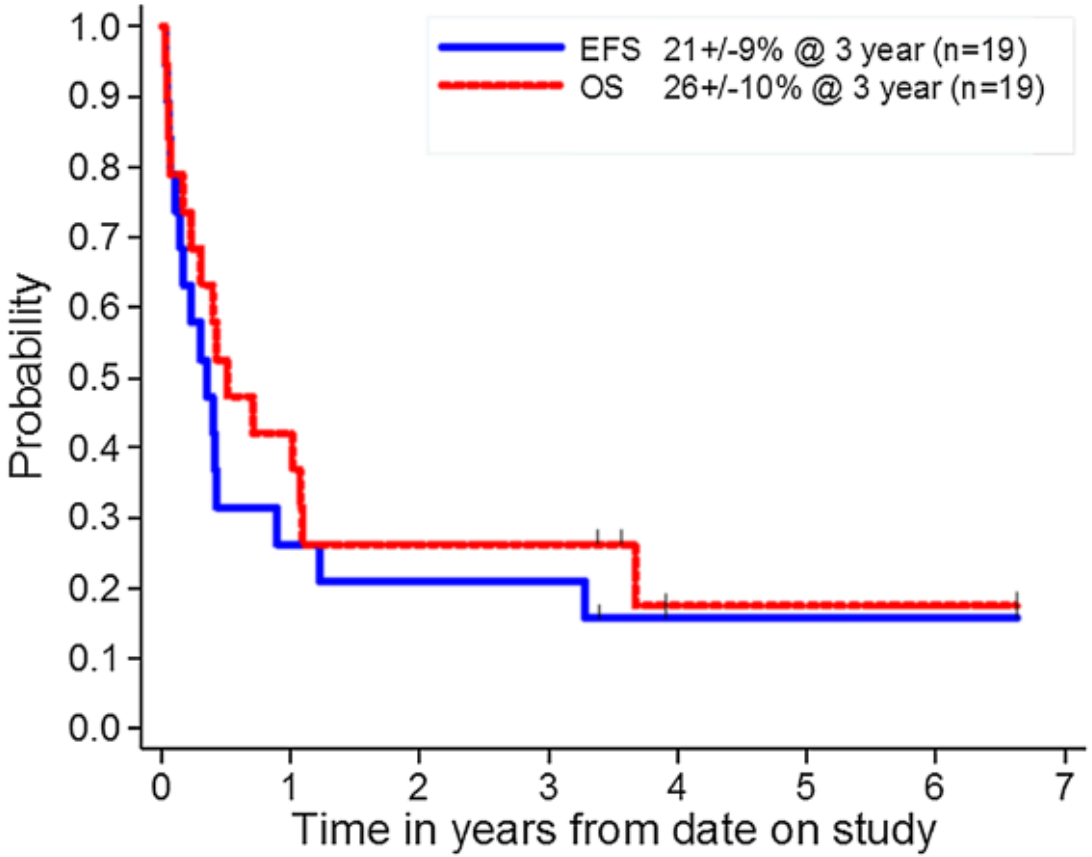
Purpose

- ATRT
  - Is RT necessary? Data:
    - No RT
    - RT with systemic therapy
    - M+

ATRT No RT:
Head Start III
19 pts High dose chemo with stem cell rescue, methotrexate

- No RT (per protocol, RT age < 6 for + residual disease only)
  - 2pts qualified for RT but did not receive

Age	
0< Age < 1.5yr	13 (68%)
1.5<= Age < 2yr	3 (16%)
2< = Age<3yr	3 (16%)



Purpose

- ATRT
  - Is RT necessary? Data:
  - RT with systemic therapy

J Neurooncol 2023

ATRT outcomes with RT

PPCR

Pediatric Proton/Photon Consortium Registry

Radiotherapy for Atypical Teratoid/Rhabdoid Tumor (ATRT) on the Pediatric Proton/Photon Consortium Registry (PPCR)

Andrew Roehrig[1] · Daniel J. Indelicato[2] · Arnold C. Paulino[3] · Ralph Ermoian[4] · William Hartsell[5] · John Perentesis[6] · Christine Hill-Kayser[7] · Jae Y. Lee[8] · Nadia N. Laack[9] · Victor Mangona[10] · Iain MacEwan[11] · Bree R. Eaton Sara Gallotto[13] · Benjamin V. M. Bajaj[13] · Paul D. Aridgides[1] · Torunn I. Yock[13]

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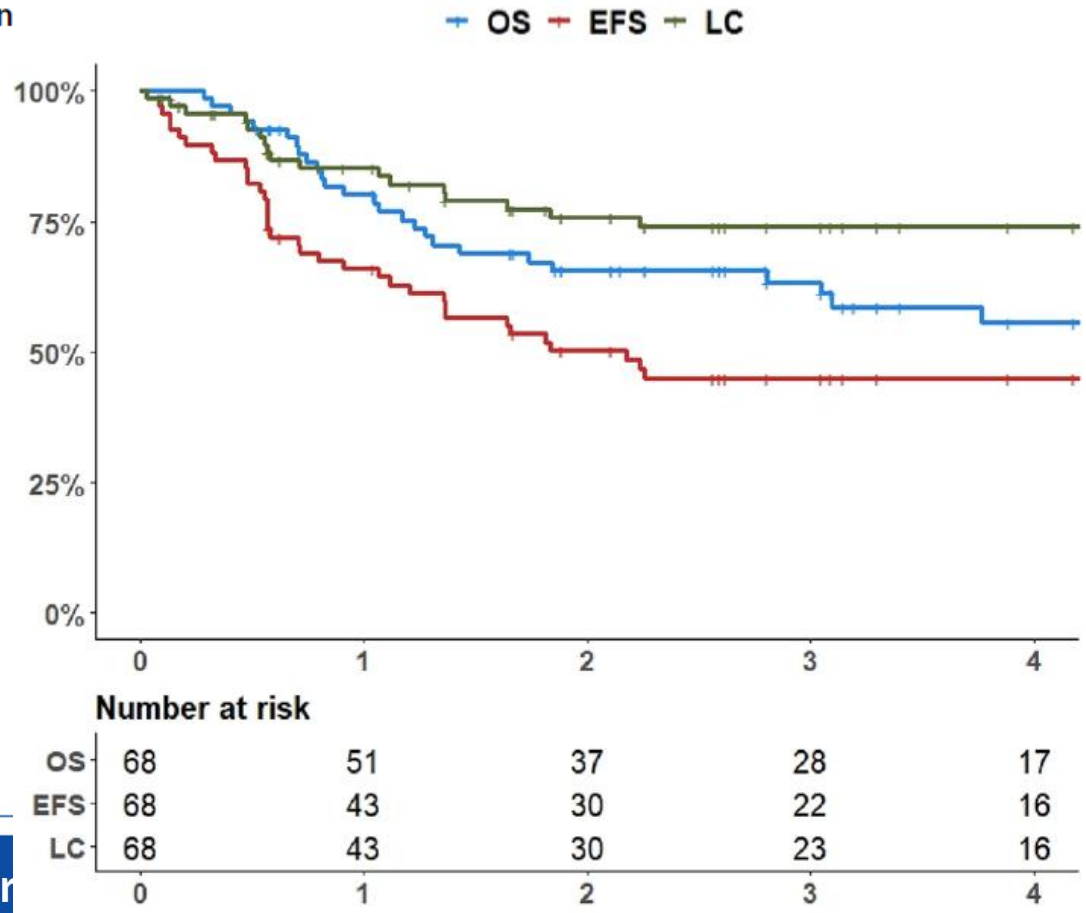
68 pts (60 M0, 8 M+)

-median followup 40.8 mos

4 year OS 56%

-ACNS0333 RT: 58.8%



Median 2.6 years old RT

In conjunction with:

Childhood Cancer International · IFSO · PROS Pediatric Radiation Oncology Society

PPCR ATRT M0: no diff focal vs CSI

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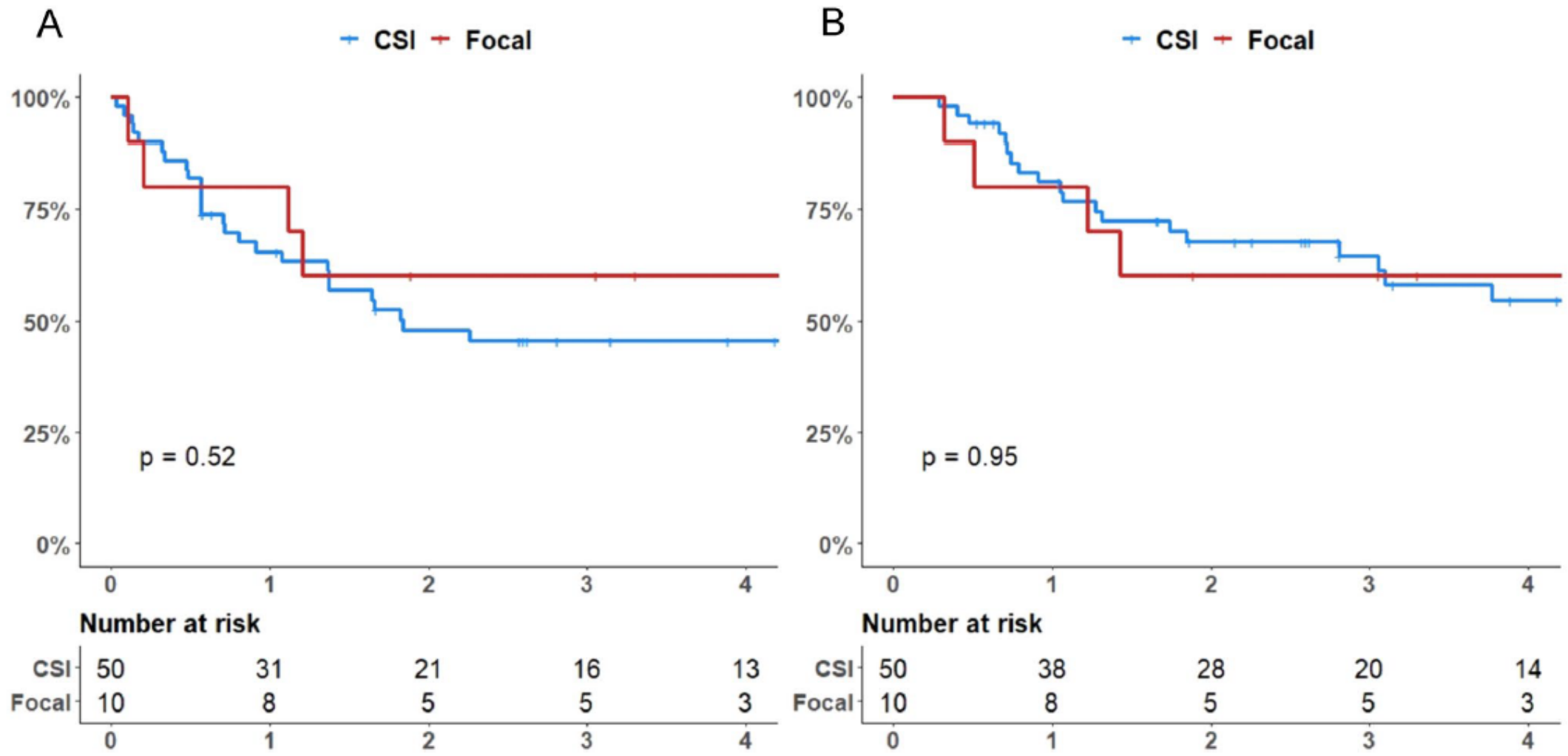


Fig. 4 Event Free Survival (**A**) and Overall Survival (**B**) of localized disease (M0) patients (n = 60) according to delivery of either craniospinal (CSI, blue line) or Focal Radiation (red line). P values represent log rank tests

PPCR
n/Photon Consortium Registry

PPCR ATRT M0: younger than 3 non-sig worse

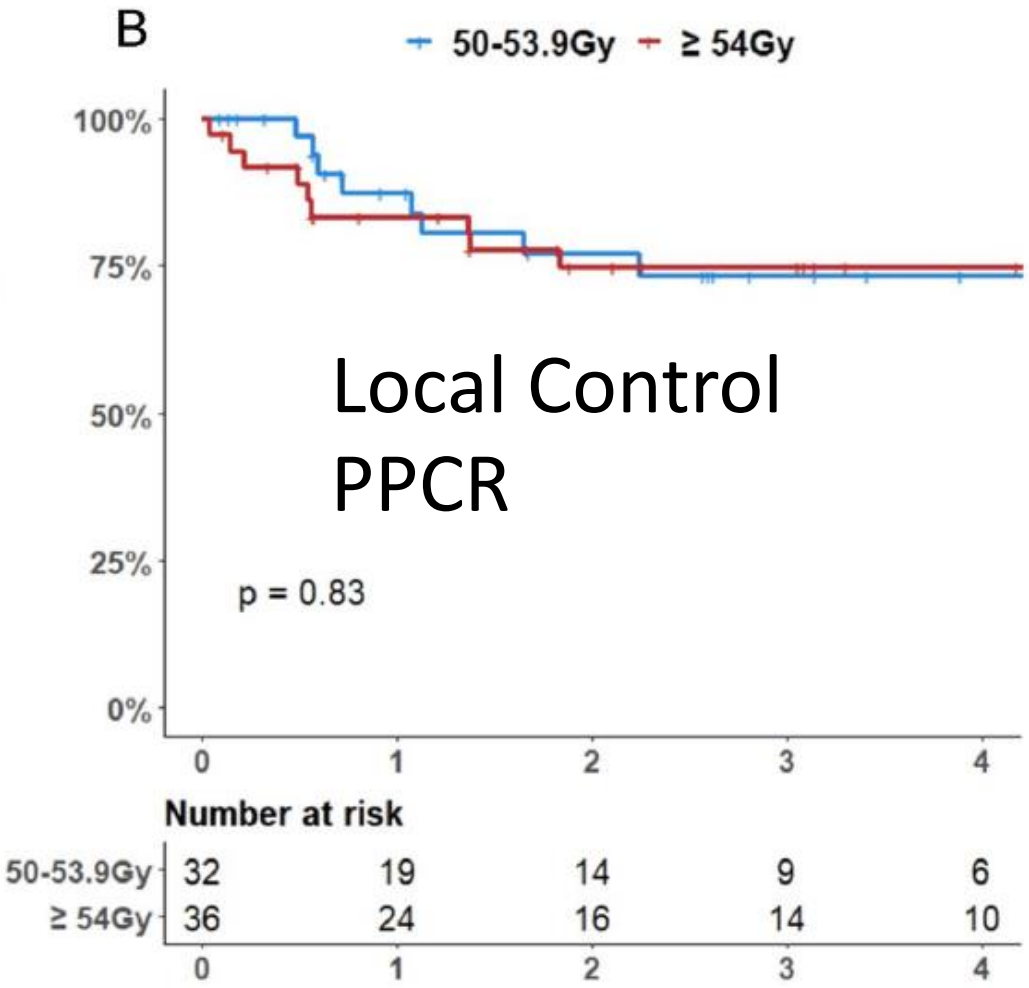
Table 1. Survival Outcomes Among M0

				Survival Rates (%)			
Outcome	**Age at RT (years)**	**N[1]**	**Event [1]**	Year 3	Year 4	**p-value[2]**	**HR[3]**
EFS						0.110	
	≤3	35	21	40.4	40.4		—
	>3	25	10	58.6	58.6		0.54
OS						0.119	
	≤3	35	17	55.3	46.8		—
	>3	25	7	75.6	67.2		0.50
LC						0.649	
	≤3	35	9	76.1	76.1		—
	>3	25	5	79.4	79.4		0.77

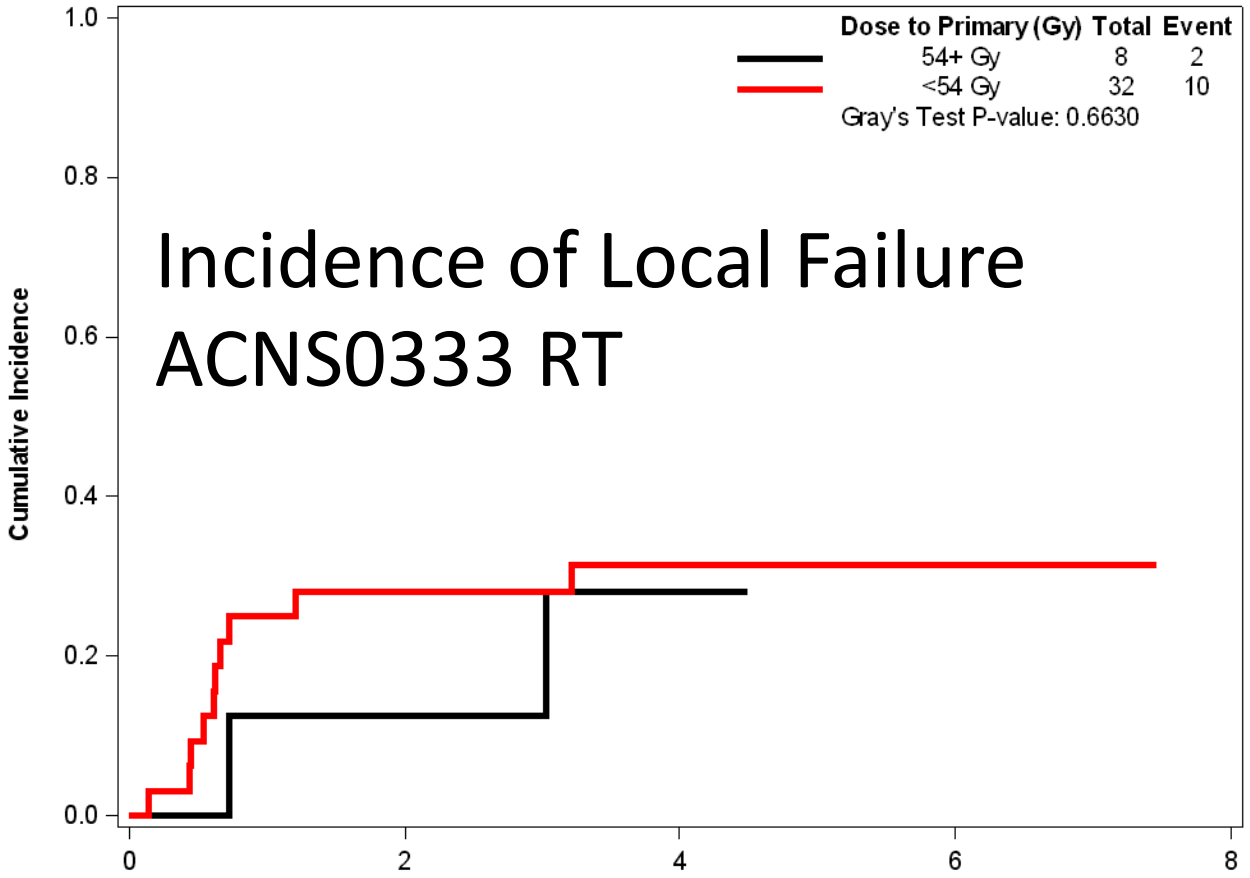
[1]n
[2]Log-rank test/Fine-Gray test
[3]HR = Hazard Ratio

PPCR
Pediatric Proton/Photon Consortium Registry

ATRT RT Primary no ≥ 54Gy



Local Control
PPCR



Incidence of Local Failure
ACNS0333 RT

CHILDREN'S ONCOLOGY GROUP

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SURVIVAL AND PATTERNS OF FAILURE FOLLOWING RADIATION (RT) IN PATIENTS WITH ATYPICAL TERATOID RHABDOID TUMORS (ATRT) ON ACNS0333: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Jared Deck, Paul Aridgides, Mark Krailo, Allen Buxton, Anita Mahajan, Thomas Merchant, Doug Strother, Jaclyn Biegel, Alexander Judkins, Ben Ho, Claire Mazewski, Victor Lewis, Ian Pollack, Maryam Fouladi, Alyssa Reddy

UPSTATE MEDICAL UNIVERSITY

In conjunction with:
Childhood Cancer International
IPSO
PROS PAEDIATRIC RADIATION ONCOLOGY SOCIETY

COG ACNS0333 Reddy 2020
Primary endpoint: Improved 4 yr EFS (p <0.0005)

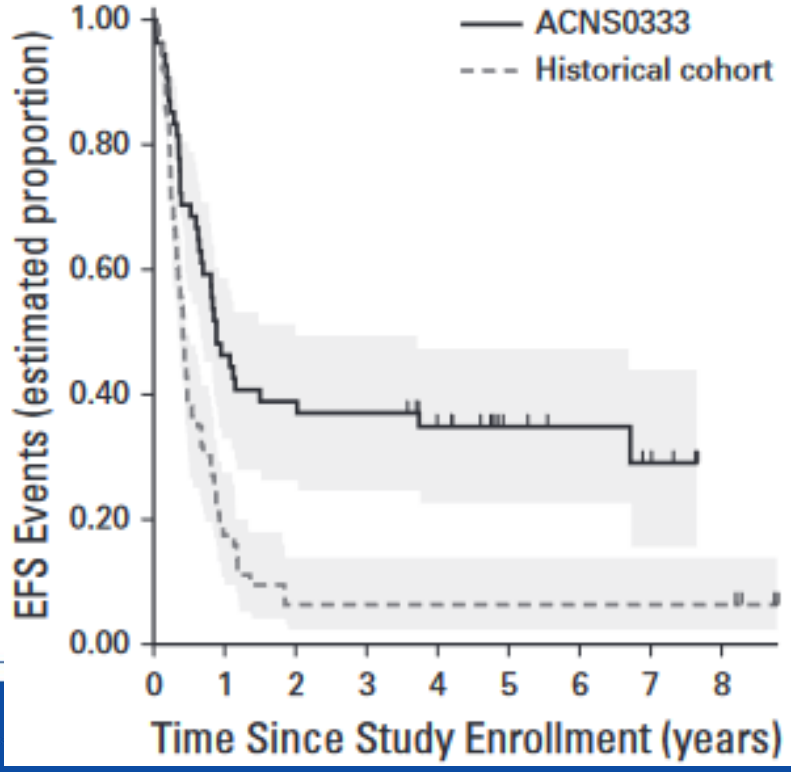
Non-randomized phase III trial of maximal safe surgery, 2 cycles induction (methotrexate, vincristine, etoposide, cyclophosphamide, cisplatin), 3 cycles consolidation with stem cell rescue (thiotepa, carboplatin) and **Radiation**

Radiation:

M0: Focal mandatory

M+: CSI optional

<36mo	≥ 36mo
50.4Gy	54Gy
23.4Gy	36Gy

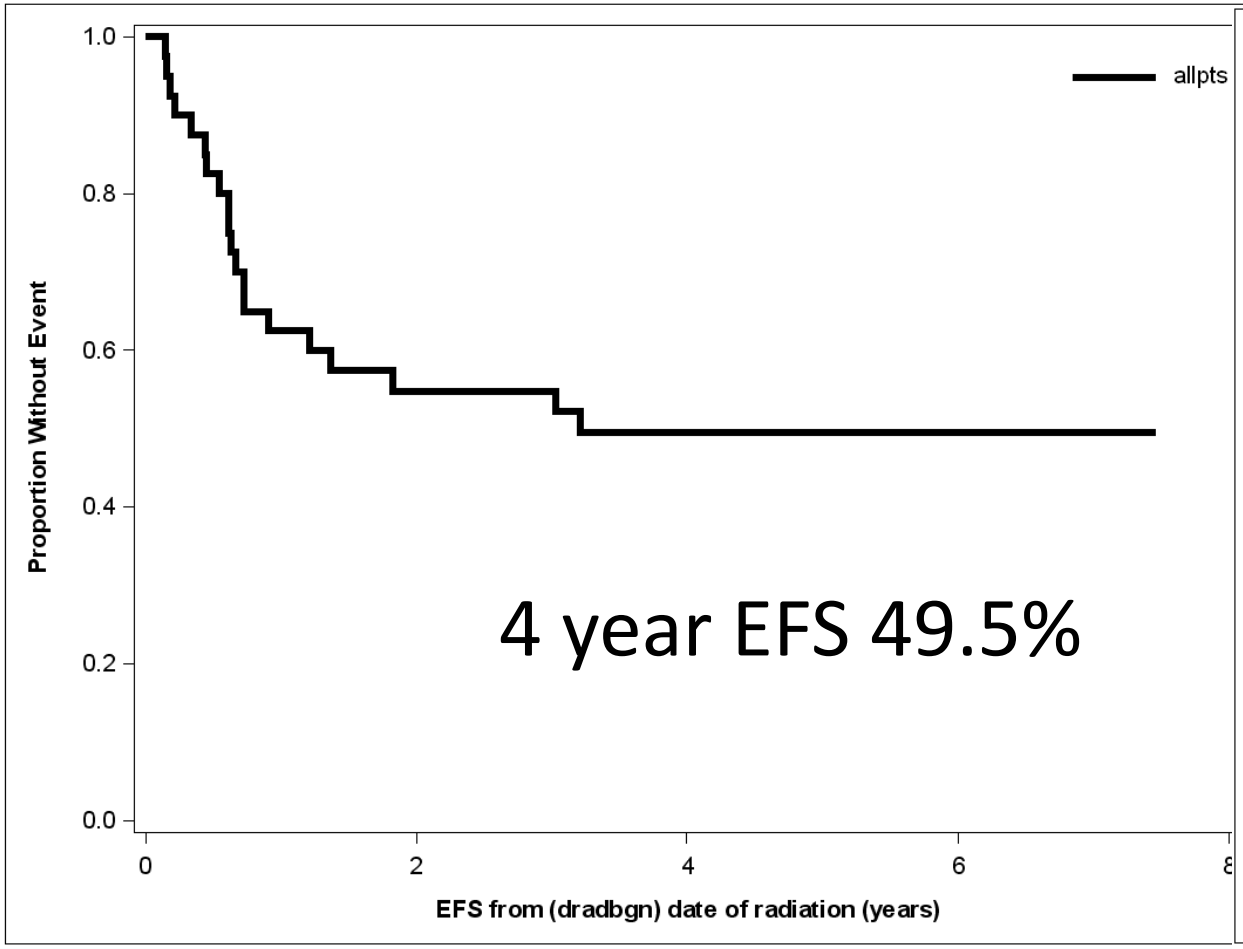


In conjunction with:

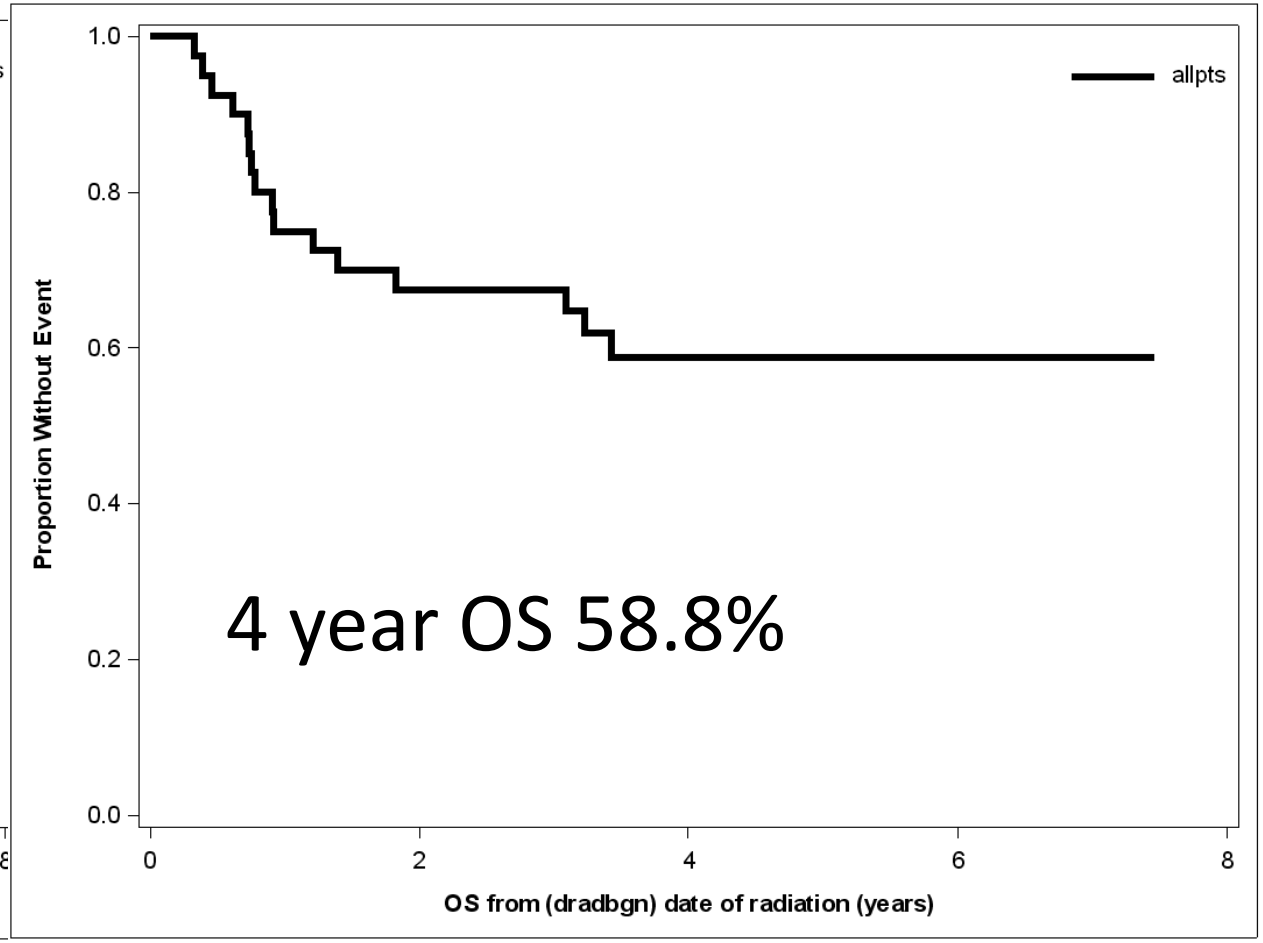
Reddy JCO 2020

ATRT COG ACNS0333 RT: Secondary analysis of 40 (of 65) RT pts

29 M0 and 11 M+, median age RT 1.8 years (0.7-13.9)

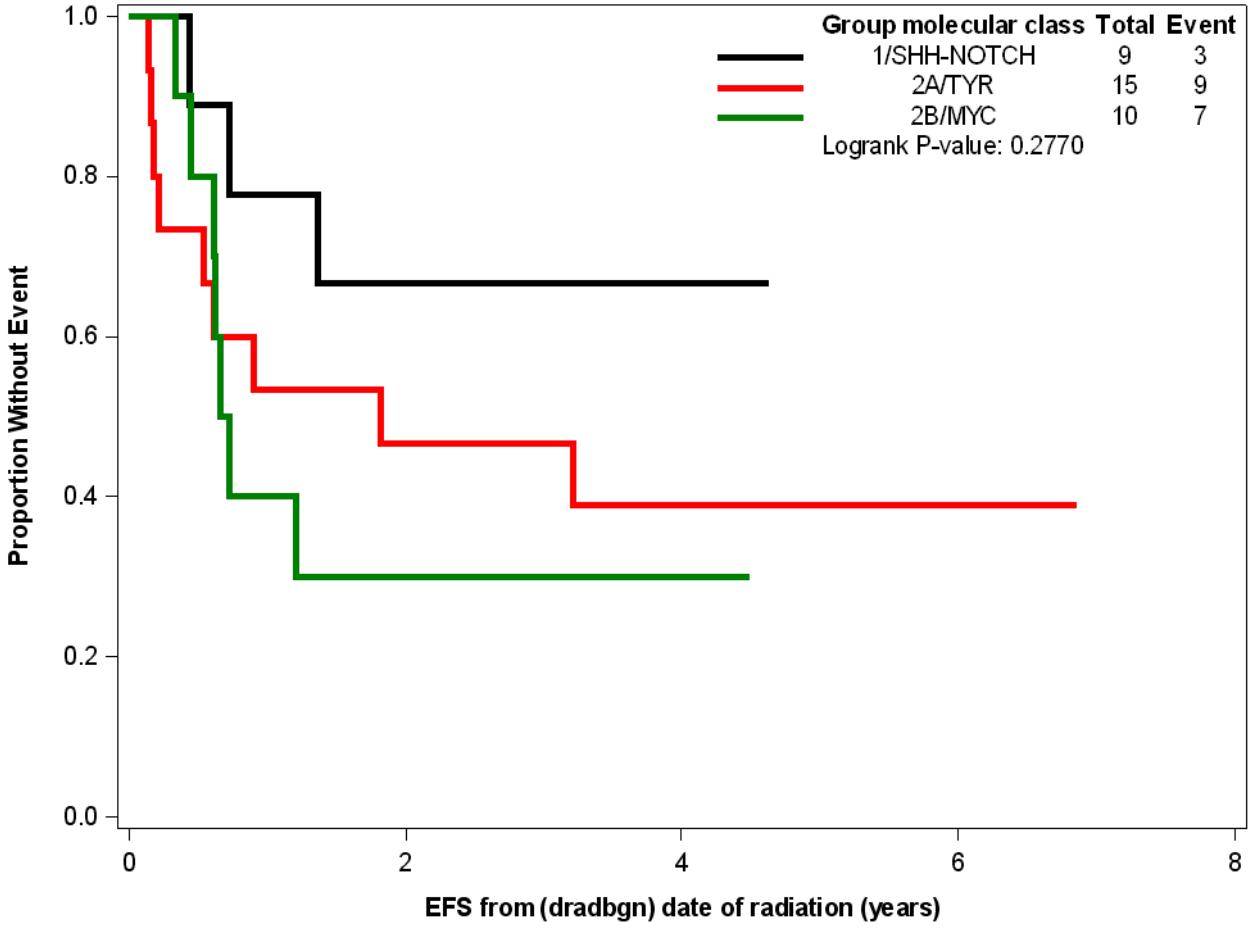


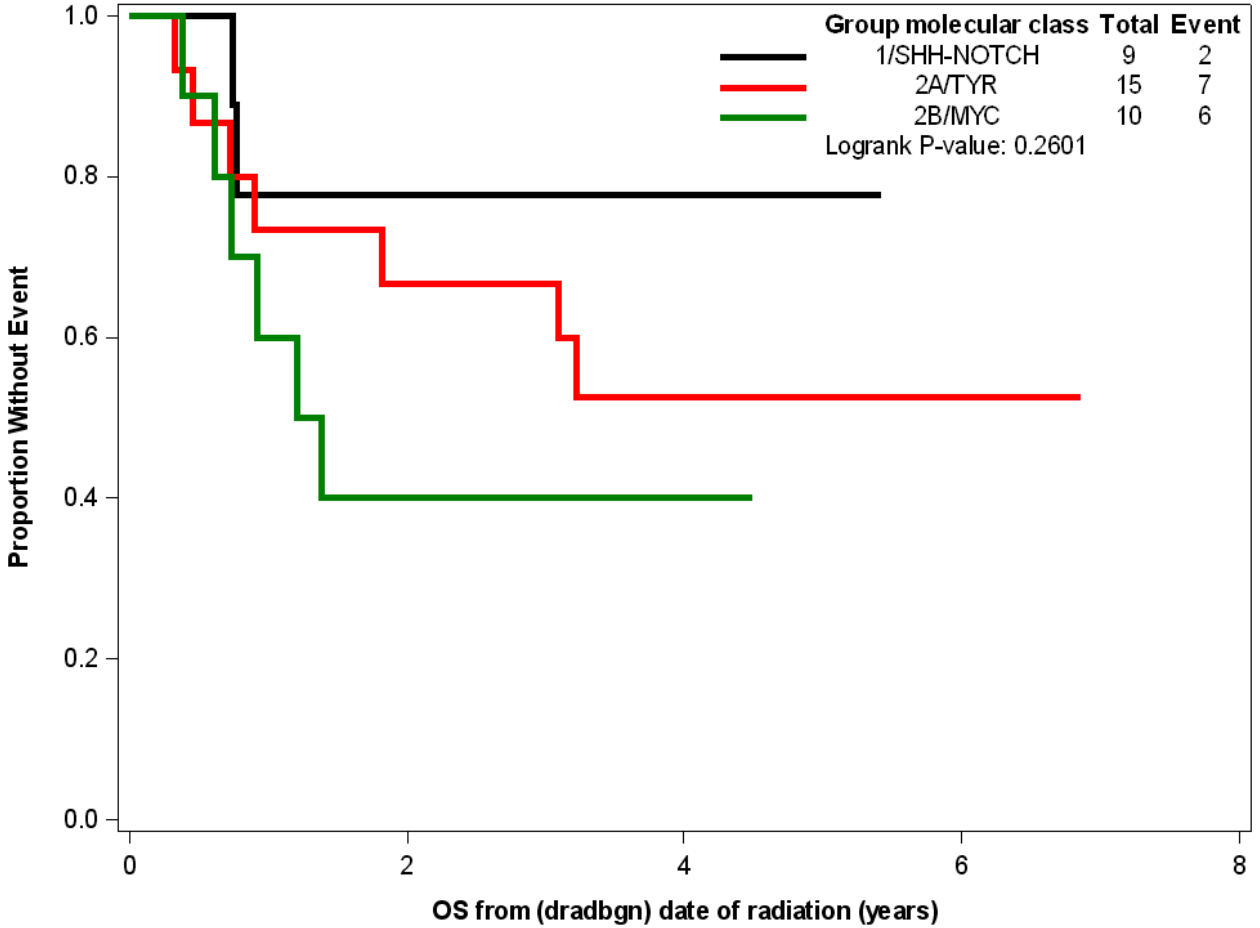
4 year EFS 49.5%



4 year OS 58.8%

ACNS0333 RT EFS/OS Molecular Group





No difference SHH-NOTCH/TYR/MYC

Only 9 pts SHH/NOTCH possibly better?

ACNS0333 Pre-RT Response, all patients: M0 Focal RT (29), M+ CSI (6), M+ Focal (5)

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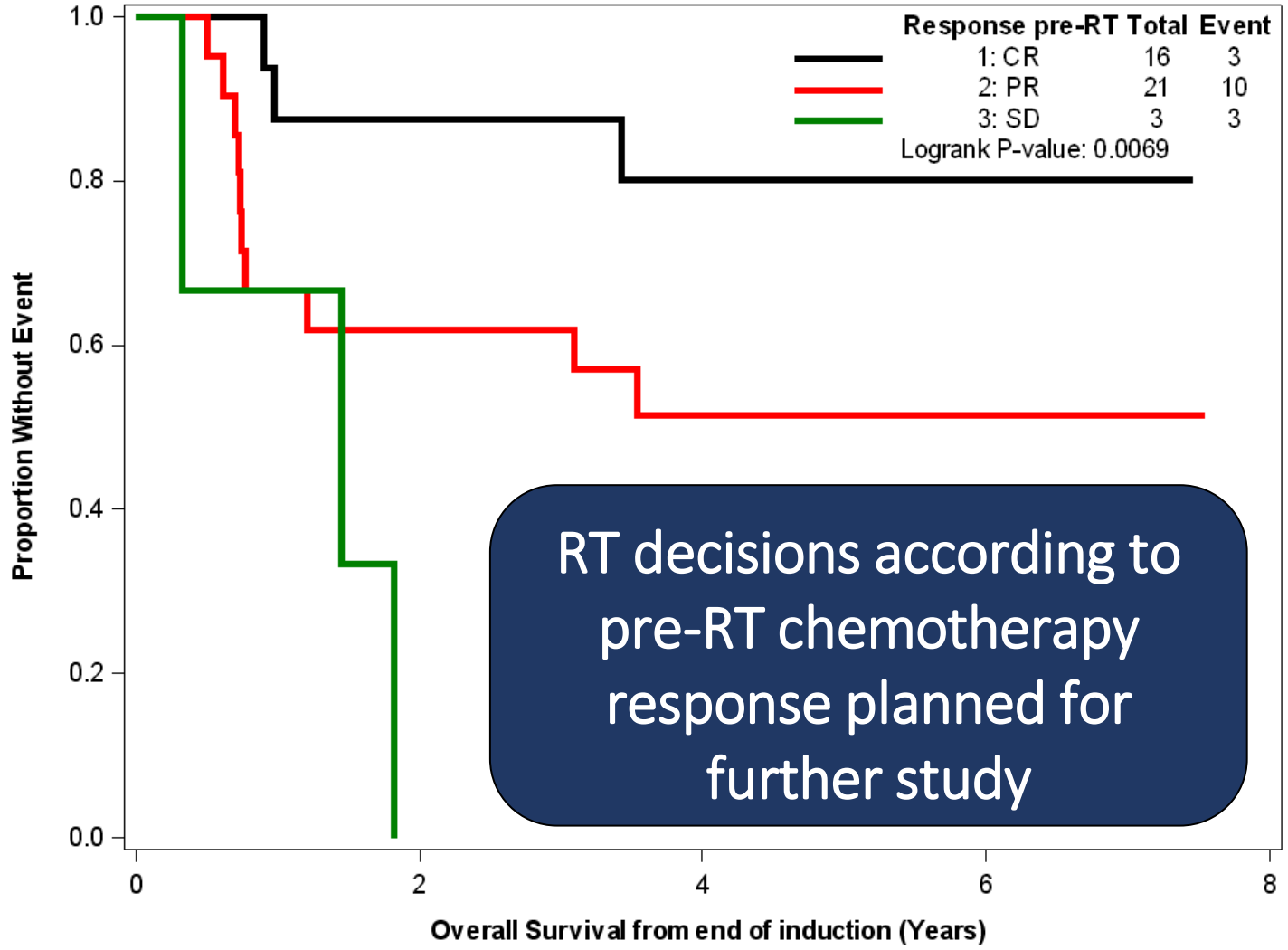
- MRI brain and spine immediately prior to radiation start
- Favorable responses (CR, PR) associated with improved OS (p=0.0069)

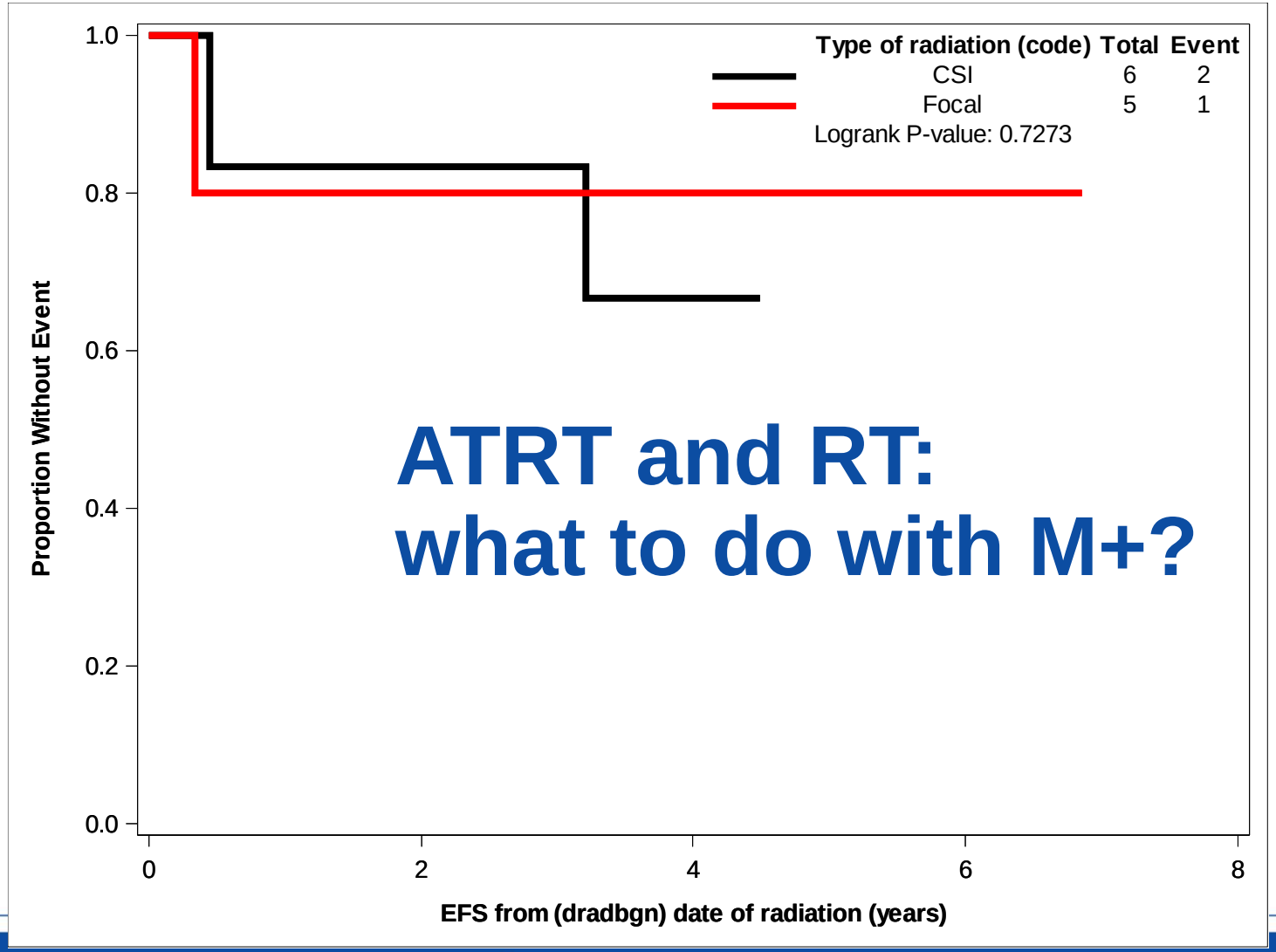


RT decisions according to pre-RT chemotherapy response planned for further study

In conjunction with:
Childhood Cancer International
IPSO
PROS PAEDIATRIC RADIATION ONCOLOGY SOCIETY

ACNS0333 RT M+

- 11 pts M+ RT
  - 5 focal RT
  - 2 CSI 23.4Gy
  - 4 CSI 36Gy
- Limited by low pt numbers
- No signal CSI improvement



Focal versus craniospinal radiation for disseminated atypical teratoid/rhabdoid tumor following favorable response to systemic therapy

Paul D. Aridgides[1] | Anita Mahajan[2] | Bree Eaton[3] | Dongliang Wang[4] | Beate Timmerman[5] | Michael C. Früwald[6] | Karolina Nemes[6] | Jared Deck[1] | Kai Yamasaki[7] | Katja Von Hoff[8] | Lucie Lafay-Cousin[9] | Alyssa Reddy[10] | Andrea C. Lo[11]

1. OS of M+ ATRT who receive radiation?

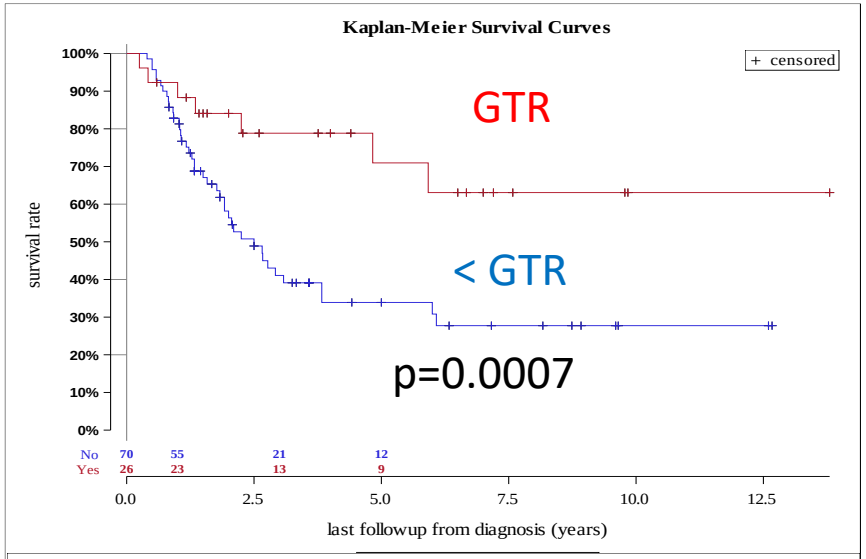
2. Any M+ disease factors in RT patients that are prognostic?

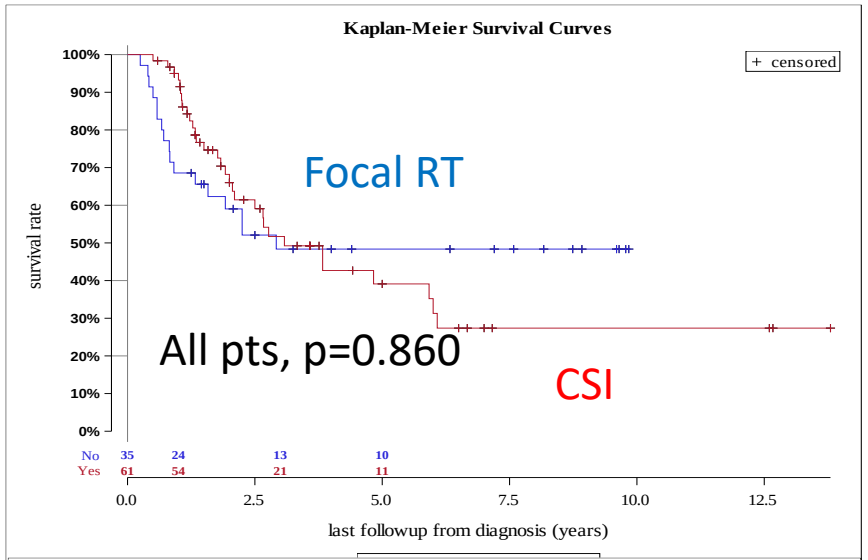
3. Any RT factors for M+ ATRT that are prognostic?

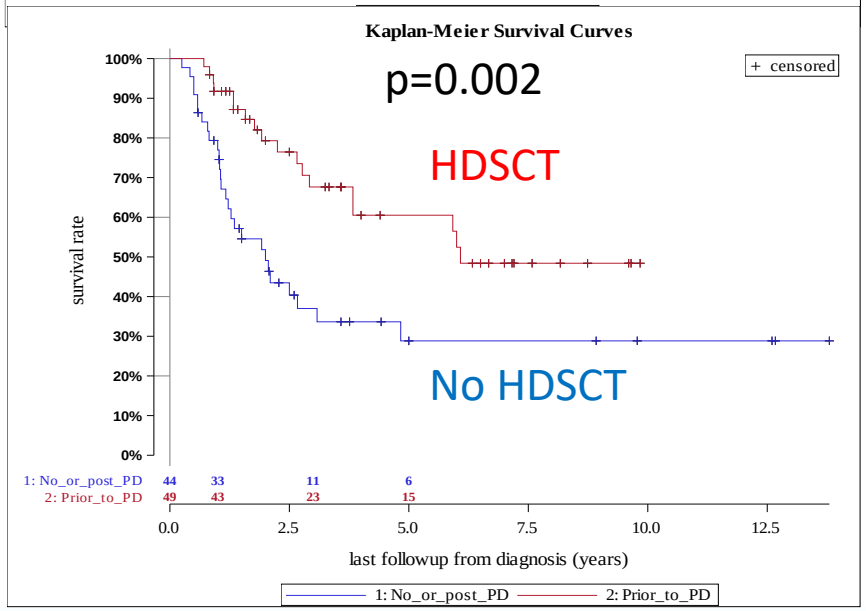
4. Impact of systemic therapy/response?

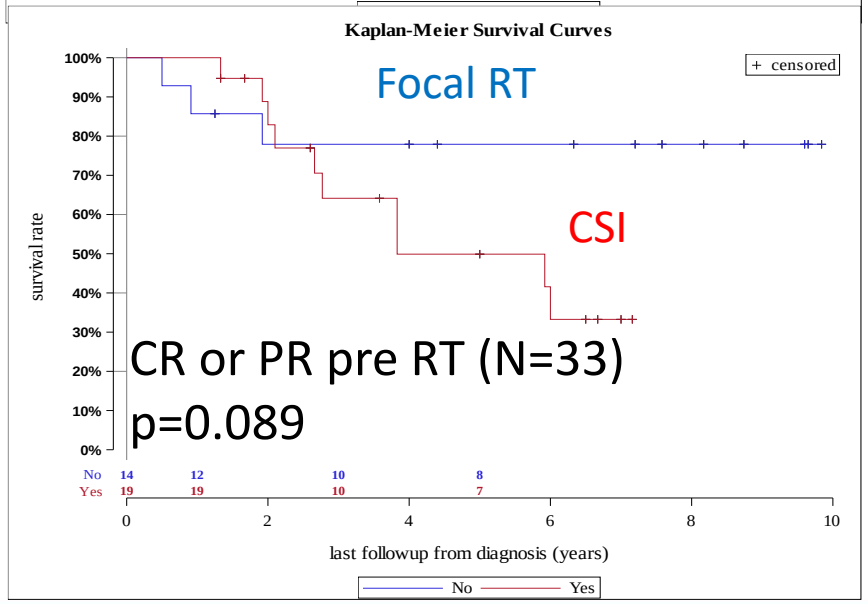
Formal librarian search, 4 rad onc screeners, collaborators invited from identified studies

M+ ATRT RT Meta-Analysis (N=96) : univariate OS









Focal RT after CR or PR interesting for further study

M+ ATRT RT MVA (N=57)

Variable	Hazard Ratio	95% confidence interval	Overall p value
High dose chemotherapy with stem cell recue (No vs Yes)	2.447	0.877, 6.825	0.072
Gross total resection achieved (No vs Yes)	4.22	1.349, 13.201	0.012
Age 3 or older at time of radiation (No vs Yes)	1.223	0.506, 2.956	0.614
Pre-radiation chemotherapy response (complete response, partial response, or stable disease/progressive disease)	-	-	0.020
Craniospinal Radiation (No vs Yes)	1.022	0.396, 2.636	0.953

OS significant:

GTR

Pre-RT chemotherapy response

Proposed RT ACNS2232 Response based Primary (50.4 or 54Gy) and Mets (CSI or Focal)

	Best Response		RT Dose (cGy) and Volume			
	Primary	Mets	CSI	Primary	Residual Mets	
M0, any age	CR	N/A	0	5040	N/A	
	PR or SD	N/A	0	5400[1]	N/A	
M+, < 36 months age at RT	CR	CR	0	5040	0	
	PR or SD	CR	0	5400[1]	0	
	CR	PR or SD	0	5040	4500-5040	Option 1
			1800	5040	4500-5040	Option 2
	PR or SD	PR or SD	0	5400[1]	4500-5040	Option 1
			1800	5400[1]	4500-5040	Option 2
M+, ≥ 36 months age at RT	CR	CR	0	5040	0	
	PR or SD	CR	2340	5400	0	
	Any	PR	2340	5400	4500-5040	
	Any	SD	3600	5400	4500-5040	

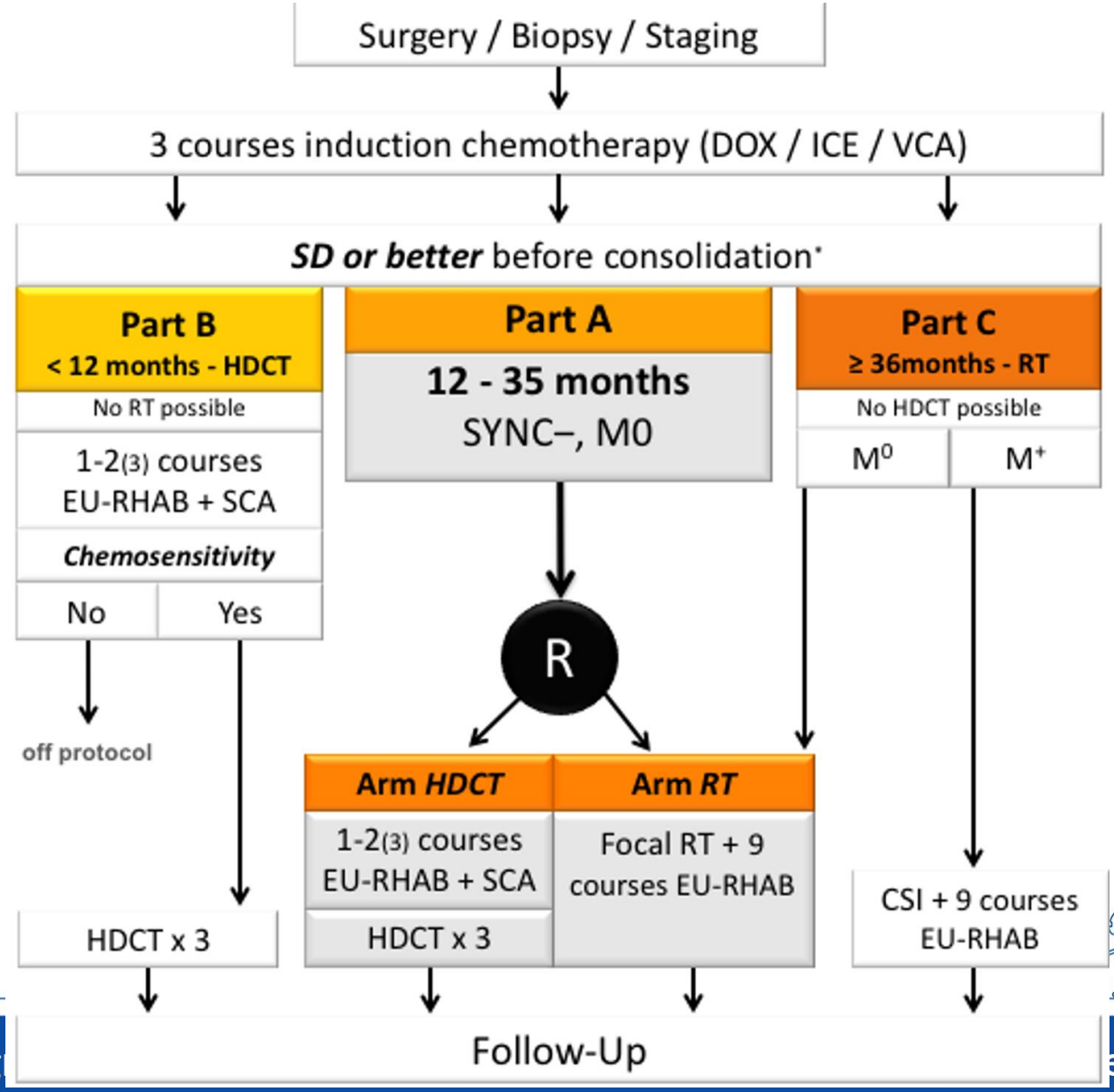
Open European SIOPE ATRT01

152 patients goal

M. Fruhwald (Sept 2023)

- 31 enrolled, 8 randomized
- 5 finished therapy in CR

Primary endpoint: 2-year OS



M0 12-35 months (randomized)

Focal RT versus HDCT

In conjunction with:

- ATRT

- Is RT necessary? Data:
  - No RT: outcomes poorer than with RT
    OPEN SIOPE ATRT01 Trial
  - RT with systemic therapy
    50.4 or 54Gy Primary Control ~80%
    4yr OS 55-60%
  - M+
    Low dose or Focal RT according to chemotherapy being considered for prospective study