Radiotherapy for Infant Brain Tumors

Panel 15: The Changing Role of Radiotherapy In Childhood Cancer

Anita Mahajan MD
MD Anderson Cancer Center
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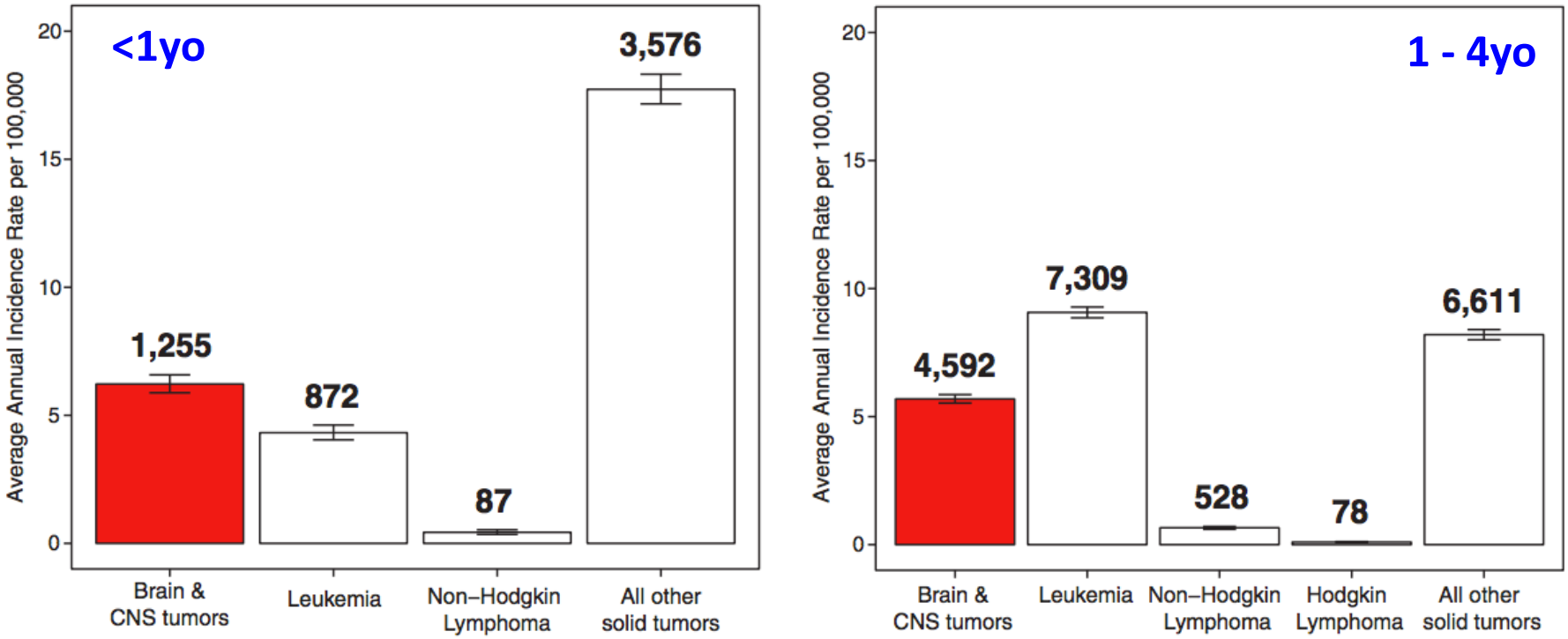
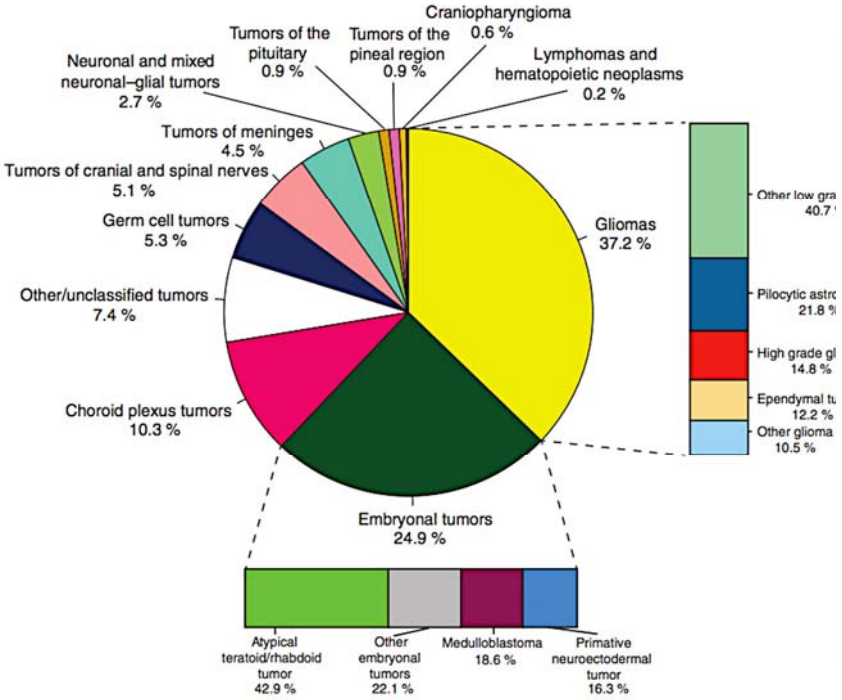
Incidence of Primary Brain Tumors in Young Children

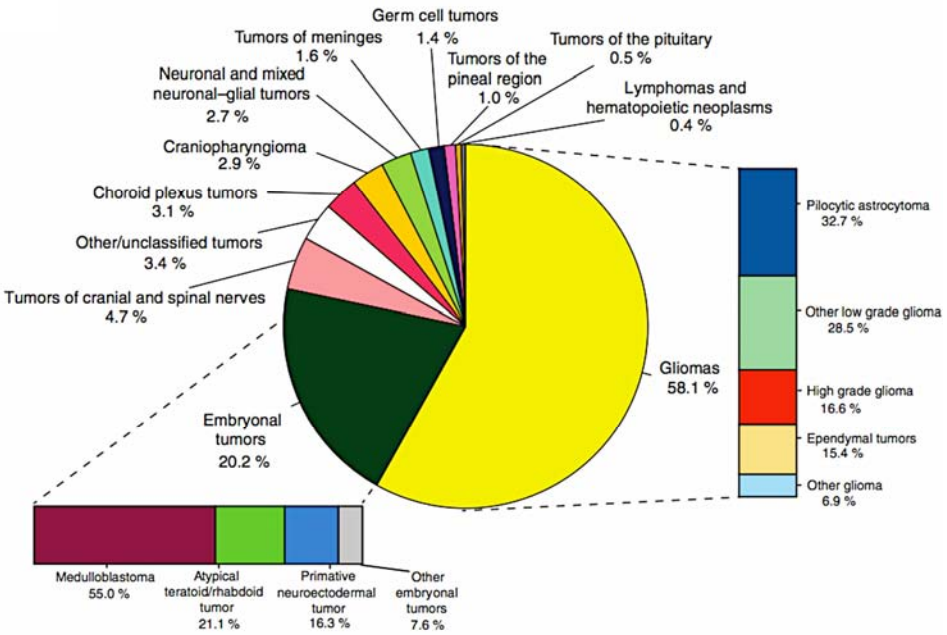


CBTRUS 2007-11, USCS 2007-2001

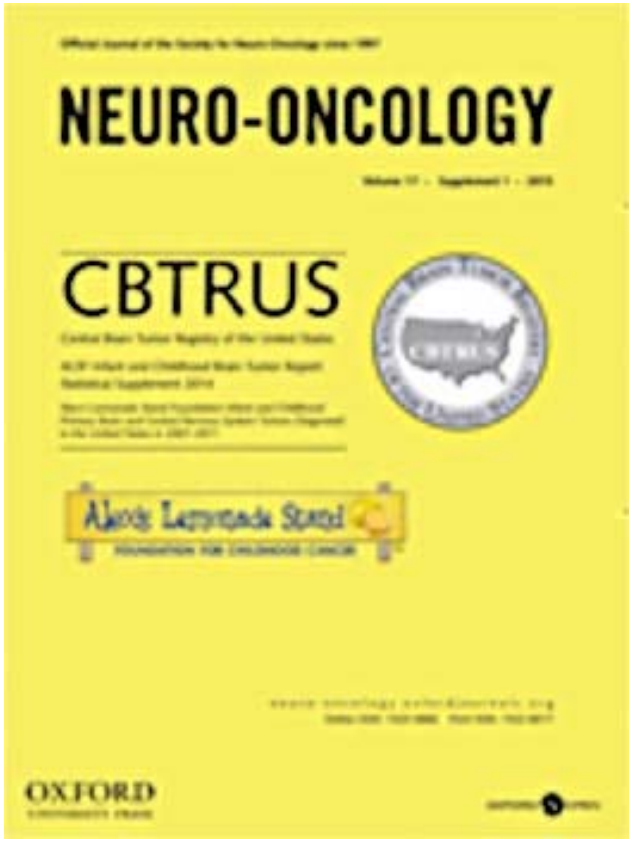
Tumor Histologies



<1 y.o.

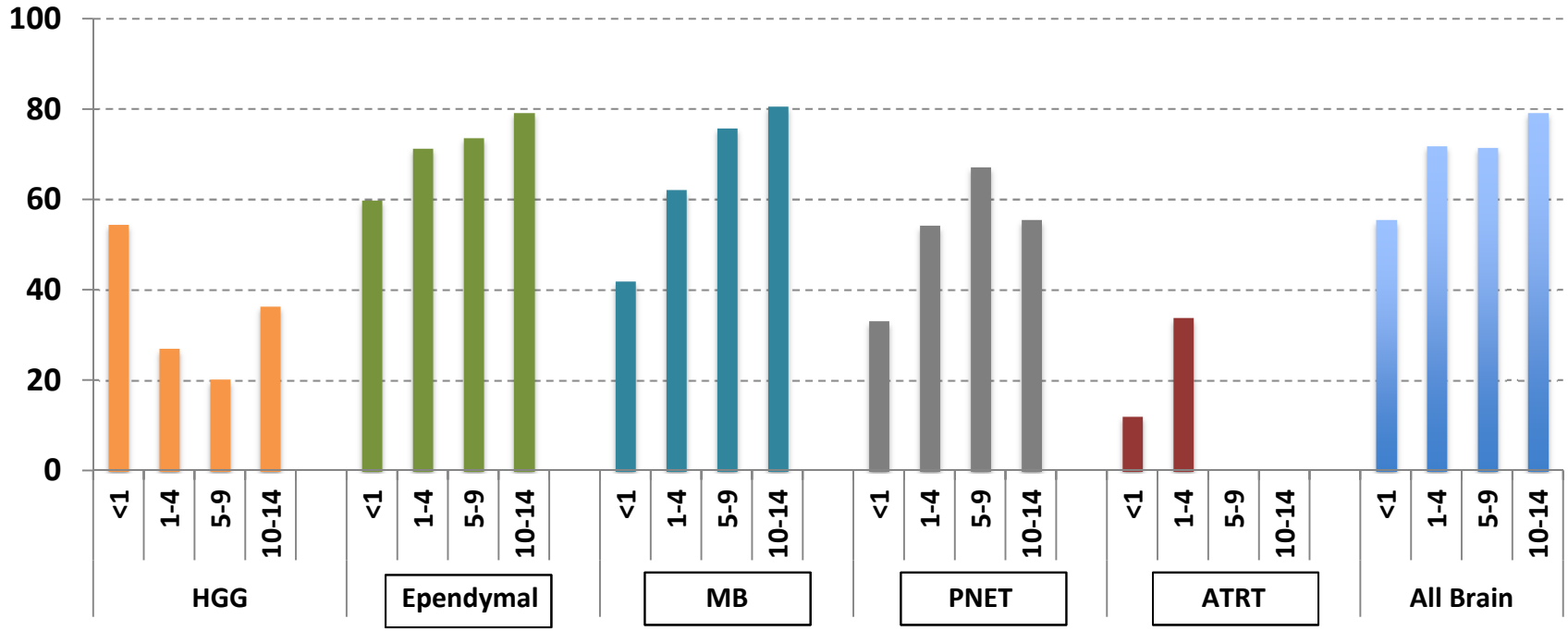


1-4 y.o.



Histology	N	% of All Tumors	Median Age	Rate
Gliomas	8,487	52.9%	6.0	2.78
Pilocytic astrocytoma	2,821	17.6%	7.0	0.93
Other low grade glioma	2,296	14.3%	6.0	0.75
High grade glioma	1,784	11.1%	7.0	0.59
Ependymal tumors	879	5.5%	4.0	0.29
Other glioma	707	4.4%	7.0	0.23
Choroid plexus tumors	362	2.3%	1.0	0.12
Tumors of the pineal region	701	4.4%	6.5	0.23
Neuronal and mixed neuronal-glial tumors	140	0.9%	9.0	0.05
Embryonal tumors	2,413	15.0%	4.0	0.79
Medulloblastoma	1,494	9.3%	6.0	0.49
Primitive neuroectodermal tumor	360	2.2%	3.5	0.12
Atypical teratoid/rhabdoid tumor	363	2.3%	1.0	0.12
Other embryonal tumors	196	1.2%	1.0	0.06
Tumors of cranial and spinal nerves	758	4.7%	7.0	0.25
Tumors of meninges	458	2.9%	9.0	0.15
Lymphomas and hematopoietic neoplasms	70	0.4%	6.0	0.02
Germ cell tumors	590	3.7%	9.0	0.19
Tumors of the pituitary	625	3.9%	12.0	0.20
Craniopharyngioma	648	4.0%	8.0	0.21
Other/unclassified tumors	792	4.9%	9.0	0.26
TOTAL[b]	**16,044**	**100.0%**	**7.0**	**5.26**

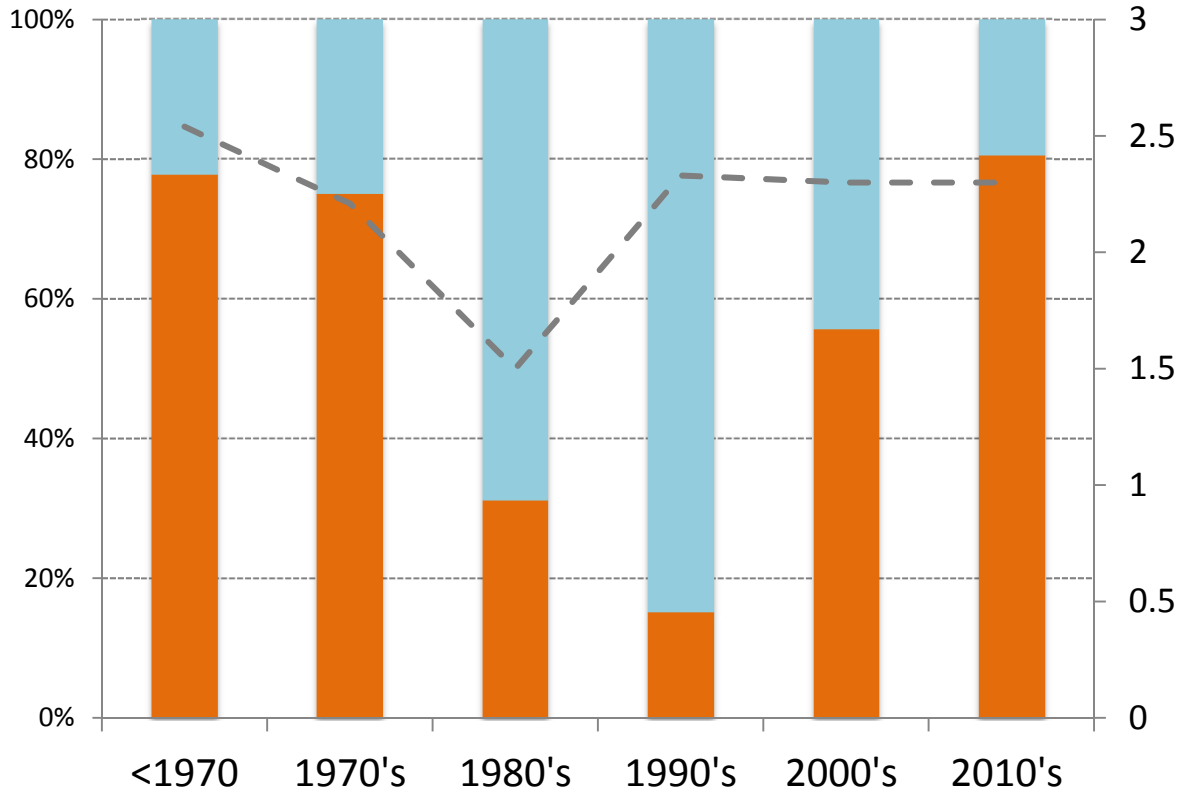
5 Y OS by histology & age of diagnosis



Why poorer survival?

- Parents chose to withhold treatment
- Toxicity
  - Neurotoxicity
  - Growth failure
  - Leukoencephalopathy
- Radiotherapy has been associated with significant toxicities and is avoided in young patients (even if better tumor control).

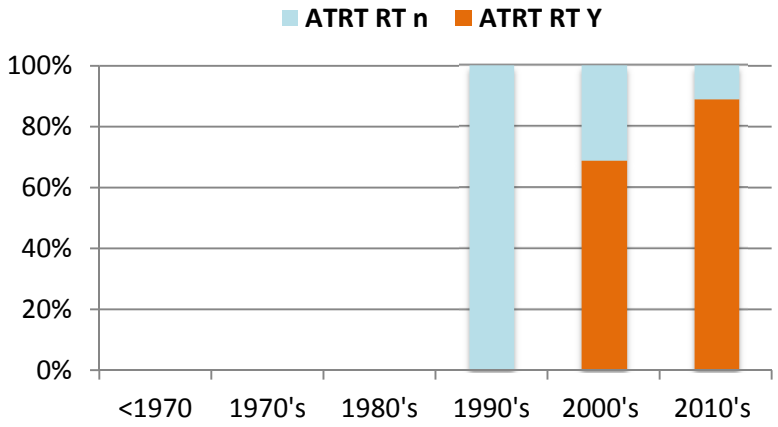
STUDY	Concept	N	yrs	Histologies	Primary Conclusion
Delay CSI- 1980's					
Baby POG 1 (8633/34)		198	86-90	MB, PNET, E, HGG, BSG, CPC	Can delay RT. Elim RT in CR, GTR's. 30% 5yPFS, 39% 5yOS
HIT-SKK 87	IT MTX	30	87-92	Malig brain tumors	5y OS 50%
Avoid RT- Salvage with CSI – 1990's					
Baby POG 2: (9233/34)	CT (std vs dose intense)	330	92-00	MB, PNET, E, HGG, BSG, CPC, ATRT, GCT, CNS Sarc	
CCG 9921:	CT	299	93-97	MB, PNET, E, HGG, BSG, CPC, ATRT, GCT, CNS Sarc	M+, PR, PD=> RT@36mo. PD =>RT. M0/CR-GTR => no RT. 5y efs 27%, 5y OS 43%
HIT-SKK 92:	CT, IT MTX	43	92-97	MB	5y PFS 58% 5y OS 66%
Headstart:	CT +HDSCRT	62	91-95	MB, PNET, E, HGG, BSG, CPC	19 pt had RT, 17 for PD. 3y efs 25%, 3 y OS 40%
CCG 99703:	CT +HDSCRT	92	98-04	MB, PNET, E, HGG, BSG, CPC	GTR was sig better. 5y efs 44%, 5y Os 64%

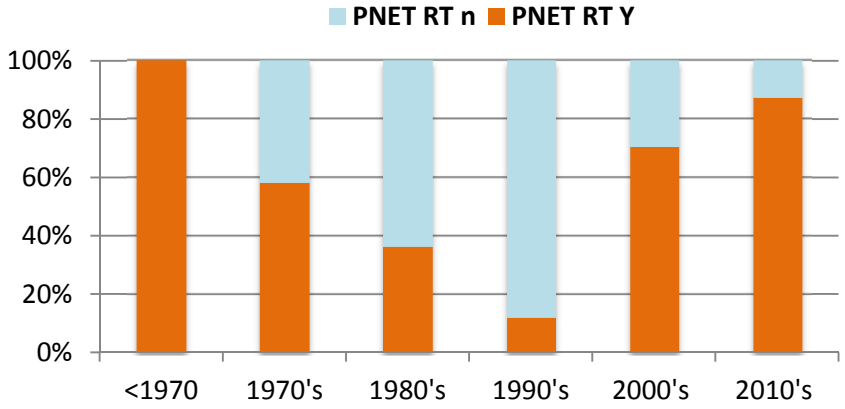


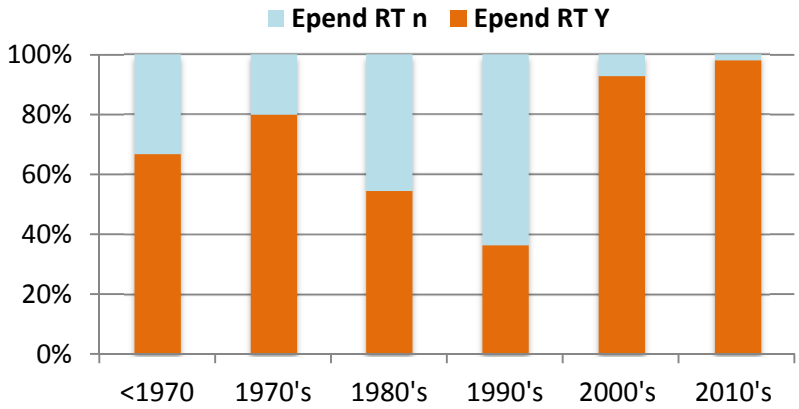
MDA Tumor Registry

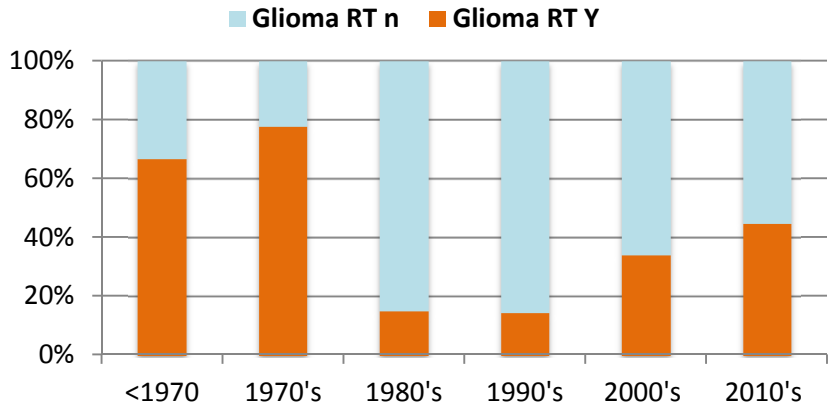
- <4 yo
- Pt's with CNS tumor
- 497 patients

MDA Experience

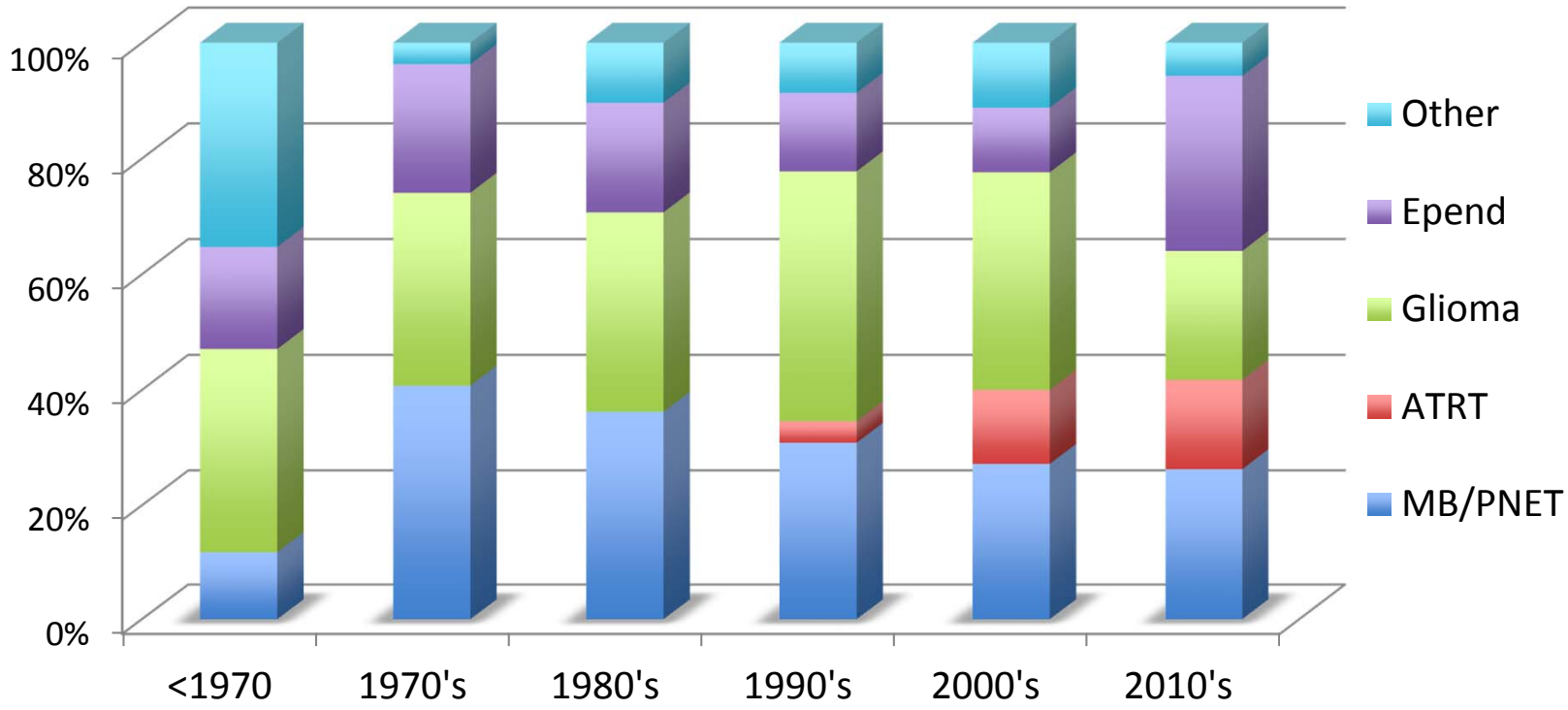








MDA Experience



POG8631/32- Lumping vs Splitting

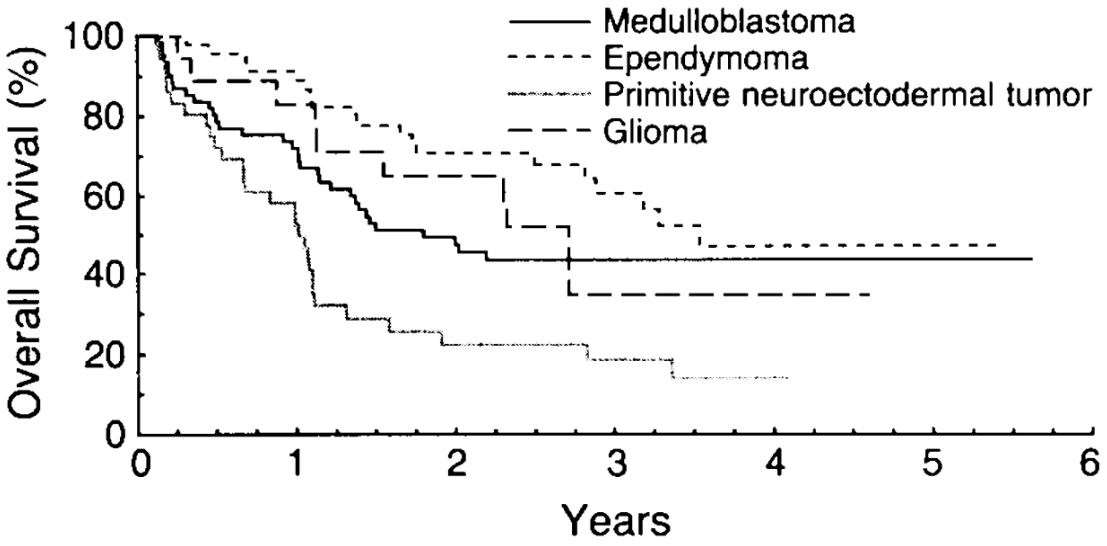


Figure 3. Overall Survival in Children with Medulloblastomas, Ependymomas, Malignant Gliomas, or Primitive Neuroectodermal Tumors.

The differences between groups were significant ($P<0.001$).

Recent Studies-Separate Histologies

- Medulloblastoma
- Ependymoma
- ATRT

RT Advances over last 40 years

- 3D CRT
- MRI planning, staging, evaluation
- IMRT
- IGRT
- Proton Therapy

Medulloblastoma

Table 1. Results of multicenter trials for infant medulloblastoma

Study	*n*	CT	RT	5-Yr EFS/PFS (±SE)	5-Yr OS (±SE)
Baby POG1 [28]	62	Conventional	Delayed adjuvant CSI	31.8% (±8.3%)	39.7 % (±6.9%)
CCG 9921 [31]	92	Conventional	Delayed adjuvant for residual disease or salvage	32% (±5%)	43% (±5%)
BB SFOP [32]	79	Conventional	Salvage	R0M0, 29%; R1M0, 6%; M+, 13%	R0M0, 73%; R1M0, 41%; M+, 13%
HIT-SKK92 [34]	43	Conventional with HD MTX + intraventricular MTX	None	58% (±9%); R0M0, 82% (±9%); R1M0, 50% (±13%); M+, 33% (±14%)	66% (±7%); R0M0, 93% (±6%); R1M0, 56% (±14%); M+, 38% (±15%)
Head Start I and II [45]	21 M0	Induction CT + (HDC&SCR) × 1	Salvage	52% (±11%)	70% (±10%)
Head Start II [17]	21 M+	Induction CT with HD MTX + (HDC&SCR) × 1	>6 yrs old or residual disease	49%[a]	60%[a]
P9934 [37]	78 M0	Conventional	Early adjuvant focal	58% (±6%)[a]	66% (±6%)[a]

[a]At 3 years.

Lafay-Cousin, Strother The Oncologist, 14 433-444, 2009

BABY POG 1

- The single most important predictor of survival was the degree of surgical resection
- 57 GTR 5 yr OS: 62%
- 113 < GTR: 31%
- GTR + M0 (44 patients), the OS was 65%
- Progression tended to occur very early within the first 3-6 months and failures beyond 2 years were uncommon

Courtesy of M. Chintagumpala

POG Study 9233/34 - Baby POG 2

Primary objective:

- To prospectively determine the outcome of patients randomized to standard or dose-intensive chemotherapy, with restricted use of RT
  - Standard Dose: Regimen A
  - Dose-Intensive: Regimen B

  => RT only for those with M+ disease at dx and those with residual M0 disease at end of chemotherapy

Courtesy of M. Chintagumpala

Summary for 9233

- As in Baby POG 1, some infants with MB cured with S & CT
  - M0: 40% survived with no RT, 36% with RT

  => RT not necessary for all, but not curative for all who need it
- More irradiated children survive (~42% vs ~31%)
- Factors?
  - Large cell/anaplastic variant; M+ disease: bad
  - Need biologic correlative studies which are now happening

Courtesy of M. Chintagumpala

Late Effects of Survivors, No RT

- Targeted late effect **reporting was voluntary**
- Non-RT vs radiated survivors late effect reporting:
  - Having "**none**" reported more often
  - **More hearing loss**
  - Fewer & **less severe developmental delays** and need for special education
  - **No endocrine problems** vs. GH, thyroid, adrenal deficiencies reported with RT

Courtesy of M. Chintagumpala

Infant M0 Medulloblastoma Strategies

1. Residual disease is associated with higher rate of progression
2. Failures are both local & metastatic
3. Possible increased survival with HDSCRT
4. Possible increased survival with IT/IV methotrexate

ACNS 0334

- SPNET & HR MB <36 mo randomized to **HDSCRT +/- MTX**
- 5/14 to 3/16 suspended, 91 accrued
- RT not mandated, only at MD discretion
  - Tumor bed only or CSI
- No results yet

PBTC 026

- 2mo-4yo MB
- Induction => Consolidation (HDSCRT) => RT for M0 => SAHA/isotretinoin
- M0 Pt get RT, others at MD discretion
- Closed, no results

ACNS 1221

- Phase II M0 desmoplastic MB in <4yo
- Induction chemo (cpm, vcr, carbo, vp16, HD MTX) x 3 cycles
  - => CR: end of tx
  - => PR: SLO then 2 cycles chemo, then end
- NO RT for this study
- Open 12/13, temporary closed 7/16, 37 of 42 accrued

Infant MB RT Thoughts

- GTR is advantageous
- M0: may do local field only but consider salvage issues of CSI needed later
- M+:
  - CSI, try to delay to >3yo
  - Dose: lower dose if CR is being explored

EPENDYMOMA

BABY POG 1: Ependymoma

- 48 children with ependymoma
- GTR: 66%
- Subtotal: 25%
- 2 yr Chemo (0-24 mo) 5 yr S: 26%
- 1 yr Chemo (24-36 mo) 5 yr S: 63%

Courtesy of M. Chintagumpala

Ependymoma Prognostic Factors

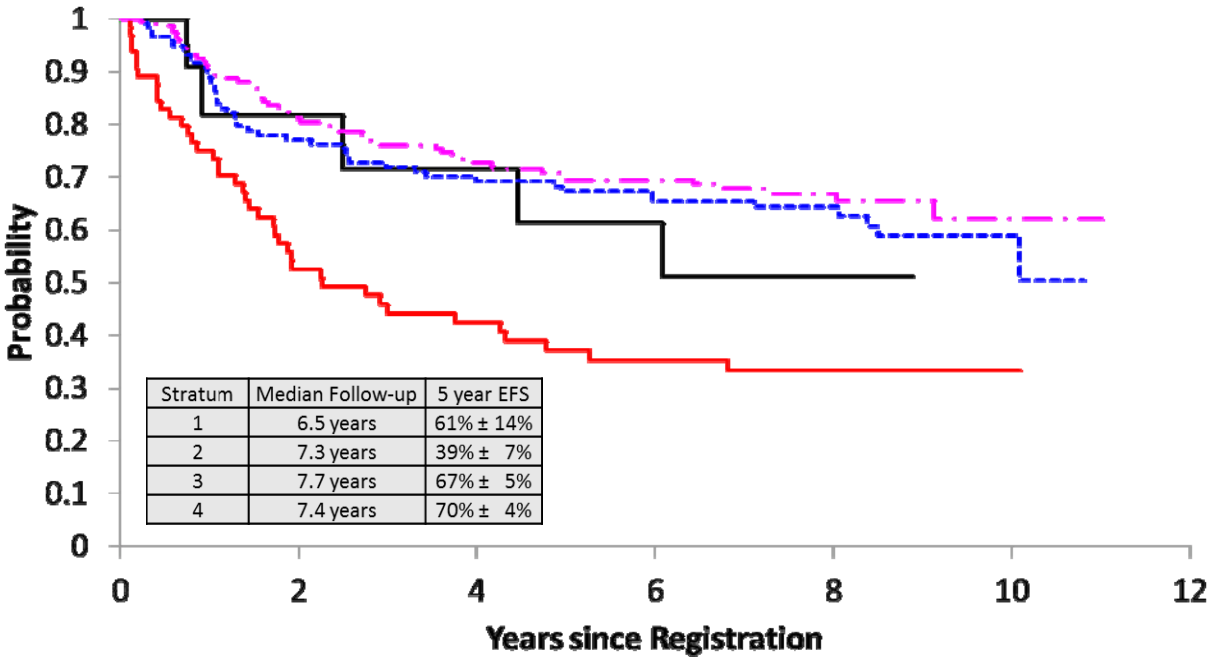
- Multivariate Analysis independent for poor risk
  - WHO grade III, male, **age**, intracranial location, no surgery
  - With STR: **no RT** associated with poor outcome HR 1.748, P=0.024

Rodriguez et al, j of surg res, vol 156 (2) 340-351, 2009

COG ACNS 0121

1) Evaluation of chemo after STR in an effort to improve resectablity
2) Evaluation of observation after microscopic GTR for grade 2 supratentorial ependymoma
3) All others RT after GTR or 2nd resection evaluation post-chemo
4) RT dose 59.4Gy/33 fractions
5) Anaplastic ependymomas stratified

Event-Free Survival by Strata



Stratum	Median Follow-up	5 year EFS
1	6.5 years	61% ± 14%
2	7.3 years	39% ± 7%
3	7.7 years	67% ± 5%
4	7.4 years	70% ± 4%

Stratum 1: Supratentorial GTR1

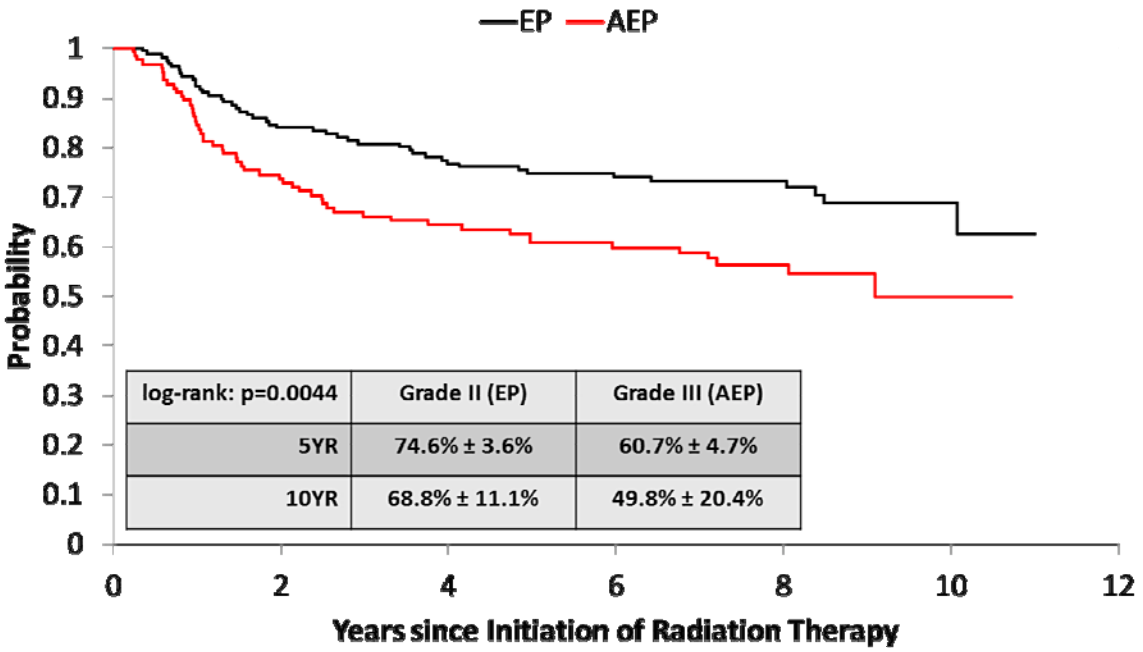
Stratum 2: STR - any grade or site

Stratum 3: <5mm resid or macroscopic GTR, any grade or site

Stratum 4: GTR1 & anaplastic or GTR with infratentorial

ACNS0121 Children's Oncology Group

EFS – Stratum 3+4 by Tumor Grade



log-rank: p=0.0044	Grade II (EP)	Grade III (AEP)
5YR	74.6% ± 3.6%	60.7% ± 4.7%
10YR	68.8% ± 11.1%	49.8% ± 20.4%

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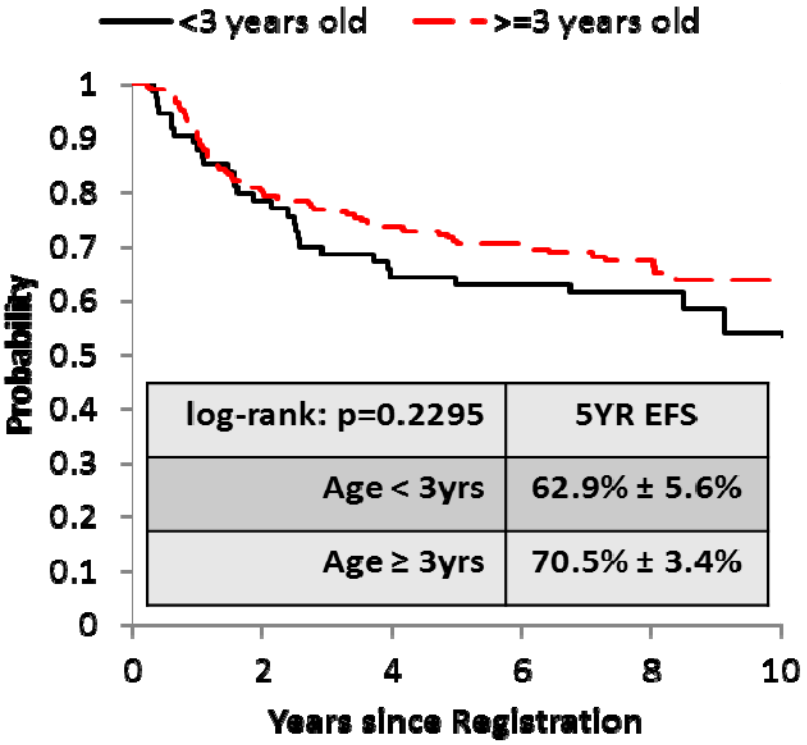
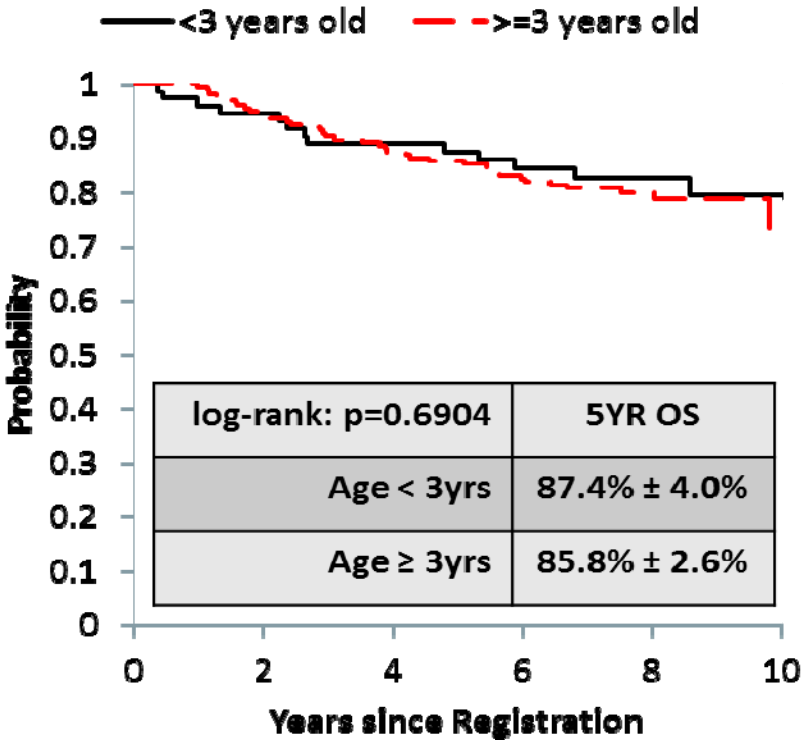
EFS and OS – Stratum 3+4 by Age





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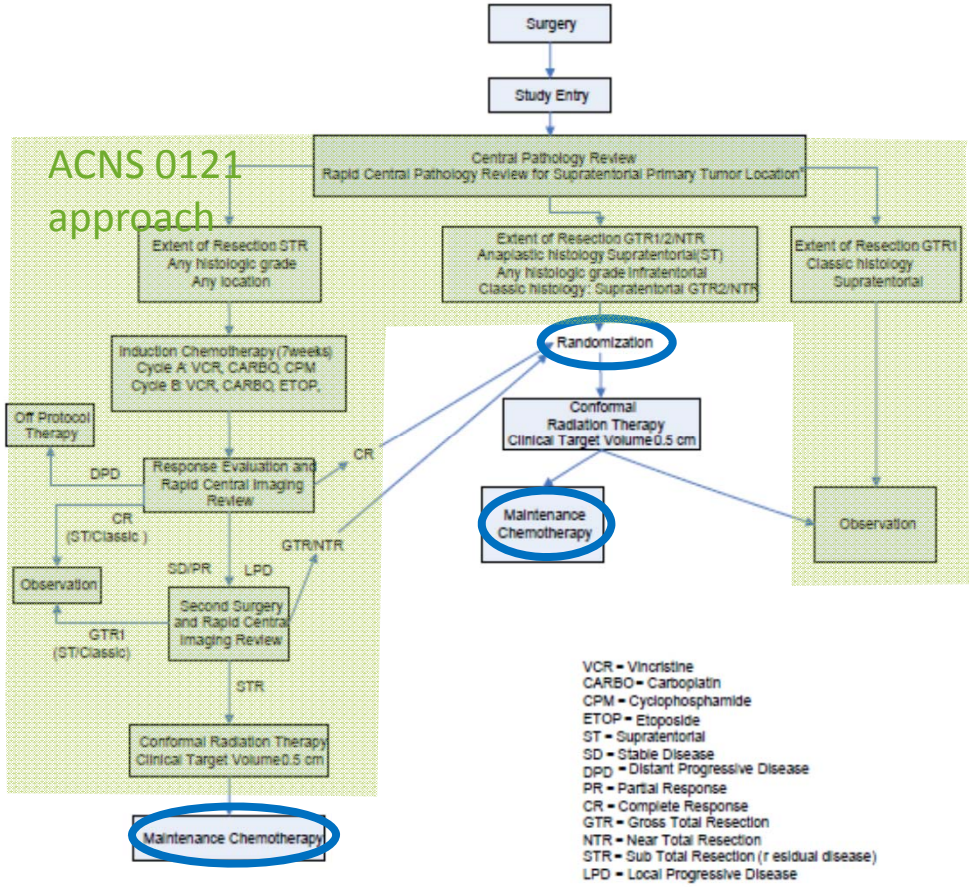
COG ACNS 0831



Role of adjuvant chemo after surgery & RT

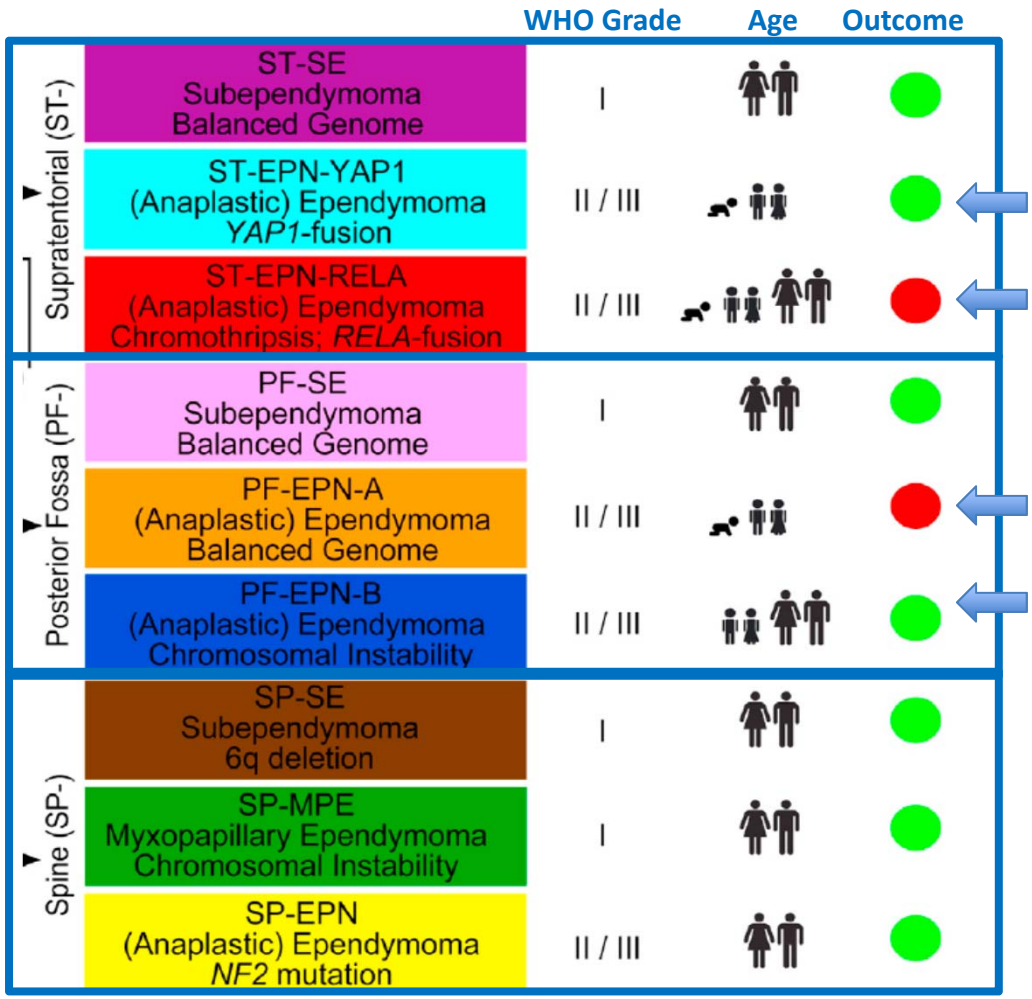
- Opened 3/2010
- 347 of 400 patient accrual goal as of 9/26/16

ACNS 0121 & 0831

- GTV 1= post op resection margin + gross disease based on pre & post op MRI
- GTV 2= GTV 1 – off spinal cord and/or OC
- CTV= GTV + 0.5mm (anatomically adjusted)
- PTV = CTV + 3mm (IGRT) or 5mm

Total Dose 59.4Gy/33 fractions

- 54 Gy to PTV 1
- 5.4 Gy boost to PTV 2



- 500 samples
- Molecular classification by DNA methylation profiling
- 9 subtypes
- Can differentiate b/w grade II/III PF and ST tumors

Pajtler et al, Cancer Cell 27, 728-43, 2015

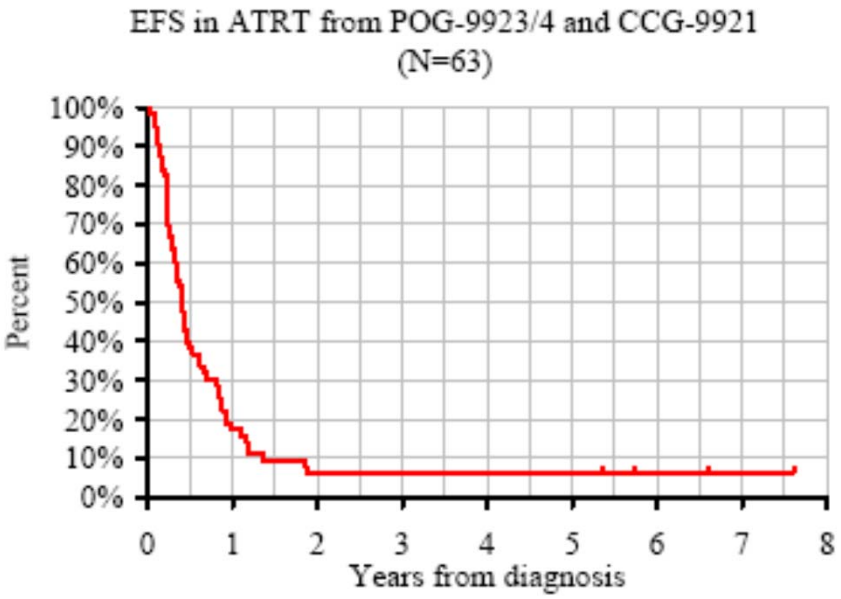
ATRT

ATRT

- First described in 1987 by Rorke et al
  - Previously dx as MB, PNET, CPC
  - US incidence 3/10^6 children = approx 3% of pediatric CNS tumors
- Poor prognosis, most die of disease

Table 6. Comparative features of CNS atypical teratoid/rhabdoid and primitive neuroectodermal tumors of childhood

	Median	
	ATT/RhT	PNET
Age	17.5 months	3 to 5 years
Posterior fossa location	65%	82%
Initial response to therapy	12%	40–60%

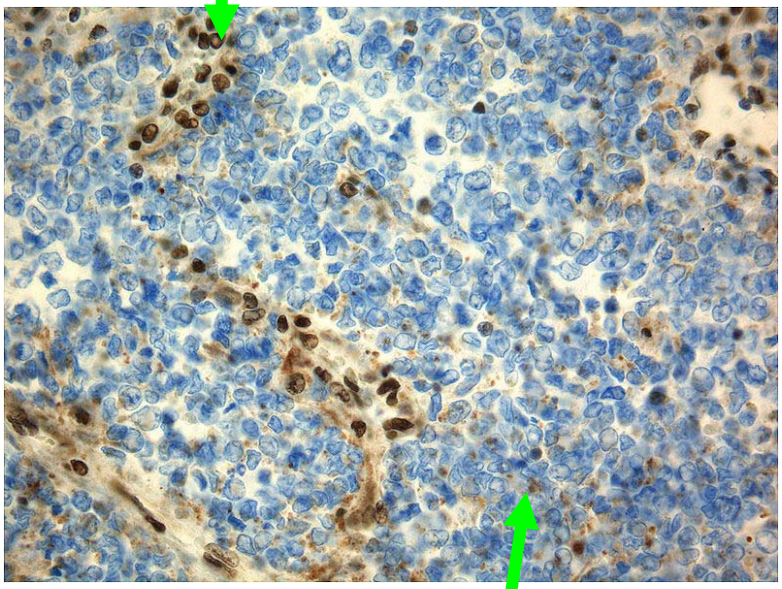


Rorke et al, J Neuro-Oncol 24, 1995

ATRT Primary Site

- 50-60% posterior fossa
- 30-40% supratentorial
- 2% spinal
- 2% multifocal

Normal staining in non-tumor cells, (control)



INI 1 protein staining absent in tumor cells

ATRT outcomes - historical

- POG 9923: 36 patients
  - 69% PD by 3-6 mo on therapy
  - 83% PD by 12 mo
  - Med OS 193 d (Strother et al)
  - Most failures in primary site, all died of disease
- CCG 9921: 28 patients
  - EFS 32% at 1 yr, 14% at 2 y (Geyer et al)
  - Failure: local 45%, local & met 29%

ATRT - Surgery

- Surgery for diagnosis
- Registry data: degree of surgery may affect survival
  - 20 GTR EFS 12.5 mo
  - 22 STR EFS 9.25 mo
  - 10/14 long term survivors had GTR
  - ? Role of second look surgery

Chemotherapy – IRS III

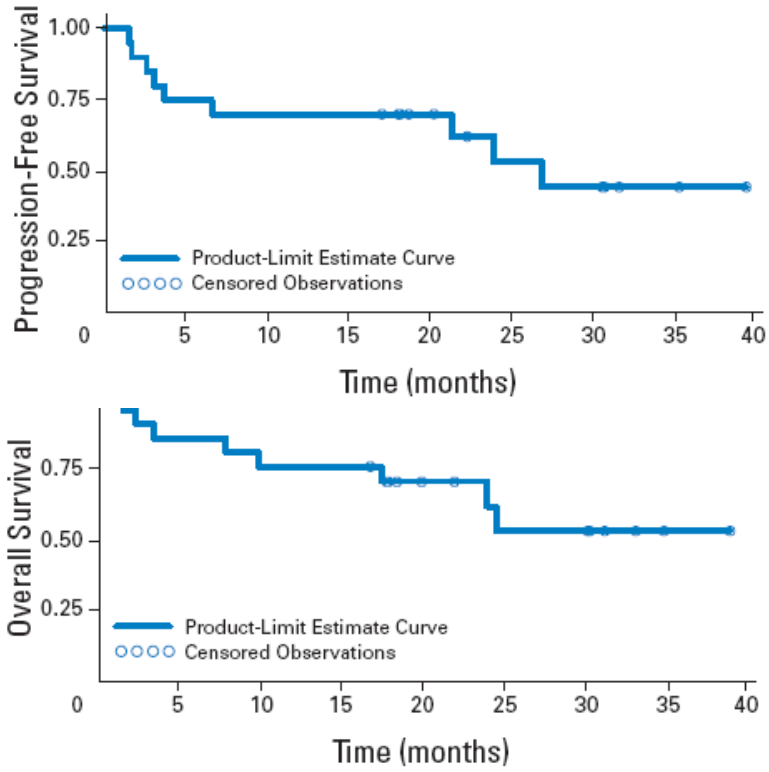
- RT, IT MTX, Ara C, hydrocortisone, multi-agent chemo
  - All 3 pt responded, 1/3 had prolonged survival
- CHOP: similar approach
  - 2 Y EFS 33% (Janss)
- Boston:
  - IRS III in 2 pt with relapsed ATRT, alive at 30 mo (Kieran)

High dose chemo with SCT

- ATRT registry 13 pt
  - 4/13 pt alive at last evaluation: **2/4 had RT**
- HS II: HDSCR + MTX, no RT:
  - 3/6 pt NED at 12, 34, 46 mo from dx
  - 1 pt salvaged w RT and chemo
- HS I: No MTX: 6/6 ATRT pt died

ATRT-Boston experience

- 2004-06: 20 pt
  - med age 26 mo
  - 14 M0, 5 M3
  - 15 pt RT: 11 CRT, 4 CSI
- 2y PFS & OS: 53% & 70%.
- **Local RT for M0**



Chi et al, JCO, 27 385-389, 2008

ATRT- Radiotherapy

- ATRT registry: 42 pt
  - 13 pt received RT as part of primary therapy
    - 9 RT to primary site
    - 4 RT to CSI + primary site
    - Median **OS 48 mo** vs. 16.7 mo for all pt on registry
    - **Of the 14 long term survivors on registry, 7 had RT**
- St Judes:
  - 22 pt <3 y at dx: chemo alone=> 3 y EFS 11%
  - **9 pt >3 y at dx: CSI +chemo => 3 y EFS 58%**

ATRT SJMB 03 - 9/04-11/09

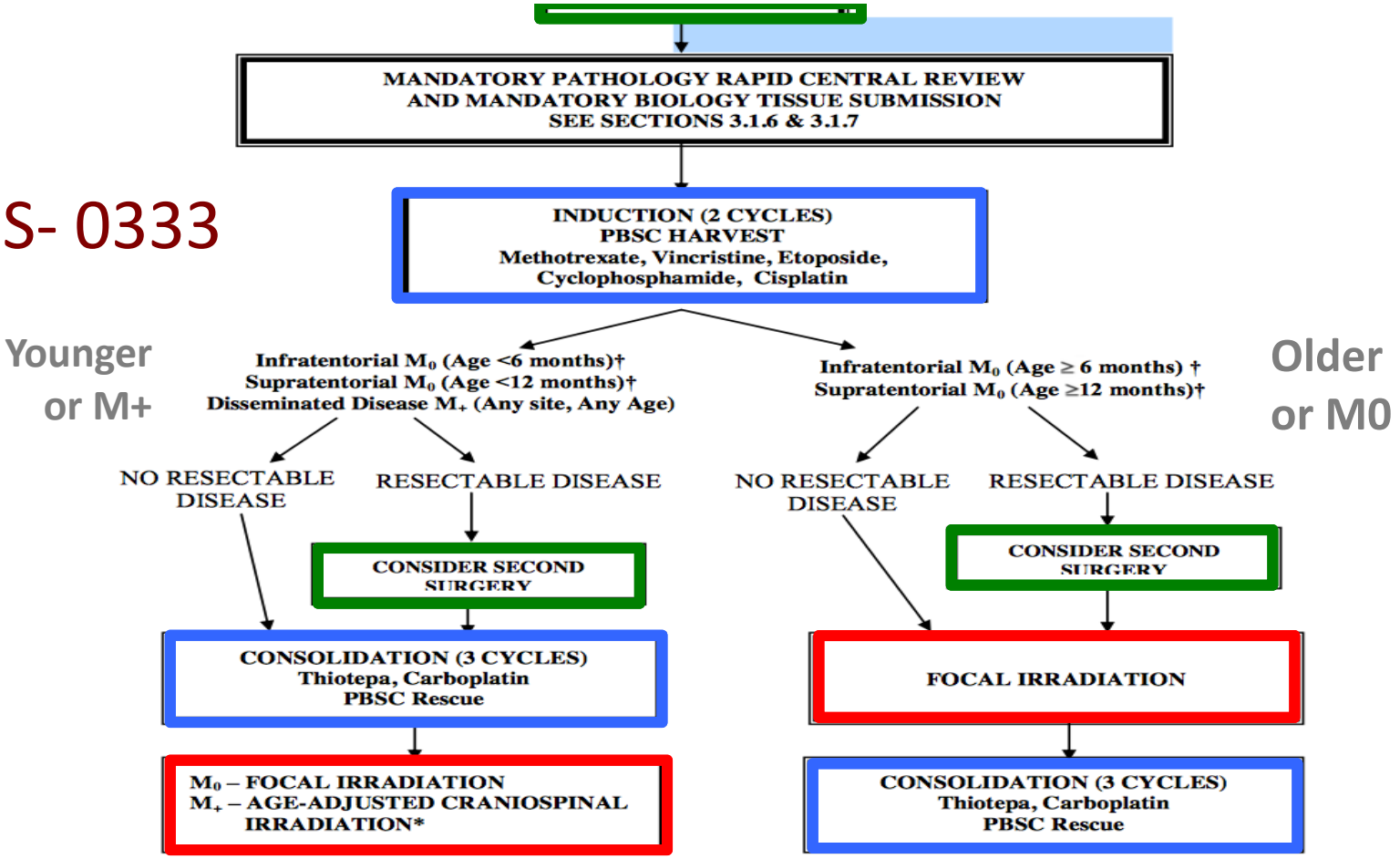
- 17 pts, mean age 5.7 y (3.1-12.1)
  - ST 8, PF 7, spinal cord 2
  - 9 AR, 8 HR (M+ 6)
  - 10/17 GTR or NTR
- Treatment regimen
  - **23.4 Gy or 36-39.6 Gy CSI + boost to 55.8Gy**
  - 4 cycles cyclo based intense chemo
- Results at median f/u 12 mo (3-64mo):
  - 16 pt received median of 4 cycles of chemo
  - 10 pt alive NED, 7 pt DOD
  - **5Y EFS 54%, 5Y OS 52%**
  - **5Y OS AR vs HR: 87.5 vs 15%**

SNO 2010 PC-03 abstract: Gajjar et al

ATRT – Overall Data Summary

- Retrospective studies: median OS +/-1 yr
- Data suggest:
  - Std & intensive chemo: good response, but high recurrence
  - **Early RT may be associated with survival**
  - CT with PBSCT may have higher control rates
  - MTX (HSII and IRS III) may be useful

ACNS- 0333



*Craniospinal irradiation is recommended but not mandated for patients with disseminated disease at the time of enrollment.
M_0 = no evidence of metastatic disease at the time of enrollment.
M_+ = evidence of metastatic disease at the time of enrollment.

ACNS 0333 continued

Age @ RT	M Stage	Primary	Volume	CSI	Primary
6-36 mo	M0	IT	Focal	0	50.4
>36 mo	M0	IT/ST	Focal	0	54
<36 mo	M+	IT/ST	Focal+CSI	23.4	27
>36 mo	M+	IT/ST	Focal+CSI	36	18

- Opened 12/08 closed 2/14
- Accrued 70 patients

Failure pattern will be studied to determine need for CSI

ACNS 0333

- So far 24 mo:
  - All: EFS 43% OS 52%
  - <36 mo: EFS 39% OS 48% ($p<0.025$)

$\Rightarrow$ ACNS 0333 better for <36 mo pt

$\Rightarrow$ Order of therapy not important

$\Rightarrow$ Further intensification not possible

$\Rightarrow$ Molecular stratification may be helpful

ATRT

- ATRT is a devastating disease
- Aggressive multimodality therapy appears to be necessary even for very young children
- Early radiotherapy advocated for all children with non-disseminated disease
- Biology of ATRT will need more study

Late Effects with Advanced RT Techniques

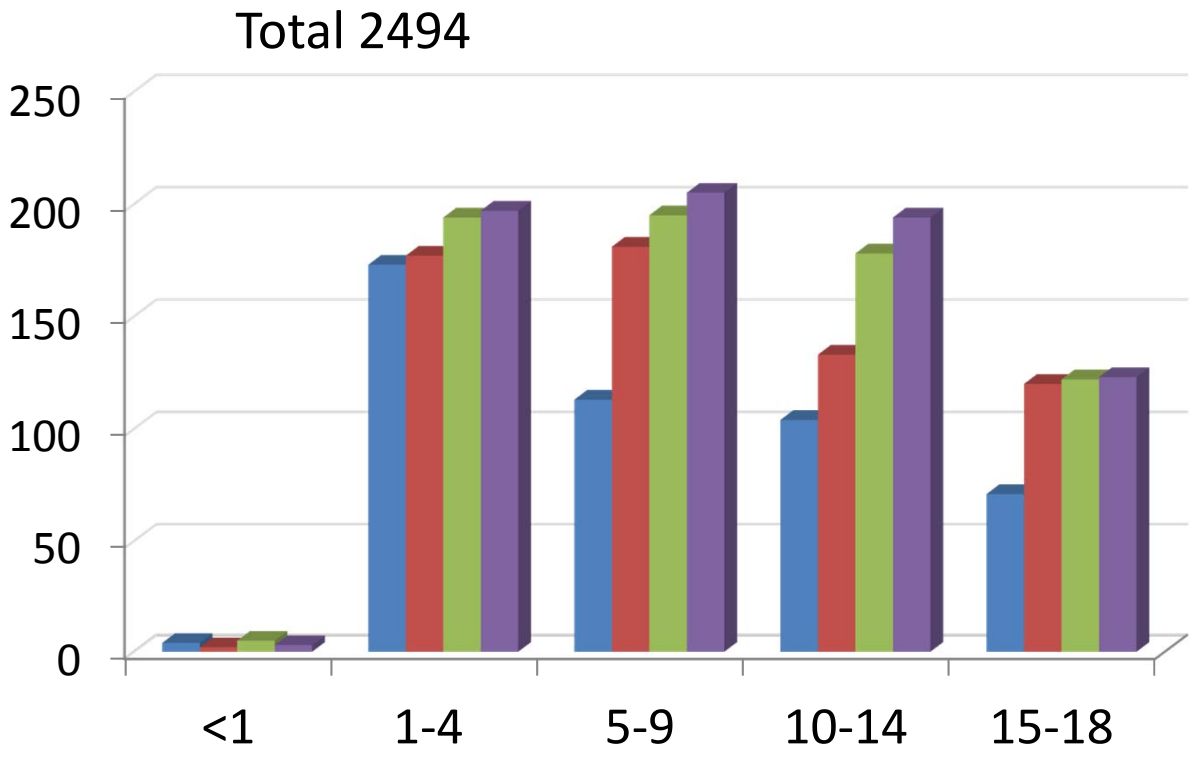
- Study for St. Judes suggests very young children with PF tumors and local RT do well with respect to cognitive function
- MDA ATRT study did not indicate significant late effects, but more follow up needed.

Proton Therapy – just a word!

MDA Proton Therapy in <4yo Pt's

Decade	Total	N malig	% Malig	N RT (X/P)	% RT
<1970	18	17	0.94	4	**0.78**
1970's	28	27	0.96	13	**0.75**
1980's	61	58	0.95	15	**0.31**
1990's	86	81	0.94	5	**0.15**
2000's	133	125	0.94	**74 (39/35)**	**0.54**
2010's	170	165	0.97	**139 (37/102)**	**0.79**

US Pediatric PRT Trends 2010-13



2010 465
2011 613
2012 694
2013 722

Courtesy of PPF

Summary

- Management of malignant infant brain tumors requires multidisciplinary approach
- Radiotherapy has made a “come back” and requires consideration of all normal tissues, MRI based planning, highly conformal dosimetry to CTV
- Continue accrual on protocols to improve outcomes further
- Follow patients to study incidence of late effects.