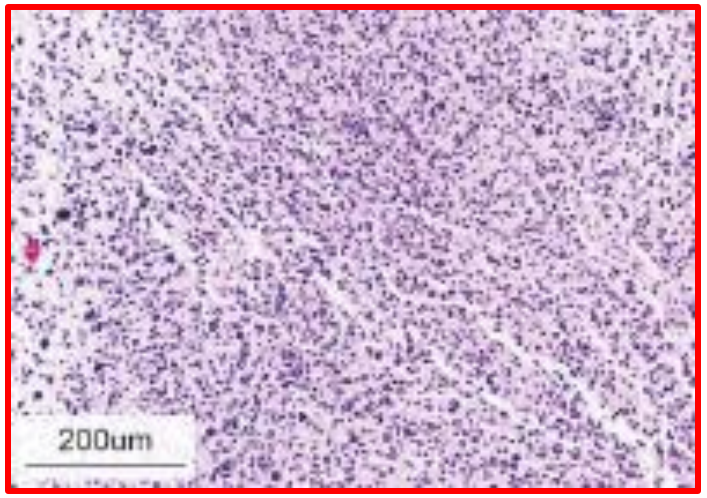
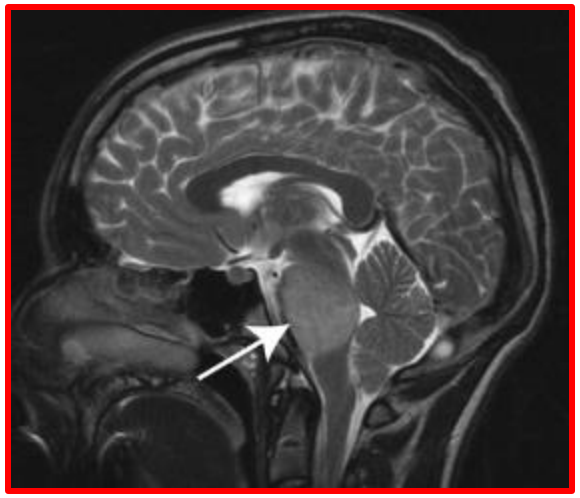
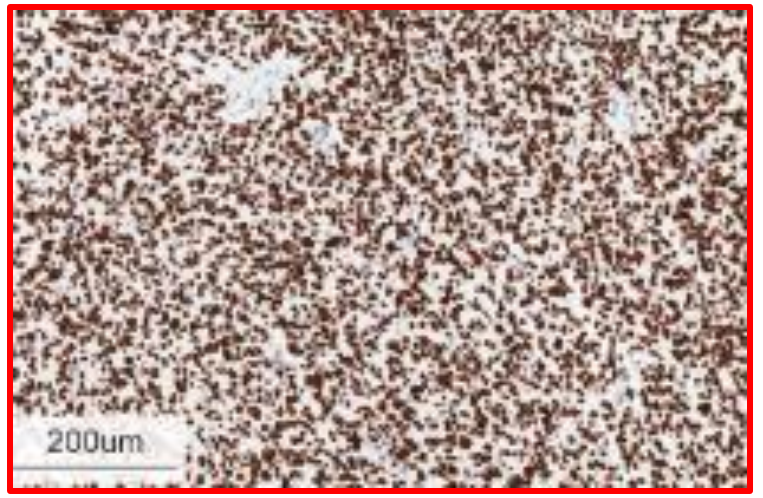






Contemporary Management of Brainstem Glioma:
Focus on Diffuse Intrinsic Pontine Glioma (DIPG)

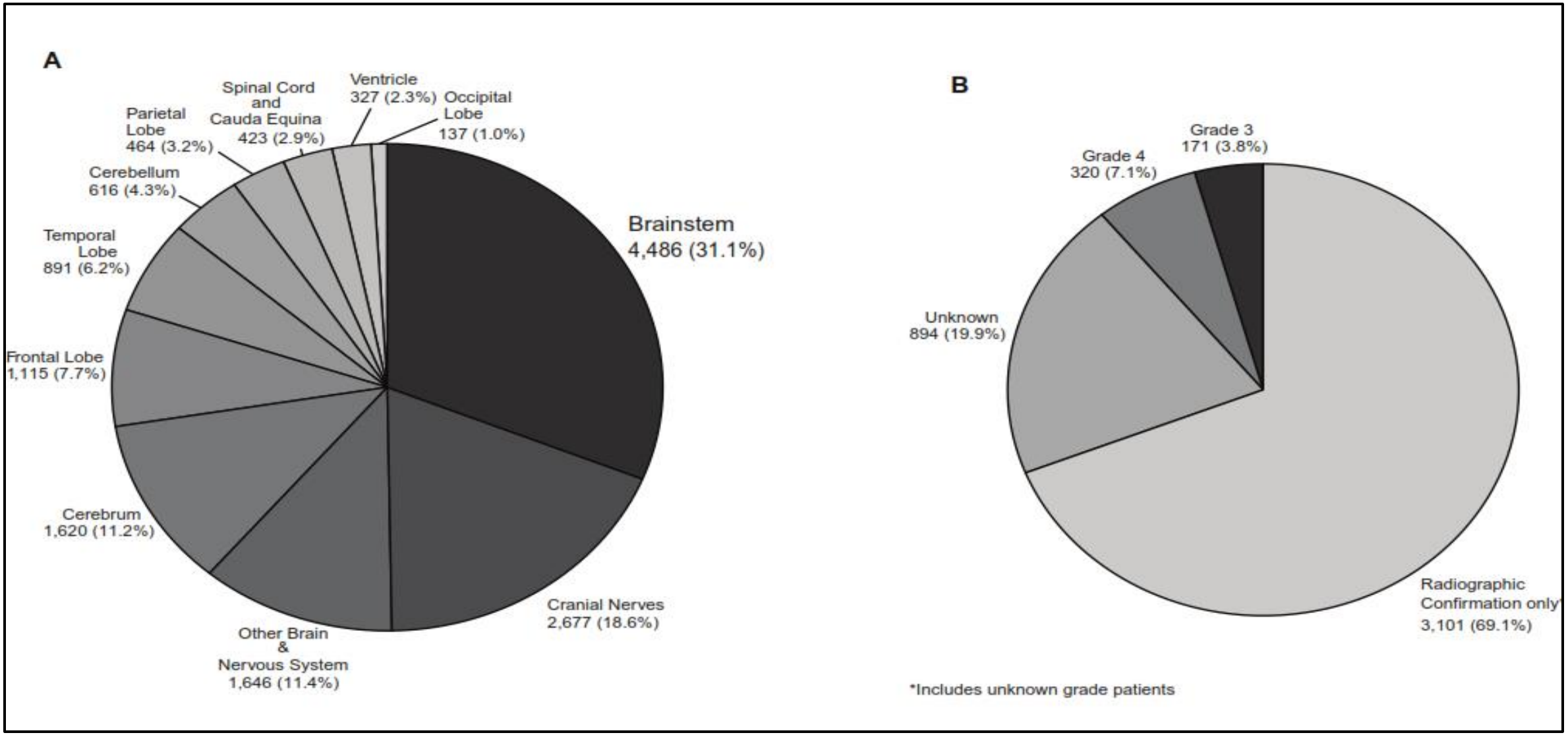
Dr Tejpal Gupta, MD, DNB
Professor, Radiation Oncology
Tata Memorial Centre, Mumbai

38th AROI-ICRO Webinar Series
Central Nervous System (CNS) Module
7th-9th July 2021 – Virtual Online

Outline of presentation

- Epidemiology and incidence
- Classification and presentation
- Contemporary management
- Molecular biology
- Emerging therapeutic avenues
- Summary and conclusions

Epidemiology



Patil et al, CBTRUS 2000-2017, Neuro-Oncol 2021 (in press)

Classification of Brainstem Glioma

- **Diffuse brainstem glioma**

DIPG is prototypical example

- **Focal brainstem glioma**

Tectal plate glioma is prototypical example
other focal gliomas are rare

- **Dorsal exophytic glioma**

Gliomas with exophytic component

- **Cervico-medullary glioma**

Arise from medulla and extend inferiorly or can also be due to superior extension of cervical spinal gliomas

Anatomic location

- Pontine: commonest
- Mesencephalic/midbrain: less common
- Medullary: least common

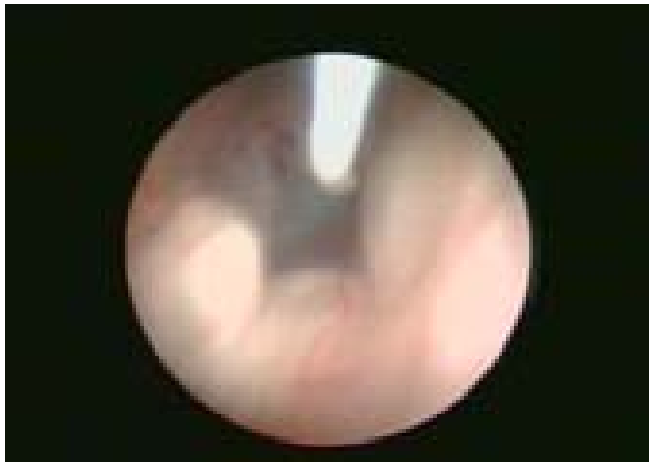
McLone et al, Pediatric Neurosurgery, 2001
Keating et al, Tumors of Pediatric CNS, 2001

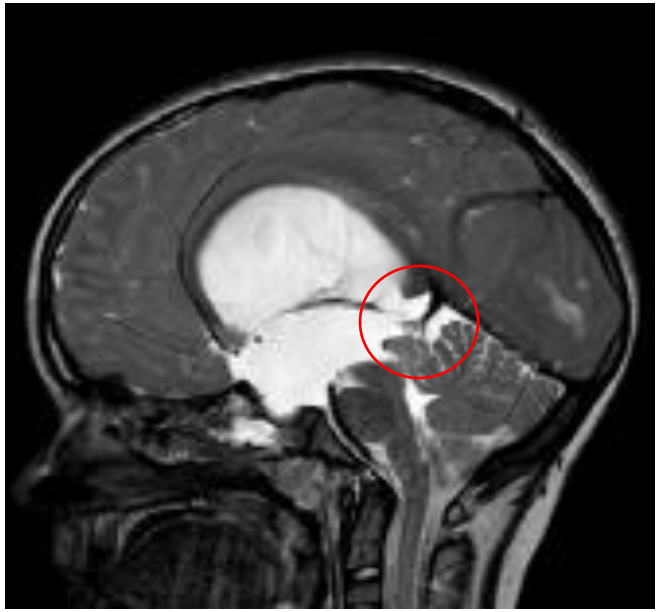
Clinical Presentation

- Can be some what variable depending upon location and size of the lesion
- Focal tectal plate gliomas present generally early with small tumors due to obstructive hydrocephalus
- Common presentation: headache, vomiting, and imbalance
- Dorsal exophytic tumors present with signs/symptoms related to involvement/compression of tracts
- Commonly present with slowly progressive dysarthria, dysmetria, and long tract signs
- Cervico-medullay gliomas are sometimes associated with NF1 and detected on surveillance imaging
- Sporadic cervico-medullary gliomas can present with nuchal pain and lower cranial nerve palsy
- DIPG the prototypical brainstem glioma presents with rapidly progressive signs and symptoms

Focal Tectal Plate Glioma

- Clinically and biologically indolent tumor
- Presents with hydrocephalus most commonly
- Only CSF diversion is recommended
- Endoscopic third ventriculostomy (ETV) is the procedure of choice
- Mostly pilocytic astrocytoma on histology (if biopsied)
- Rarely progresses after CSF diversion
- Occasionally may warrant intervention for progression
- Can be treated with chemotherapy (LGG protocol) in children
- Rarely definitive RT is offered for growth arrest in older children/adults





Dorsal Exophytic Glioma and Cervico-medullary Glioma

- Only biopsy is recommended for histological diagnosis
- Sometimes safe debulking in dorsal exophytic gliomas may be considered
- Commonest histologic diagnosis is Pilocytic Astrocytoma
- BRAF alterations (particularly fusions) are commonly seen in children
- In pre-pubertal children, chemotherapy with low-grade glioma protocol is advisable
- The typical 5-year progression-free survival with chemotherapy is 40%
- In post-pubertal children, focal conformal radiation therapy can be offered
- Radiation therapy provides good symptomatic relief and durable local control
- Targeted therapy is still investigational in pediatric LGG including brainstem glioma

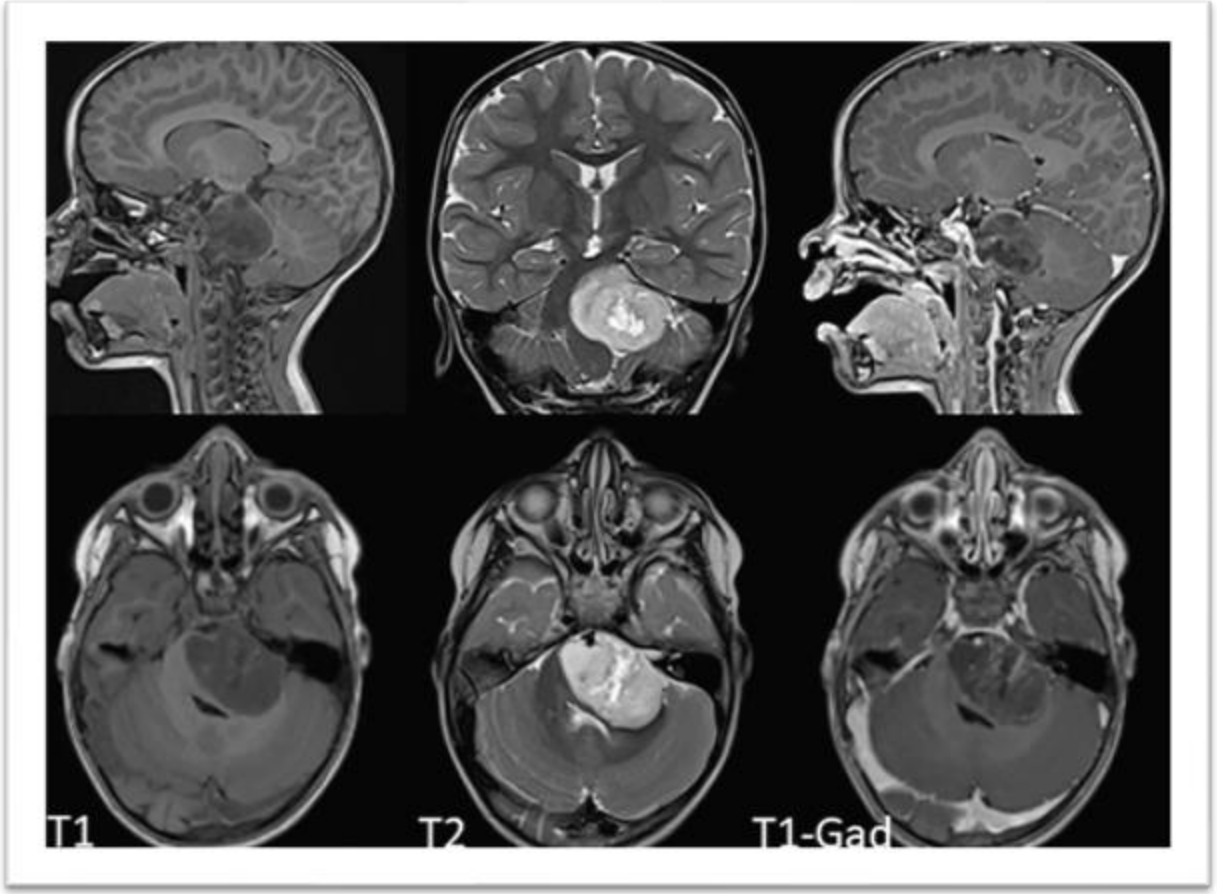
DIPG: prototypical brainstem glioma

- Short latency - 2-3 months

- Classical triad of symptoms:
  - Cerebellar signs
  - Long tract signs
  - Multiple cranial nerve abnormalities

- Classical radiology
  - T1 hypointense, T2 hyperintense
  - >2/3rd of Pons, >180 degree basilar artery
  - Nil/minimal contrast enhancement

Clinico-radiological diagnosis



MR Imaging features of Diffuse Intrinsic Pontine Glioma (DIPG)

Table 3. Baseline imaging characteristics in 357 DIPGs

Imaging Feature	N	% cases*	Note
Tumor Extension			
No extension beyond Pons	15	4.2	
Cerebellum	85	23.8	
Midbrain	245	68.6	
Thalami	25	7.0	
Medulla	260	72.8	
Internal Capsule	24	6.7	
Brachium Pontis	284	79.6	
Extension Beyond Pons and BP	319	89.4	
% Pons involved			
1-33%	1	0.3	
34-66%	21	5.9	
67-100%	335	93.8	
< 50%	3	0.8	
> 50%	354	99.2	
Tumor Morphology			
Margin (well-defined)	15	4.2	
Eccentric	50	14.0	
Exophytic	229	64.1	
Heterogeneity (marked)	54	15.1	
Atypical features but likely DIPG	92	25.8	
Tumor Signal			
T1 hypointense/T2 hyperintense	336	95.7	351 with both T1 and T2 sequences
T2 hypointensity (any)	189	53.2	2 missing T2 sequence
Non-necrotic T2 hyperintensity (any)	128	36.1	2 missing T2 sequence
Stripes visible	251	70.5	1 incomplete data
Enhancement			
Enhancement (any)	239	68.9	of 347 that had contrast
Homogeneous	2	0.8	of 239 that had enhancement
Ring Enhancement	122	51.5	of 239 that had enhancement
Patchy Enhancement	162	67.4	of 239 that had enhancement
Patchy and Ring Enhancement	46	19.2	of 239 that had enhancement
Diffusion/Hemorrhage/Necrosis			
Diffusion restriction (any)	184	63.2	of 291 with diffusion sequence
Hemorrhage (any)	102	28.6	
Hemorrhage (> minimal)	40	11.2	
Hemorrhage (any, GRE/SWI)	73	50.0	of 146 with SWI or GRE sequence
Hemorrhage (>minimal.,GRE/SWI)	31	21.2	of 146 with SWI or GRE sequence
Necrosis (any)	156	43.6	
Necrosis + Ring Enhancement	118	34.0	of 347 that had contrast
Necrosis with no Ring Enhancement	37	10.7	of 347 that had contrast
Spectroscopy			
NAA/Cr (decreased)	66	75.0	of 88 with spectroscopy
Cho/Cr (increased)	74	84.1	of 88 with spectroscopy
Cho/NAA (increased)	75	85.2	of 88 with spectroscopy
mI/Cr (increased)	34	41.0	of 83 with assessable mI
Lactate present	56	64.4	of 87 with assessable lactate
Other Features			
Hydrocephalus	79	22.1	
Subependymal signal	78	21.8	*see note
Distant Disease	11	3.1	of 357 cases
Distant Disease (spine available)	9	6.8	of 133 with spine imaging

Leach et al, IDIPG Registry, Neuro-Oncol 2020

Is biopsy needed in DIPG?

- Associated with significant morbidity (nearly 10-20%)
- Limited therapeutic options based on biopsy results
- Widespread availability of MRI with characteristic neuro-imaging

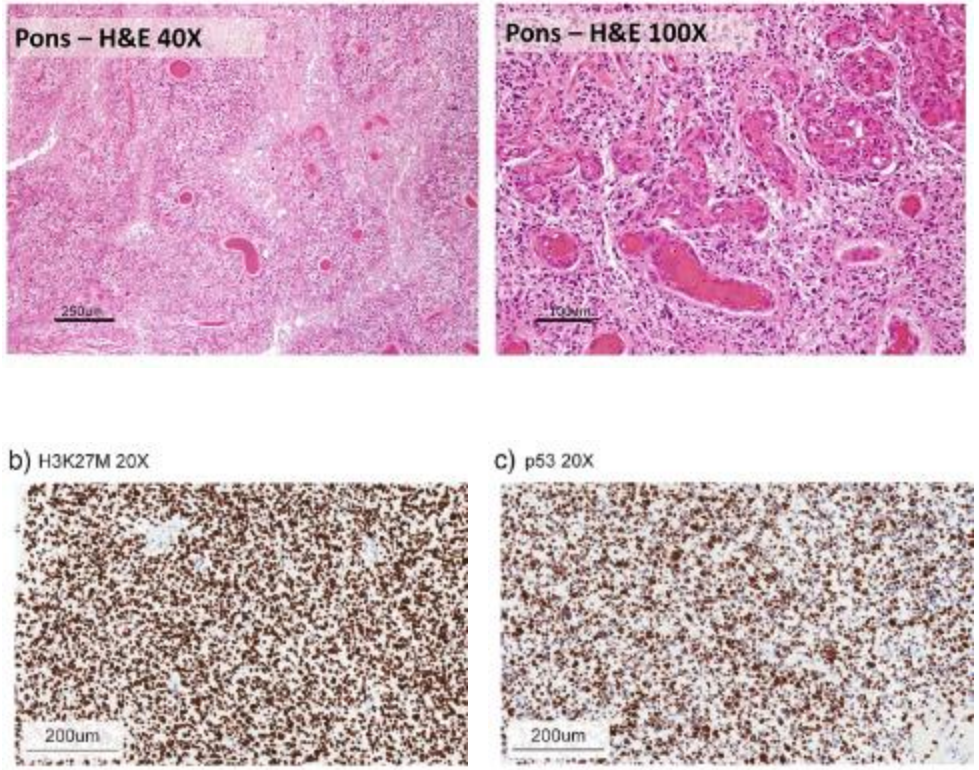
Magnetic Resonance Scans Should Replace Biopsies for the Diagnosis of Diffuse Brain Stem Gliomas: A Report from the Children's Cancer Group

A. Albright;Roger Packer;Robert Zimmerman;Lucy Rorke;James Boyett;G. Hammond;

Biopsy in DIPG is typically reserved for doubtful diagnosis or biological/translational research

Histo-pathological spectrum

- Majority are high-grade tumors
- Sometimes lower grade astrocytomas seen
- Grade does not correlate with prognosis
- H3K27/ACRV1/PDGFR mutations
- A subset demonstrates PNET-like features



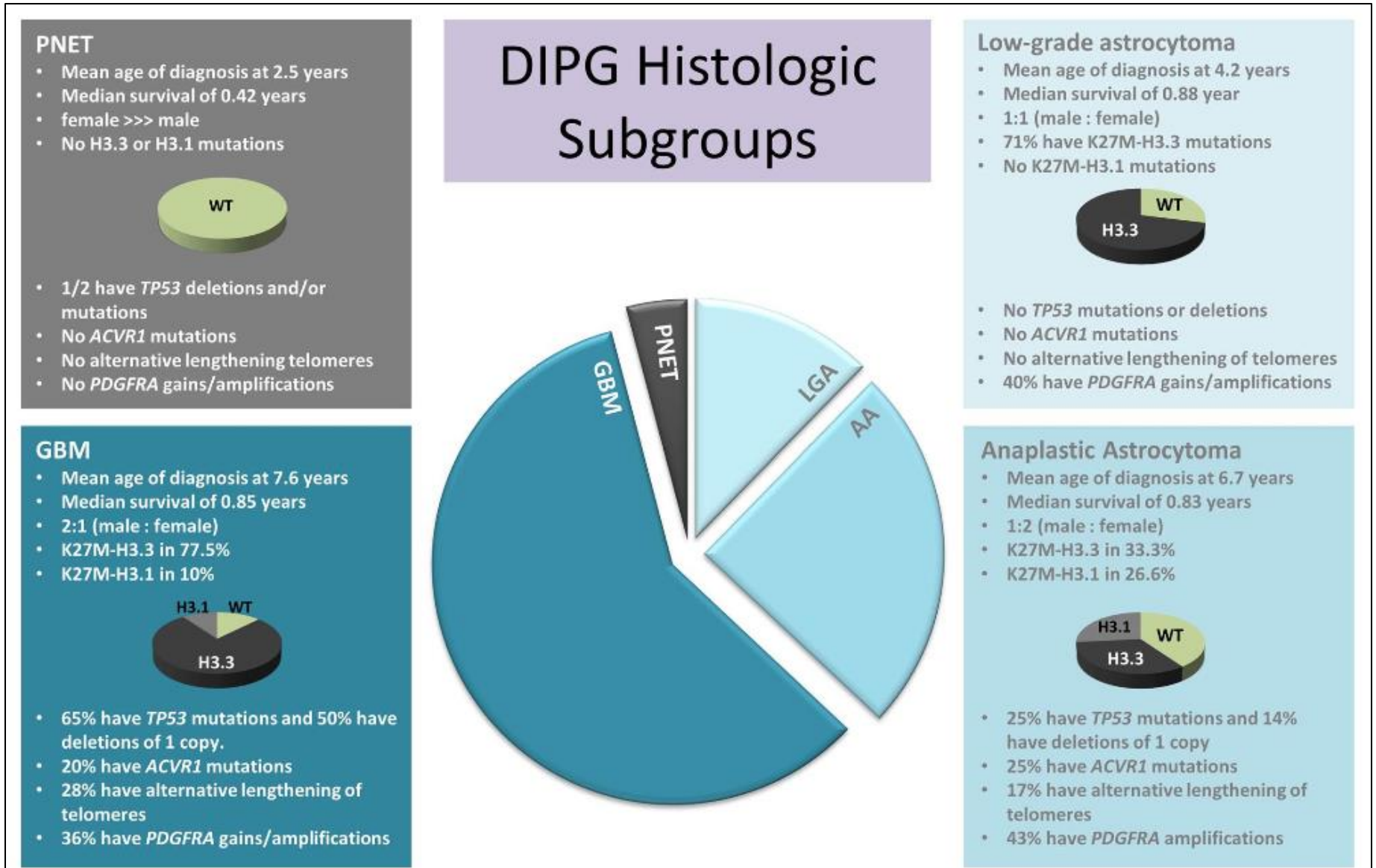
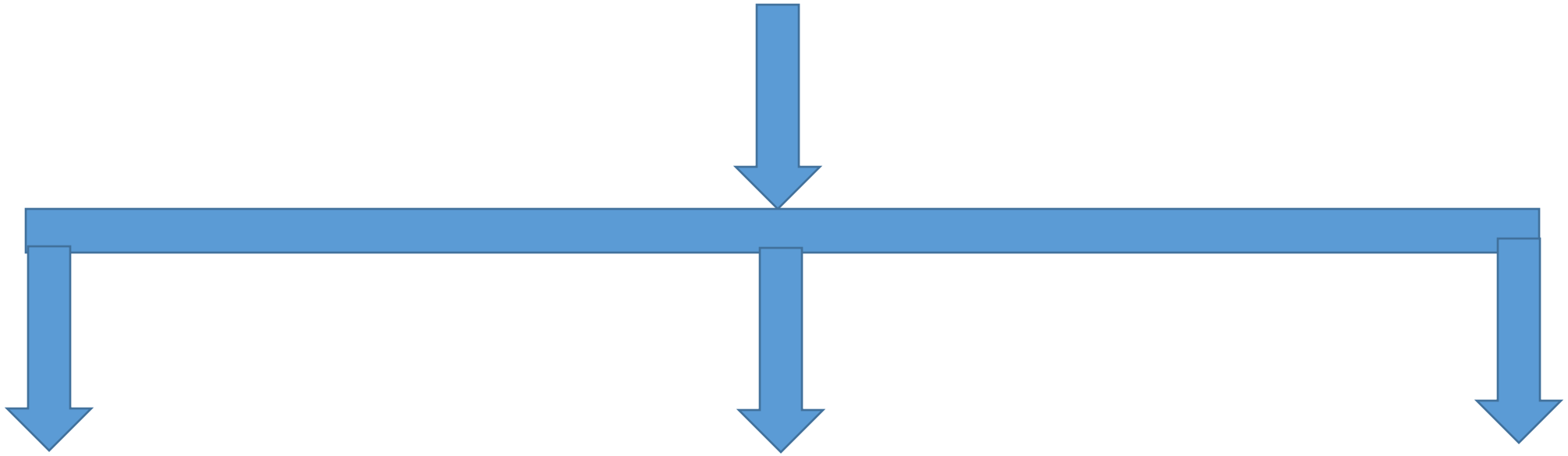


Fig. 3 DIPG histologic subgroups have some unique clinical and molecular features including mean age of diagnosis, sex, H3.3 and H3.1 mutations, *TP53* mutations and deletions, *ACVR1* mutations, *PDGFRA* gains/amplifications and alternative lengthening of telomeres (ALT)

Buczkowicz et al, Acta Neuropathol 2014

Management Options for DIPG



SURGERY

NOT ADVISED due the significant morbidity and mortality caused

SYSTEMIC THERAPY
(chemotherapy, targeted therapy, immunotherapy)

Unsatisfactory response

RADIOTHERPY

Standard of care

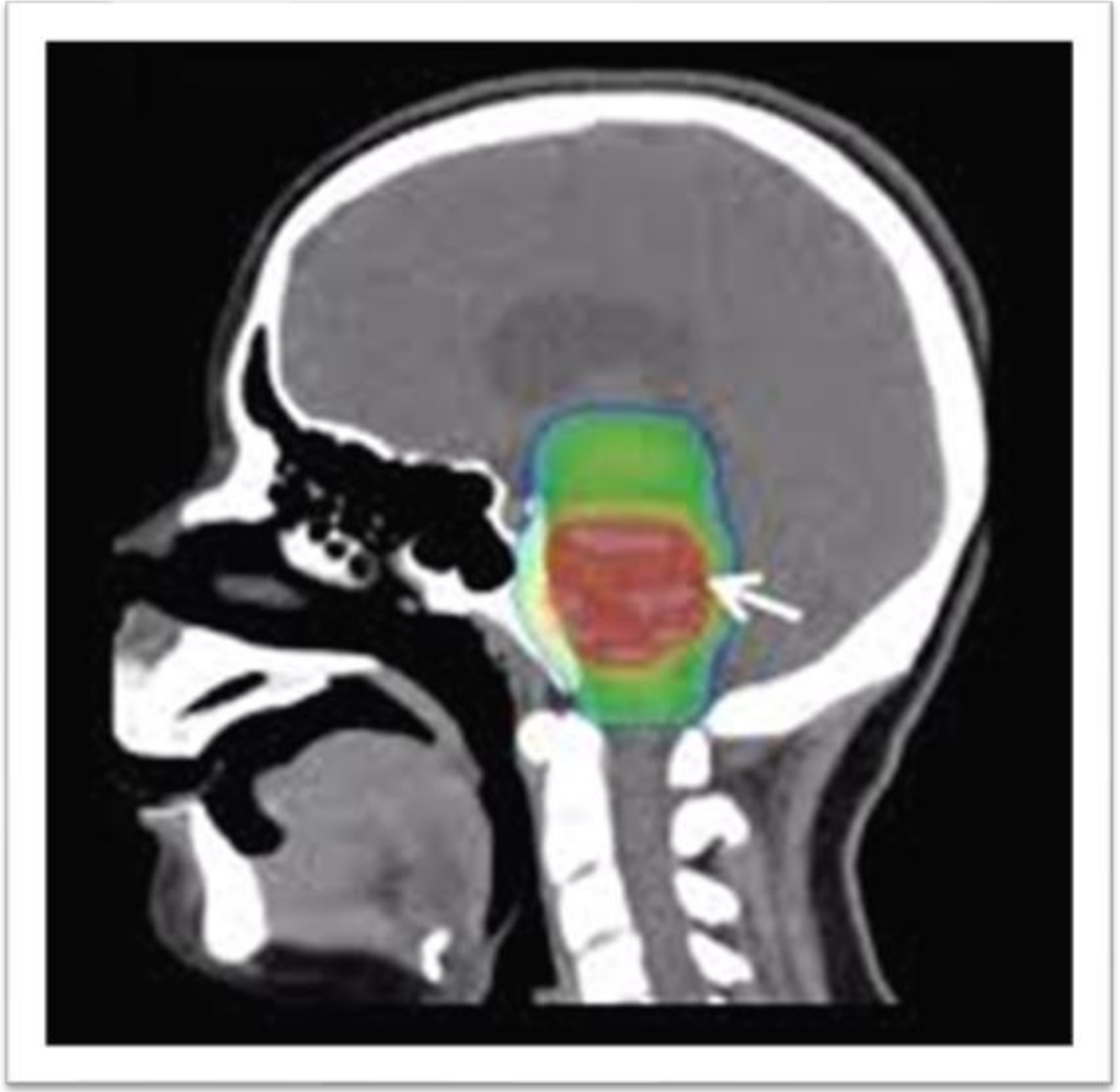
Best Supportive care

RADIOTHERAPY

- Most effective therapy in DIPG

- It induces
  - Neurological improvement (around 85%)
  - Reduction/discontinuation of steroids
  - Radiological response (around 50%)

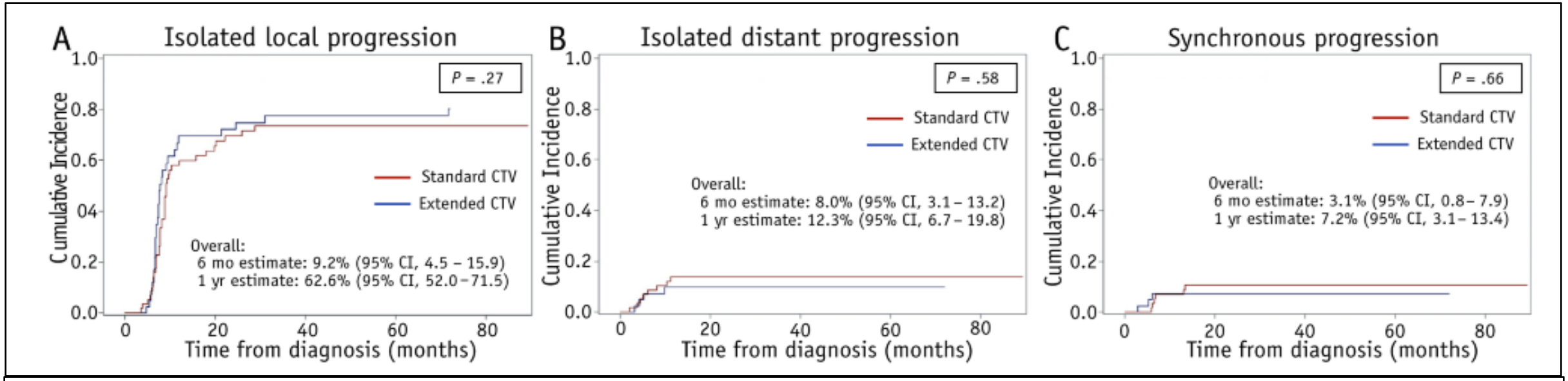
- Numerous studies have proven effectiveness

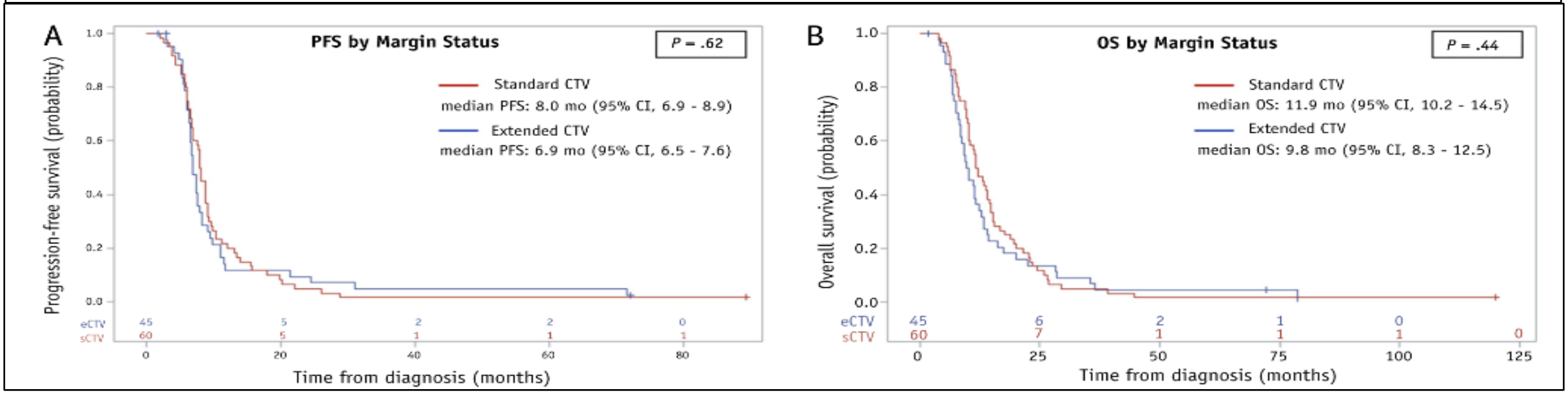


Radiation Therapy in DIPG

- Fractionation schedules
  - *Conventional fractionation (1.8-2.0Gy/fraction): considered as standard*
  - *Hypofractionated RT: non-inferior to standard fractionation*
  - *Hyperfractionated RT: no benefit over standard fractionation*
- Standard dose-fractionation: 54Gy/30 fractions
- RT techniques: Conventional/3D-CRT/IMRT
- Target Volumes and Margins: Variable practice globally

Recommended Target Volumes and Margins





Tinkle et al, IJROBP 2020

Advances in Radiation Oncology (2019) 4, 520-531

advances
in radiation oncology

www.advancesradonc.org

Critical Review

Role of Radiation Therapy in the Management of Diffuse Intrinsic Pontine Glioma: A Systematic Review

Matthew Gallitto BA [a], Stanislav Lazarev MD [a], Isaac Wasserman MPH [a], James M. Stafford PhD [b], Suzanne L. Wolden MD [c], Stephanie A. Terezakis MD [d], Ranjit S. Bindra MD, PhD [e], Richard L. Bakst MD [a,*]

Table 1 Survival outcomes for selected reviewed studies with definitive RT with or without systemic therapy

Reference	No. of patients	Total RT dose (Gy)	RT dose per fraction (Gy)	Biologically effective dose (Gy_{10})	Median OS (mo)
Conventional RT					
[25]	44	55.8	1.8	66	—
[95]	43	54	1.8	64	9.9
[48]	22	54	1.8	64	10.4
[27]	25	59.4	1.8	70	12.1
[96]	26	54	1.8	64	12
[39]	25	54	1.8	64	13.3
[97]	22	54-59.4	—	—	—
[44]	43	54	1.8	64	9.5
[69]	64	54	1.8	64	—
[98]	22	50-70	1.5	57-81	14.2
[47]	25	54	1.8	64	—
[56]	50	54	1.8-2	64-65	13
[99]	32	54.7	—	—	11.7
[49]	21	54	1.8	64	11.7
[40]	23	54	—	—	26.1
[100]	38	54	—	—	14.8
[50]	58	59.4	1.8	70	9.6
[46]	35	54	1.8	64	—
[73]	31	54	1.8	64	6.3
[64]	37	54	1.8	64	13.6
[55]	20	54	1.8	64	9.2
[57]	30	54	1.8	64	9
[28]	21	54	1.8-2	64-65	12
[71]	23	54	2	65	17
[37]	33	55.8	—	—	12
[45]	32	54	1.8	64	8.3
[65]	20	54	1.8	64	8
[51]	38	54	1.8	64	11
[101]	36	50-55	1.6-1.8	58-66	10

Does hyperfractionated RT help improve outcomes?

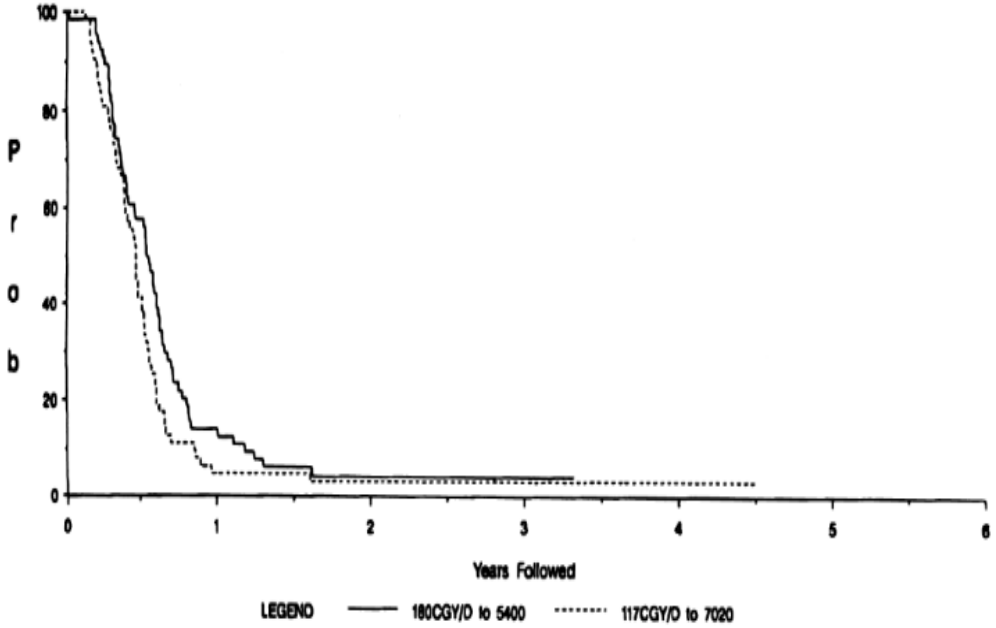


Fig. 1. Event-free survival (arm 1, 66 patients; arm 2, 65 patients).

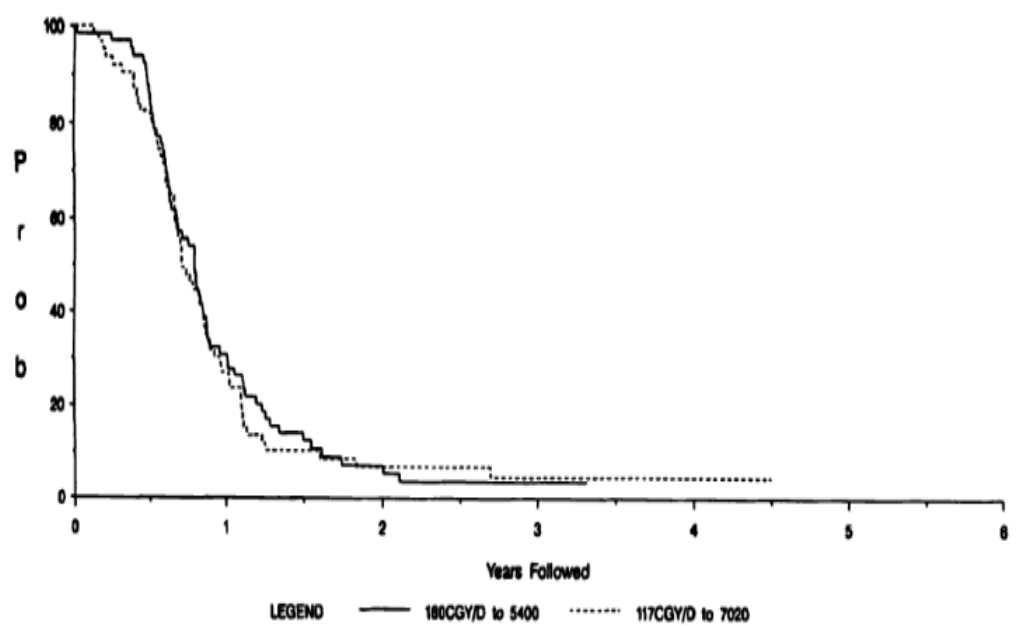


Fig. 2. Survival of eligible patients (arm 1, 66 patients; arm 2, 65 patients).

Conclusion: The major conclusion from this trial is that the hyperfractionated method of Rx 2 did not improve event-free survival ($p = 0.96$) nor did it improve survival ($p = 0.65$) over that of the conventional fractionation regimen of Rx 1, and that both treatments are associated with a poor disease-free and survival outcome.

POG-9239, Mandell et al, IJROBP1999

What about hypofractionated RT?

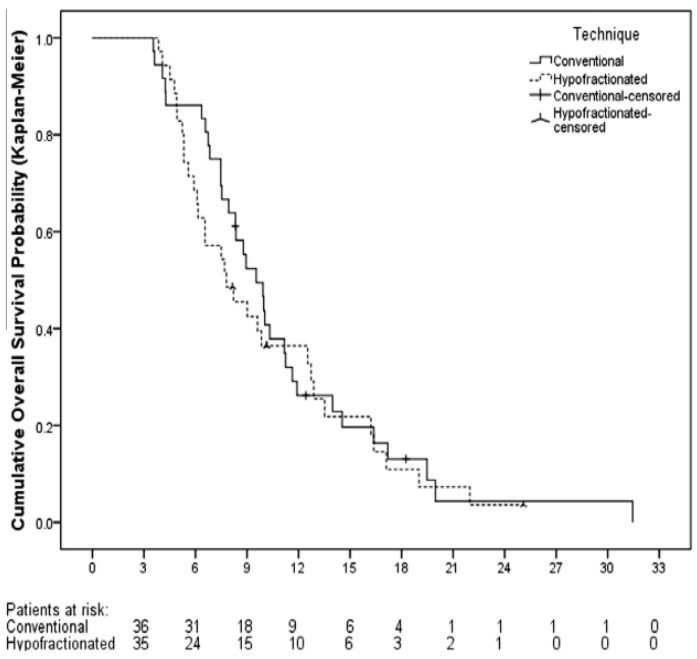


Fig. 2. The overall survival curves for the randomized arms: conventional fractionation and hypofractionation.

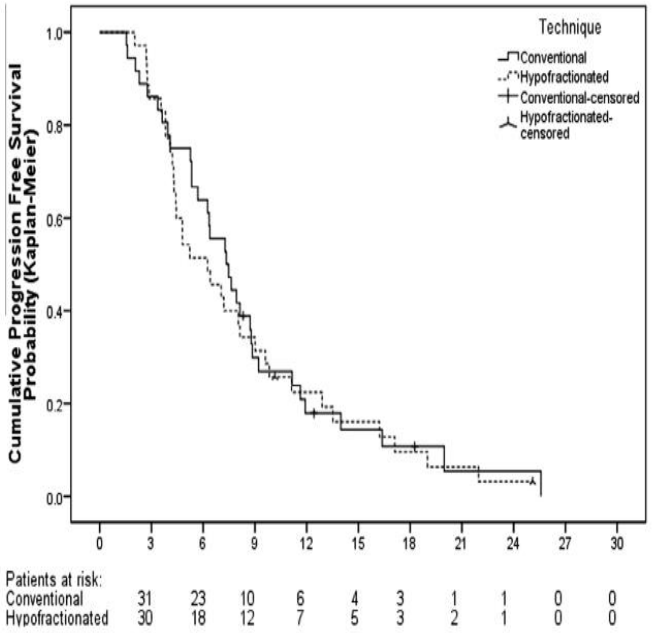


Fig. 3. The progression-free survival curves for the randomized arms: conventional fractionation and hypofractionation.

Conclusions: Hypofractionated radiotherapy offers lesser burden on the patients, their families and the treating departments, with nearly comparable results to conventional fractionation, though not fulfilling the non-inferiority assumption.

Table 3
Radiotherapy –related acute side effects related to suffered by children in the two groups (hypofractionated and conventional).

Side effect	Score	Hypofractionated	Conventional	*p*
Skin	0	19	19	0.829
	1	10	12	
	2	6	5	
Hearing	0	33	34	0.655
	1	2	1	
	2	1	1	
Decreased appetite	0	32	34	0.586
	1	1	2	
	2	2	0	
Dysphagia	0	31	33	0.648
	1	2	2	
	2	2	1	
Fatigue	0	20	22	0.647
	1	5	6	
	2	10	8	
Insomnia	0	33	33	0.669
	1	2	3	
Night mares	0	33	34	0.977
	1	2	2	
Seizures	0	35	35	0.324
	1	0	1	

Zaghloul e al, R&) 2014

Systematic review of hypofractionated RT in DIPG

Systematic Review and Meta-Analysis

Medicine®

OPEN

Hypofractionated radiotherapy versus conventional radiotherapy for diffuse intrinsic pontine glioma

A systematic review and meta-analysis

Jaehyeon Park, MD, Ji Woon Yea, MD, PhD, Jae Won Park, MD, PhD*

Table 1

Summary of the included studies.

Study	Country	Year	Number (CFRT/HFRT)	Randomization	Median age	Dose	Chemoradiotherapy
Hayashi[10] (2020)	Japan	2000–2018	15/9	No	6.3 (1.6–14)	50.4–59.4 Gy/28–33 fx. vs 44.8 Gy/16 fx.	No
Izzuddeen[11] (2020)	India	2016–2018	18/17	Randomized phase II	7 (4–35)	60 Gy/30 fx. vs 39 Gy/13 fx.	Yes (concurrent and adjuvant temozolomide)
Jansssens[7] (2013)	Netherlands, UK, Canada, Belgium	2002–2010	27/27	Matched cohort	7.5 (3.7–13.7)/7.3 (2.8–14.6)	54 Gy/30 fx. vs 44.8 Gy/16 fx. or 39 Gy/13 fx.	No
Zaghloul[8] (2014)	Egypt	2007–2011	35/36	Randomized phase III	7.9 ± 3.6	54 Gy/30 fx. vs 39 Gy/13 fx.	No

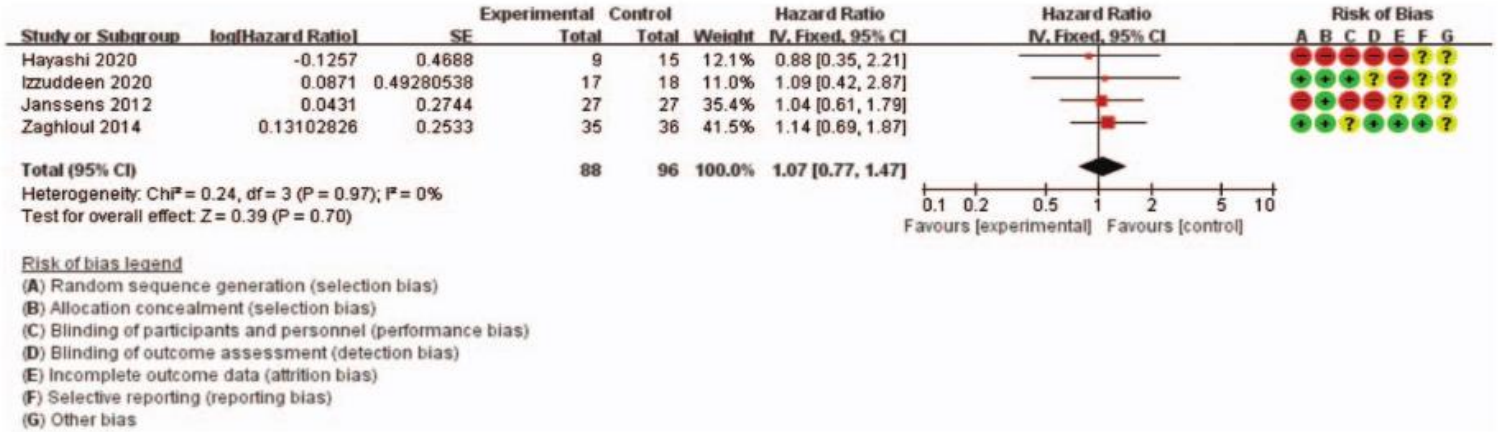


Figure 2. Forest plot of overall survival.

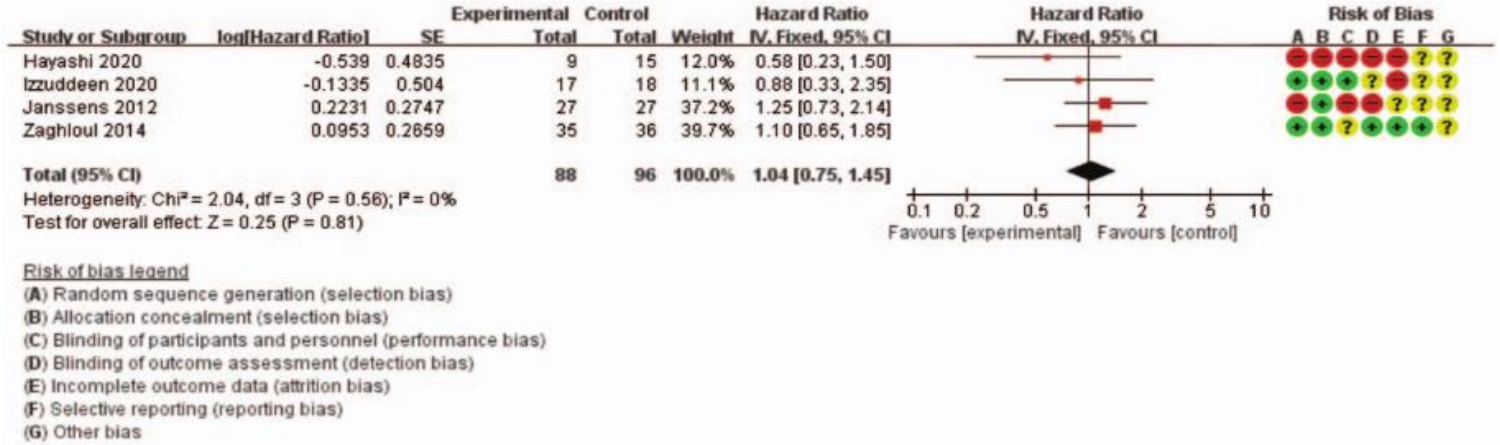
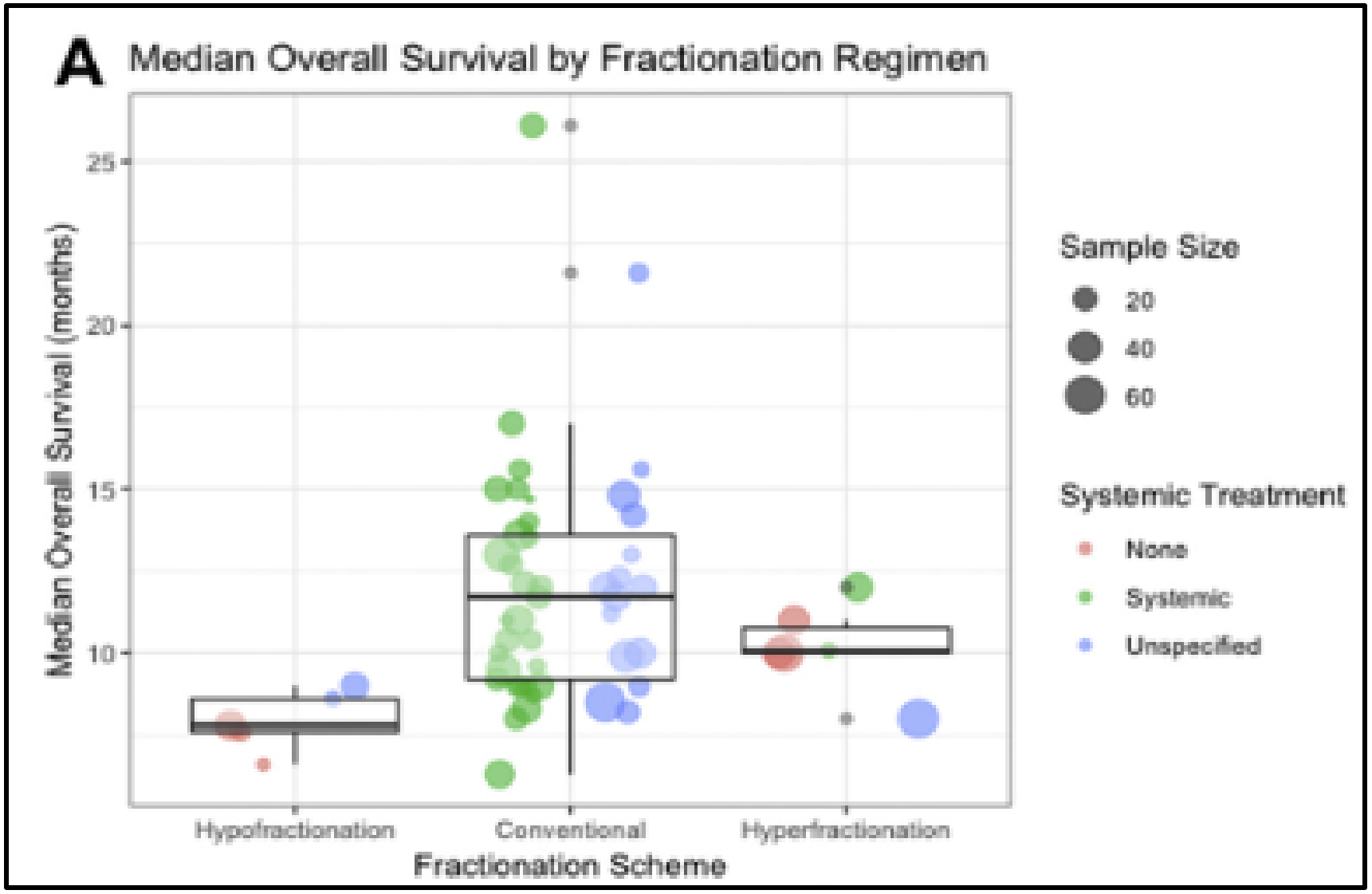


Figure 3. Forest plot of progression-free survival.

No difference in outcomes with hypofractionated RT



Altered fractionation RT no better than standard fractionation RT

The Tale of 100 DIPGs and Radiotherapy

RONC-07

Rahul Krishnatry[*1,2], Jayant Sastri Goda[2,3], Amita Kadam[1], Tejpal Gupta[2,3], Girish Chinnaswamy[1,2], Rakesh Jalali[1,2], Vijay Patil[1,2], Amit Janu[1,2]

1: Tata Memorial Center, Mumbai, India, 2: HBNI University, Mumbai, India,
3: ACTREC, Navi-Mumbai, India

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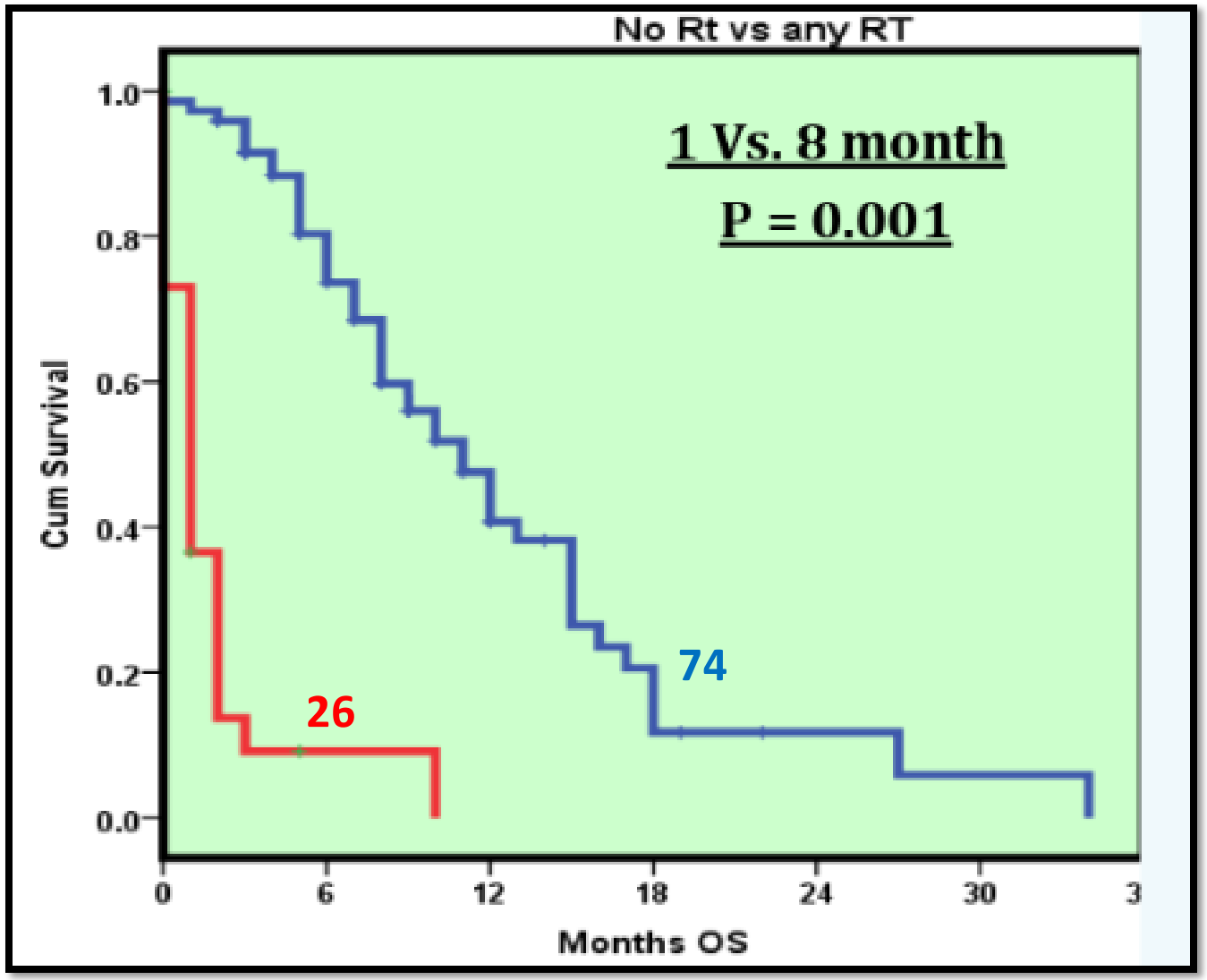
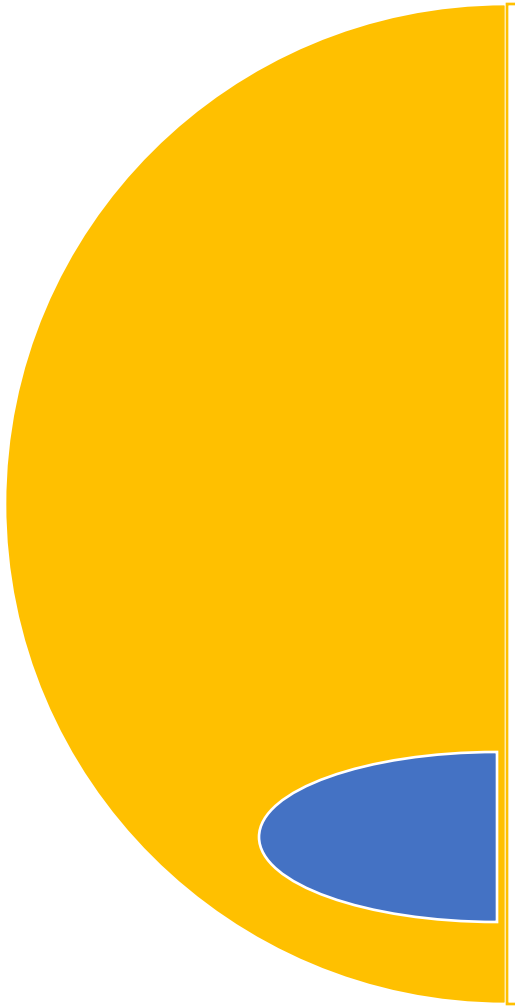


Does adding systemic therapy to RT help?

Chemotherapy – Targeted Therapy – Immunotherapy --- Vaccine



Single and combination regimens

- **PCV regimen**
- **Etoposide, Vincristine, Cyclosporin A**
- **Temozolomide (TMZ)**
- **Platins – Carboplatin, Cisplatin**
- **Topotecan**
- **Interferon**
- **Tamoxifen**

Neoadjuvant, concurrent, and/or adjuvant to RT

Journal of Neuro-Oncology (2020) 146:91–95
https://doi.org/10.1007/s11060-019-03340-7

CLINICAL STUDY

Hypofractionated radiotherapy with temozolomide in diffuse intrinsic pontine gliomas: a randomized controlled trial

Yousra Izzuddeen[1] · Subhash Gupta[1] · K. P. Haresh[1] · Dayanand Sharma[1] · Prashanth Giridhar[2] · Gour Kishore Rath[1]

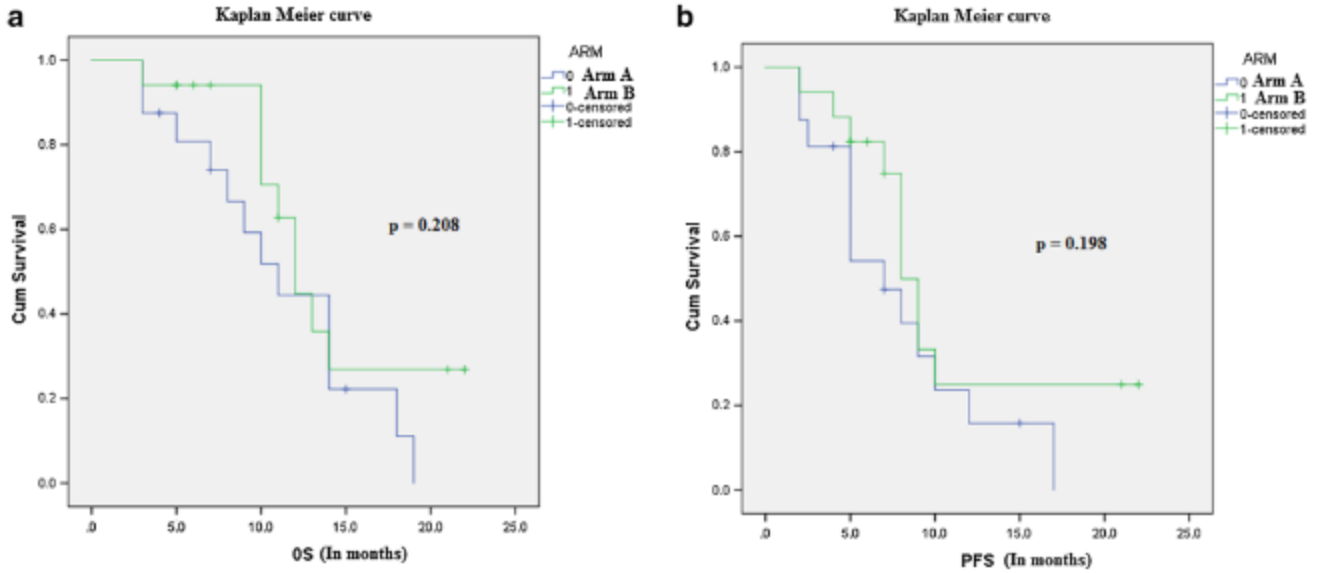


Fig. 1 **a** Kaplan Meier curve comparing cumulative overall survival between arms, **b** Kaplan Meier curve comparing cumulative progression free survival between arms

Table 2 Hematological toxicity in arm B

Patient	Arm	Anemia	Thrombocyto-penia	Leukopenia	Neutropenia
1	B	Grade 2	Grade 4	Grade 4	Grade 4
2	B	Grade 2	Grade 3		
3	B		Grade 3	Grade1	Grade 1
4	B	Grade 3	Grade 4	Grade 3	Grade 4
5	B		Grade 3		

Conclusion The above study shows that hypofractionated radiotherapy with concurrent and adjuvant temozolomide does not improve OS and has higher hematological toxicity. Conventional radiotherapy remains the standard of care.

PROSPECTIVE EVALUATION OF RADIOTHERAPY WITH CONCURRENT AND ADJUVANT TEMOZOLOMIDE IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA

IJROBP2010

RAKESH JALALI, M.D.,* NIRMAL RAUT, M.D.,* BRIJESH ARORA, D.M.,† TEJPAL GUPTA, M.D.,* DEBNARAYAN DUTTA, M.D.,* ANUSHEEL MUNSHI, M.D.,* RAJIV SARIN, F.R.C.R.,* AND PURNA KURKURE, M.D.†

Methods and Materials: Pediatric patients with newly diagnosed DIPGs were prospectively treated with focal RT to a dose of 54 Gy in 30 fractions along with concurrent daily TMZ (75 mg/m^2, Days 1–42). Four weeks after completing the initial RT-TMZ schedule, adjuvant TMZ (200 mg/m^2, Days 1–5) was given every 28 days to a maximum of 12 cycles. Response was evaluated clinically and radiologically with magnetic resonance imaging and positron emission tomography scans.

Results: Between March 2005 and November 2006, 20 children (mean age, 8.3 years) were accrued. Eighteen patients have died from disease progression, one patient is alive with progressive disease, and one patient is alive with stable disease. Median overall survival and progression-free survival were 9.15 months and 6.9 months, respectively. Grade III/IV toxicity during the concurrent RT-TMZ phase included thrombocytopenia in 3 patients, leucopenia in 2, and vomiting in 7. Transient Grade II skin toxicity developed in the irradiated fields in 18 patients. During the adjuvant TMZ phase, Grade III/IV leucopenia developed in 2 patients and Grade IV thrombocytopenia in 1 patient. Patients with magnetic resonance imaging diagnosis of a high-grade tumor had worse survival than those with a low-grade tumor ($p = 0.001$). Patients with neurologic improvement after RT-TMZ had significantly better survival than those who did not ($p = 0.048$).

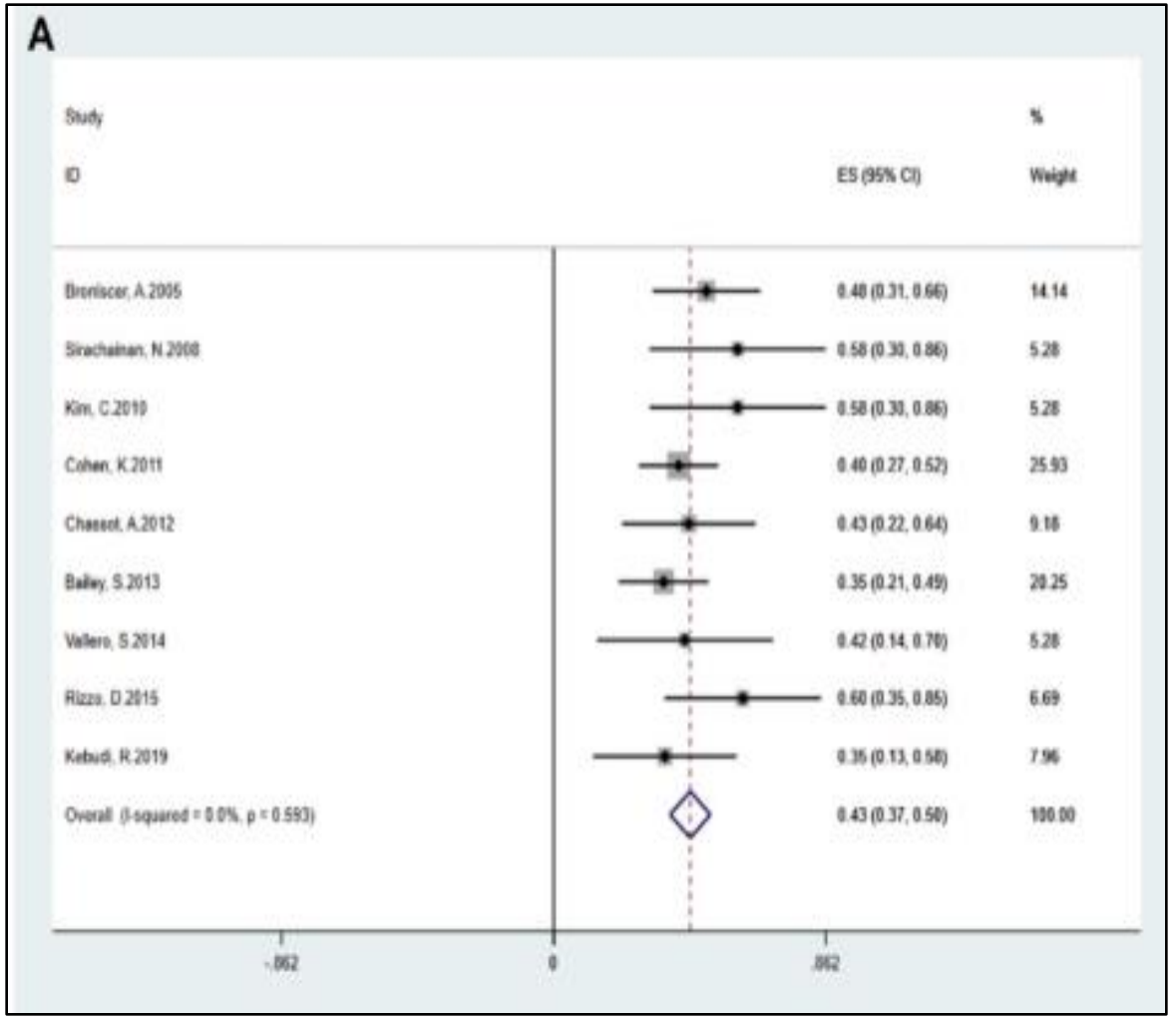
Conclusions: TMZ with RT has not yielded any improvement in the outcome of DIPG compared with RT alone. Further clinical trials should explore novel treatment modalities.

Impact of RT + TMZ in DIPG: No survival benefit

Table 1. Characteristics of the Included Studies

Study	Location	Period	Size (n)	Male (n, %)	Follow-Up (month)	Study Quality	Radiotherapy		OS/PFS	TMZ	Other Drugs
							Dose (Gy)	Fractions (n)			
Broniscer et al., 2005[14]	USA	1999–2002	33	18, 55%	NR	6	1.8	30	OS/PFS	Y	N
Sirachainan et al., 2008[15]	Thailand	NR	12	3, 25%	14.6	6	1.8	30	OS/PFS	Y	Cis-retinoic acid
Chiang et al., 2010[10]	China	2004–2008	18	10, 56%	14.8	6	1.8	30	PFS	Y	N
Jalali et al., 2010[5]	India	2005–2006	20	15, 75%	NR	7	1.8	30	NR	Y	N
Kim et al., 2010[16]	Korean	2004–2008	12	NR	12	7	1.8	30	OS/PFS	Y	Thalidomide
Cohen et al., 2011[8]	USA	2004–2005	58	28, 48%	NR	5	1.8	30	OS/PFS	Y	N
Chassot et al., 2012[17]	France	2005–2009	21	NR	NR	5	1.8	30	OS/PFS	Y	N
Aguilera et al., 2013[9]	USA	2008–2009	2	1, 50%	42	6	1.8	30	NR	Y	Bevacizumab
Bailey et al., 2013[18]	UK	2008–2010	43	24, 56%	NR	5	1.8	30	OS	Y	N
Zaky et al., 2013[19]	USA	2007–2007	6	1, 17%	NR	5	1.8	30	NR	Y	Irinotecan
Vallero et al., 2014[20]	Italy	1999–2013	24	11, 46%	NR	5	1.8	30	OS/PFS	Y	N
Muller et al., 2014[9]	Germany	2007–2012	2	0	9.1	6	35.2	5	NR	Y	N
Rizzo et al., 2015[21]	Italy	2007–2011	15	3, 20%	15	5	1.8	30	OS/PFS	Y	N
Kebudi et al., 2019[22]	Turkey	2010–2017	17	NR	17	6	1.8	30	OS	Y	Nimotuzumab

OS, overall survival; PFS, progression-free survival; TMZ, temozolomide; NR, not reported; Y, yes; N, no.

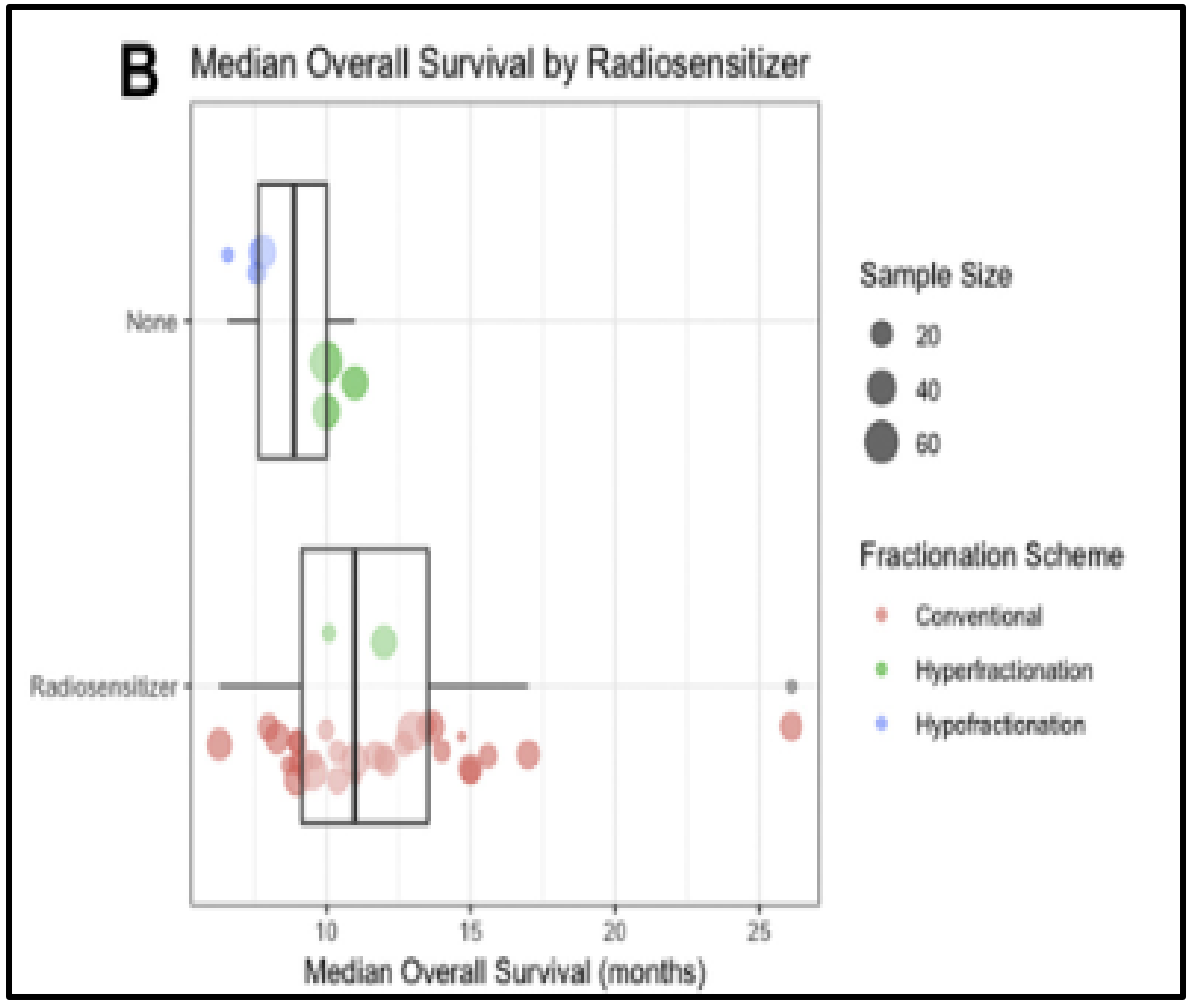


Shi et al, WNS 2021

Table 3 Survival outcomes and chemotherapy-related toxicities based on radiosensitizing agent

Agent	Total Number of Patients	Mean median OS (mo)	Mean 1-year OS (%)	Mean median PFS (mo)	Mean 1-year PFS (%)	Toxicities	
						CTCAE 3	CTCAE 4
Alkylating agent[28,31,38,40,44,49,50,55,56,59,62,64,66]	323	13.4	48.0	12.1	27.1	Nausea (5), neutropenia (2), leukopenia (2)	Leukopenia (2), thrombocytopenia (3), neutropenia (2)
						Lymphopenia (39), neutropenia (13), leukopenia (11), infection (4)	thrombocytopenia (16),
Topo-isomerase inhibitor[28,32,45,53,57,58,61,64-66]	237	11.2	40.6	6.0	21.0	Neutropenia (2), constipation (1), seizures (2), hematological side effects (2)	Neutropenia (7), anemia (11), hematological side effects (3), thrombocytopenia (3)
						Neutropenia (33), thrombocytopenia (5), anemia (9), nausea/vomiting (3), infection (7), leukopenia (8), lymphopenia (12), nausea (1)	
Anti-microtubular agent[28,31,39,40,52,53,56,57,60]	171	12.8	40.0	13.5	23.0	Hypokalemia (1), constipation (1), seizures (2)	Neutropenia (1)
						Anemia (9), neutropenia (14), nausea/vomiting (3), infection (7)	
Platinum agent[18,28,32,42,51,52,56,64,66]	285	11.7	37.2	6.7	21.0	Neutropenia (2), leukopenia (1), thrombocytopenia (2)	Neutropenia (6), thrombocytopenia (3)
						Thrombocytopenia (5)	
Anti-metabolic agent[25,28,63]	74	10.4	45.0	5.9	18.6	Lymphopenia (17), leukopenia (3), neutropenia (5), hepatotoxicity (2)	Lymphopenia (2), neutropenia (2)
EGFR inhibitor[27,39,48]	54	11.9	–	7.5	29.6	Anemia (2), neutropenia (6), lymphopenia (26), hepatotoxicity (5), hypokalemia (1)	
Blood vessel growth inhibitor[46,47,54]	75	10.4	44.8	8.2	–	Hepatotoxicity (2), lymphopenia (14), neutropenia (2)	Thrombocytopenia (2), neutropenia (2), lymphopenia (11)
						Anemia (5), neutropenia (5), thrombocytopenia (1)	
Other agents[69-74,102]	–	–	–	–	–	Lymphopenia (14), hepatotoxicity (7), hypertension (5), vomiting (2), motor neuropathy (2), constipation (2), rash (2), skin desquamation (1)	Pain syndrome (1), allergy (1), leukopenia (1), neutropenia (2), DVT/PE (1)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DVT = deep vein thrombosis; EGFR = epidermal growth factor receptor; OS = overall survival; PE = pulmonary embolism; PFS = progression-free survival; RT = radiation therapy.

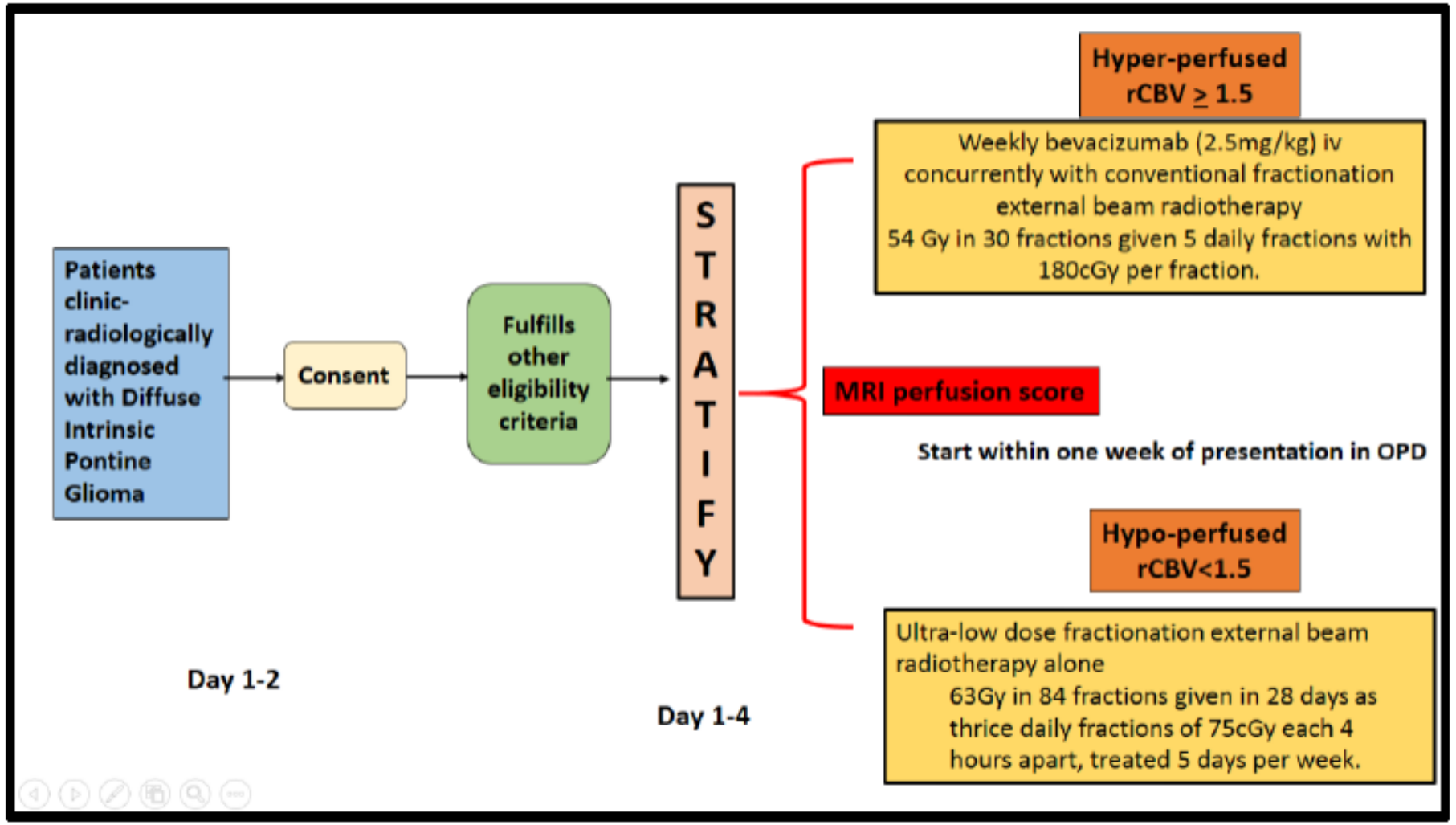


Gallitto et al, ARO 2019

No benefit of adding any radiosensitizing therapy to RT in DIPG

Thinking out of the BOX for improving outcomes

LoBULarDIPG study (NCT04250064): PI: Dr Rahul Krishnatry, TMC-Mumbai



Funding support: Anchit Ahuja Fund/Brain Tumor Foundation (BTF) of India

Prognosis of DIPG: DISMAL

- Universally fatal with in 2 years
- Median OS 10-12 months

- Deviations generally with
  - Age <3-years or >10-years
  - Prolonged interval between onset of symptoms and diagnosis >6 months
  - Absence of <2/3 classical clinical or radiological triad

- Above ones are called “Atypical” (colloquially)

Prognostic scoring system for DIPG

Table 3. Results of the multivariate Cox proportional hazards analysis and translation into risk score

Predictor	Hazard Ratio (95% CI)	*P*	Coefficient After Shrinkage	Contribution to Risk Score
Age ≥3 y	1.95 (1.01-3.80)	.046	0.667	7
Symptom duration, mo	0.92 (0.86-0.97)	.003	−0.085	−1
Ring enhancement	1.41 (1.07-1.84)	.013	0.354	4
Chemotherapy:		.013		
Oral chemotherapy	0.66 (0.49-0.88)	.048	−0.398	−4
Intensive chemotherapy	0.63 (0.40-0.99)	.047	−0.418	−4

The formula to calculate the DIPG risk score for an individual patient = months of symptom duration (x − 1) + age ≥3 y (+7) + ring enhancement (+4) − the use of oral/intensive chemotherapy (=4).

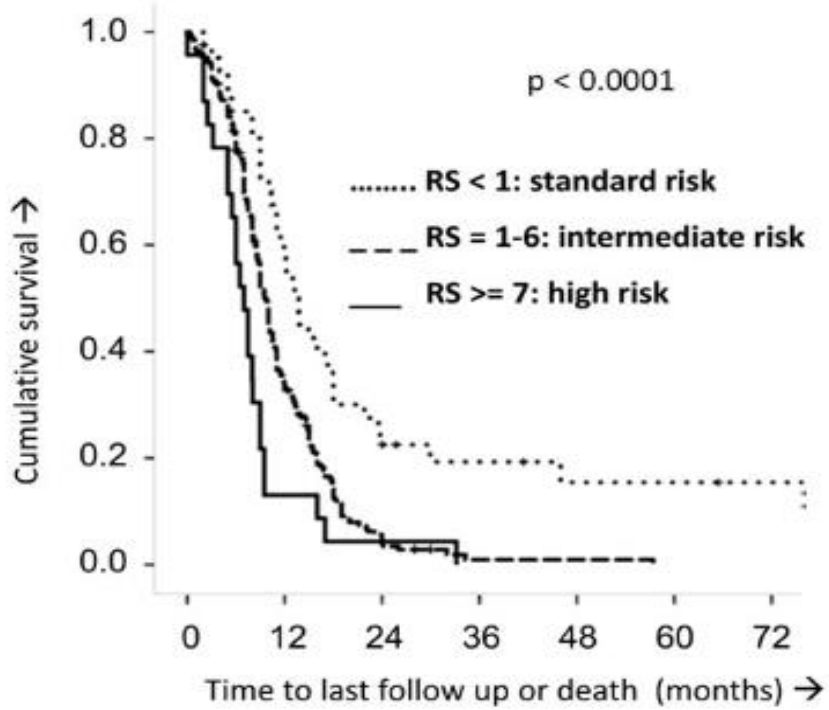


Fig. 2. Kaplan–Meier estimates of the DIPG risk score (RS). Based on the risk score, 3 categories were identified: a standard risk arm (RS <1), an intermediate risk arm (RS 1–6), and a high-risk arm (RS ≥ 7). The increasing risk arms correlated with decreasing OS time (log-rank $P <$ .0001 and generalized Wilcoxon $P <$ .0001).

Jansen et al, Neuro-Oncol 2014

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries

Lindsey M. Hoffman, Sophie E.M. Veldhuijzen van Zanten, Niclas Colditz, Joshua Baugh, Brooklyn Chaney,

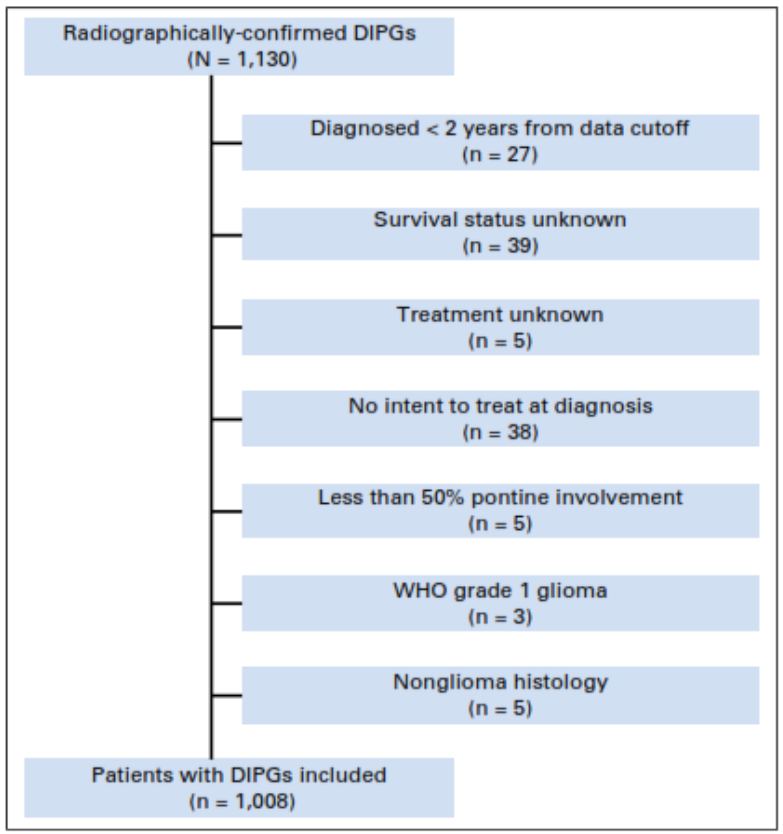
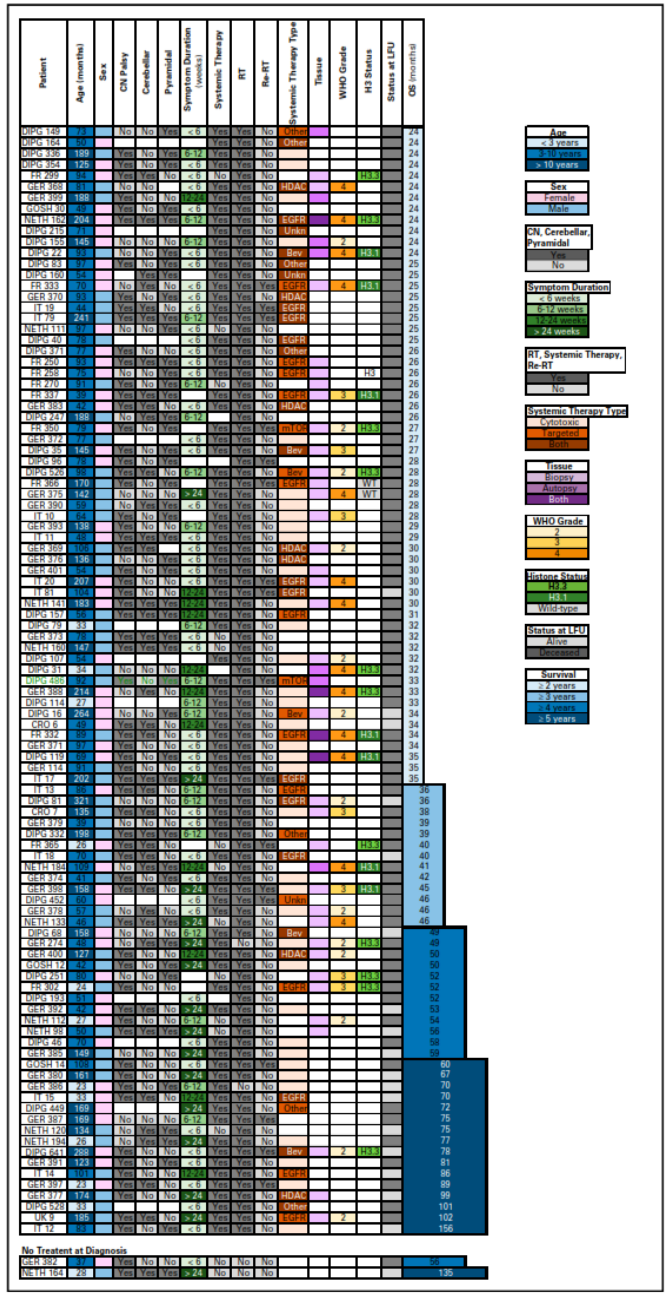


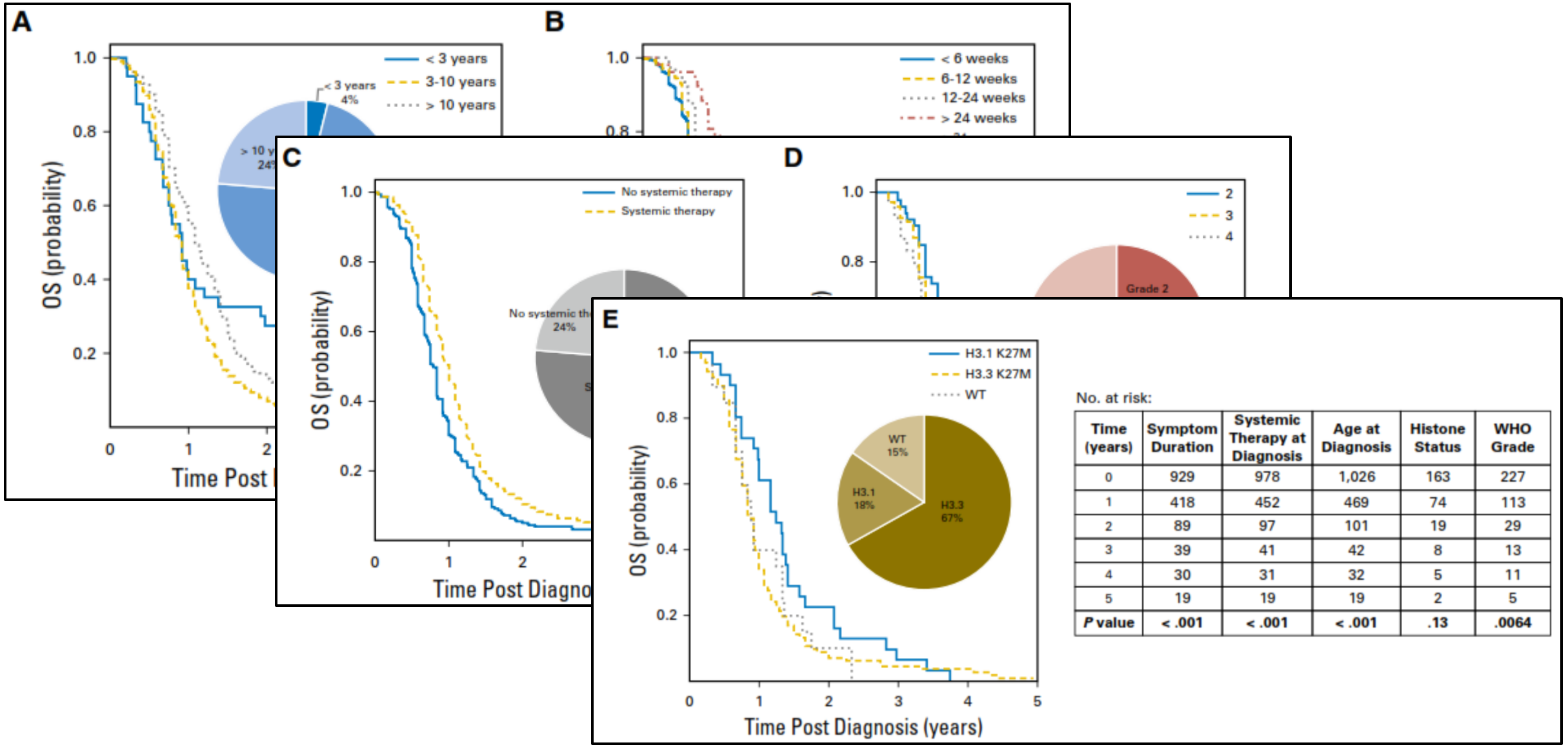
Fig 1. Flowchart of patients excluded from this study. DIPG, diffuse intrinsic pontine glioma.

Table 2. Results of Multivariable Cox Proportional Analysis of Clinical, Radiologic, and Molecular Variables Predicting Survival

Variable	Odds Ratio (95% CI)	*P*
Clinical		
Age, years		.02
< 3	2.82 (1.06 to 10.28)	
3-10	1.0	
> 10	2.24 (1.27 to 3.96)	
Symptom duration, weeks		< .001
< 6	1.0	
6-12	1.49 (0.76 to 2.92)	
12-24	2.43 (1.04 to 5.75)	
> 24	5.7 (2.77 to 14.54)	
Cranial nerve palsy		.08
Yes	0.57	
No	1.0	
Systemic therapy at diagnosis		.01
Yes	3 (1.46 to 7.3)	
No	1.0	
Category of systemic therapy		.14
Cytotoxic chemotherapy	1.0	
Targeted chemotherapy	1.03 (0.51 to 2.09)	
Both	1.84 (0.99 to 3.41)	
Systemic therapy type		
Cytotoxic	1.59 (0.73 to 3.45)	.24
EGFR inhibitor	2.32 (1.1 to 4.82)	.03
HDAC inhibitor	1.49 (0.62 to 3.6)	.38
mTOR inhibitor	0.98 (0.11 to 8.66)	.98
Bevacizumab	2.67 (1.09 to 6.55)	.03
Other targeted agent	0.71 (0.22 to 2.28)	.56



Prognostic factors for long-term survivors (>2-years)



No. at risk:

Time (years)	Symptom Duration	Systemic Therapy at Diagnosis	Age at Diagnosis	Histone Status	WHO Grade
0	929	978	1,026	163	227
1	418	452	469	74	113
2	89	97	101	19	29
3	39	41	42	8	13
4	30	31	32	5	11
5	19	19	19	2	5
P value	< .001	< .001	< .001	.13	.0064

MRI and clinical predictors of survival

Table 4. Univariable analysis of Imaging features and overall survival (significant findings)

Univariate	HR	p
Clinical		
Age (continuous)	*1.00*	*0.033*
Age		*0.001*
Symptom duration		*0.018*
Chemotherapy	*0.46*	*<0.001*
Midbrain extension	*1.36*	*0.008*
Extension Beyond Pons and BP	*1.64*	*0.002*
Extension Beyond Pons	*2.15*	*0.001*
AP Tumor dimension	*1.02*	*0.023*
Trans Tumor dimension	*1.01*	*0.031*
AP X Trans Tumor dimension	*1.00*	*0.029*
CC Tumor dimension	*1.01*	*0.009*
AP Tumor / AP pons ratio	*2.29*	*0.005*
AP X TR Tumor > AP X TR Pons	*1.30*	*0.012*
Enhancement (any)	*1.36*	*0.010*
Ring Enhancement vs. Non-enhancing	*1.45*	*0.007*
Patchy Enhancement vs. Non-enhancing	*1.44*	*0.005*
Patchy and Ring Enhancement vs. Non-enhancing	*1.93*	*0.001*
Diffusion restriction (any)	*1.46*	*0.003*
Hemorrhage (any)	1.22	0.098
Hemorrhage (GRE/SWI)	*1.43*	*0.028*
Necrosis (any)	*1.47*	*0.0006*
Necrosis + Ring Enhancement	*1.40*	*0.005*
Necrosis with no Ring Enhancement	*1.48*	*0.034*
Distant Disease	*2.95*	*0.0005*
Distant Disease (spine available)	*2.64*	*0.0031*

Table 5. Multivariable analysis of clinical and imaging features and OS. *Diffusion status removed for missing >10%, AP x Trans and AP x CC for high correlation with AP, midbrain extension since it is included in the definition of extension beyond Pons or BP, extension beyond pons and brachium pontis due to correlation with extension beyond pons, enhancement subtypes due to correlation with enhancement, and hemorrhage with SWI or GRE sequences due to missing >10%).*

Variable		HR	p
Age			**0.0187**
	<3	**0.76**	
	3-10	**1.00**	
	10+	**0.66**	
Symptom duration			0.1164
	< 6 weeks	1.00	
	6 - 12 weeks	0.78	
	12 - 24 weeks	0.76	
	> 24 weeks	0.60	
Chemo		**0.45**	**<0.0001**
Extension beyond Pons or BP		1.10	0.9247
AP Tumor dimension		0.99	0.3246
Trans Tumor dimension		1.00	0.8672
CC Tumor dimension		1.01	0.1996
AP Tumor / AP pons ratio		2.26	0.0631
Beyond Pons		1.33	0.7807
Enhancement (any)		1.21	0.2167
Heterogeneity (marked)		0.94	0.7601
Necrosis		1.21	0.1932
Distant Disease		**2.97**	**0.0021**

Leach et al, IDIPG Registry, Neuro-Oncol 2020

Recurrence/Progression: Rule

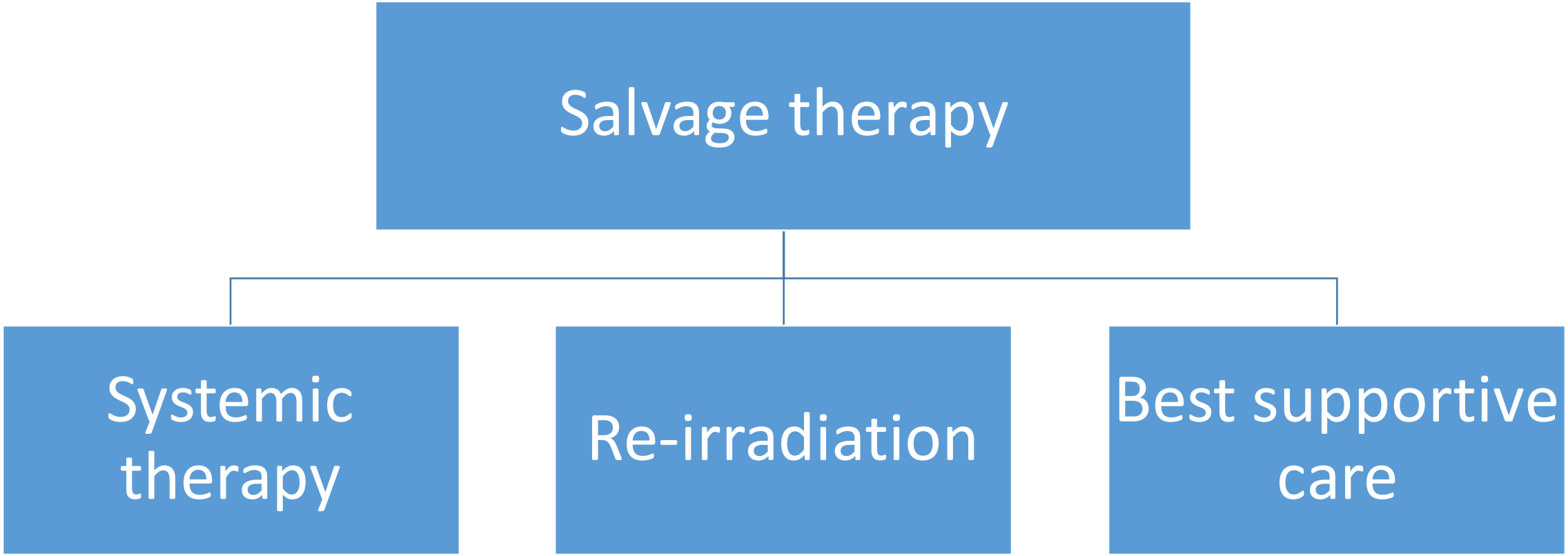
- Inevitable
- Median PFS – 6-8 months
- Median survival –10-12 months

Gallitto et al, ARO, 2019

- Progression - local recurrence with or without dissemination
  - Disseminated disease: 15-20%
- Cause of death – rapid local progression

Wagner et al, BJC, 2006

Options at recurrence/progression



Re-irradiation

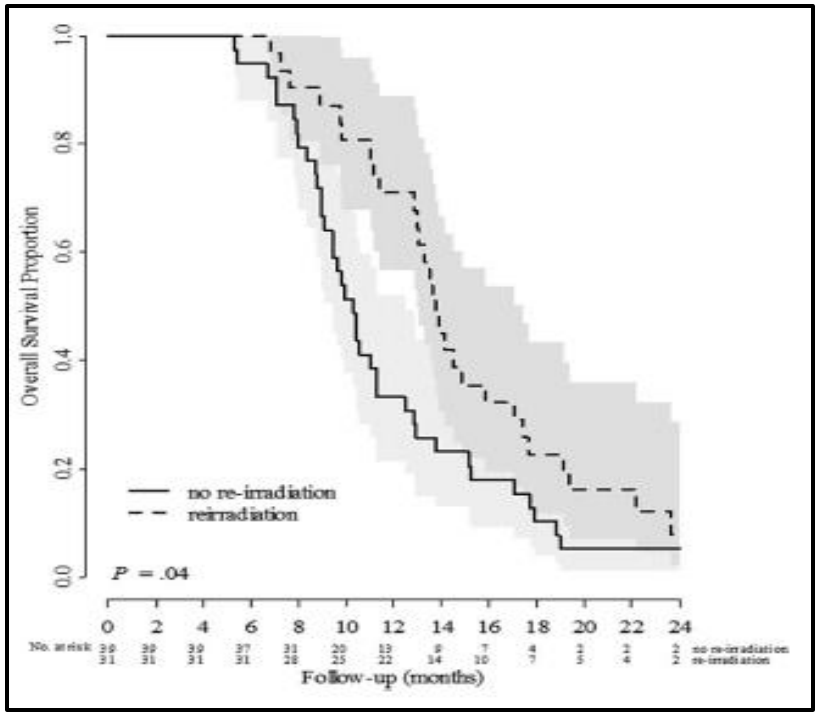
- Benefit compared to other options shown consistently
- Aims –
  - Effective palliation
  - Steroid independence
- Multiple studies (majorly retrospective)
  - Pan-European, Pan-American studies, some single-institution studies
- No randomized data available

Case selection for Re-irradiation

Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: A matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group☆

Geert O. Janssens [a,*], Lorenza Gandola [b], Stephanie Bolle [c],

- **Longer PFS: Typically ≥6 months**
- **Good response to index course of RT**
- **Reasonable performance score LPS >40**



A Phase I/II Trial of Reirradiation for Diffuse Intrinsic Pontine Glioma

Mark J. Amsbaugh, MD, Anita Mahajan, MD, Peter F. Thall, PhD, Mary Frances McAleer, MD PhD, Arnold C. Paulino, MD, David Grosshans, MD PhD, Soumen Khatua, MD, Leena Ketonen, MD PhD, Hiral Fontanilla, MD, Susan L. McGovern, MD PhD

- Only prospective study of Re-RT in DIPG
- To identify optimal dose for Re-RT in DIPG
- 12 patients completed Re-RT in 3 dose levels
  - 24Gy/12# (6 patients),
  - 26.4Gy/12# (4 patients)
  - 30.8Gy/14# (2 patients)

	Toxicity Severity Level			
	Mild	Moderate	High	Severe
Efficacy Response	(D1, D2, D3)	(D1, D2, D3)	(D1, D2, D3)	(D1, D2, D3)
0 of 3 good indicators	(0,0,0)	(0,1,0)	(0,0,0)	(0,0,0)
1 of 3 good indicators	(0,1,0)	(0,0,0)	(0,0,0)	(0,0,0)
2 of 3 good indicators	(4,1,0)	(1,0,0)	(0,0,0)	(0,0,0)
3 of 3 good indicators	(1,1,0)	(0,0,0)	(0,0,1)	(0,0,0)

D1 = 24.0 Gy / 12 fx, D2 = 26.4 Gy / 12 fx, D3 = 30.8 Gy / 14 fx

*Patient 9 does not have an efficacy response

24Gy in 12 fractions was the recommended dose-fractionation based on utility analysis

Dose at Re-irradiation

Reference	n	First radiation therapy dose	Re-irradiation dose	Clinical response	Median survival from progression or re-irradiation	Absolute median survival gain with re-irradiation
[30]	31	n/a	19.8–30 Gy	77% (crude)	n/a*	3.4 months
[34]	16	n/a	21.6–36 Gy	81% (crude)	6.5 months	4.1 months
[35]	14	n/a	n/a	n/a	7 months	3.5 months
[36]	11	54 Gy	19.8 Gy	91% (crude)	6 months	2.7 months (n.s.)
[37]	5	54–55.8 Gy	18–20 Gy	80% (crude)	5 months	n/a

Trend of increase in median survival with increase in Re-RT dose

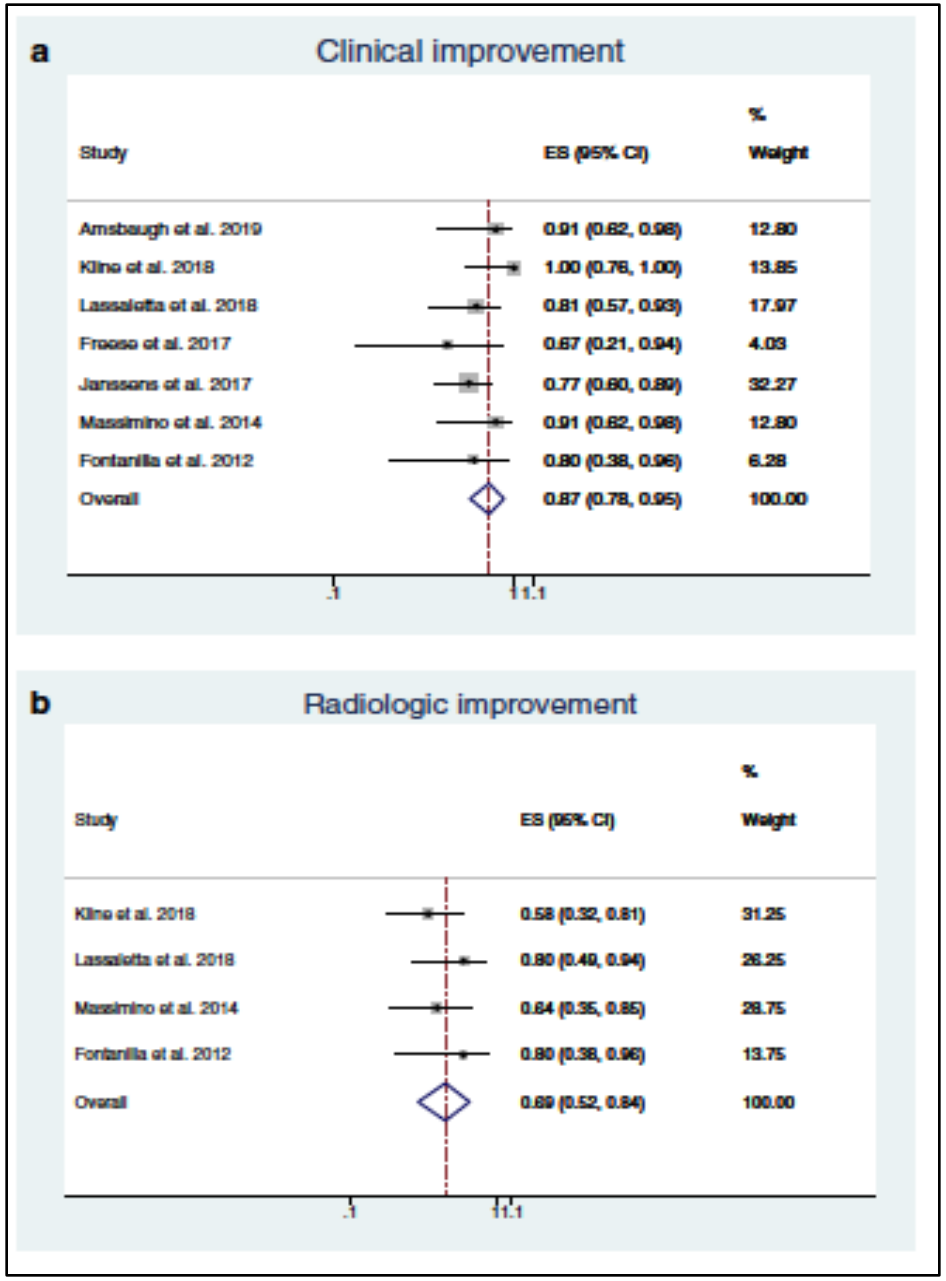
Tsang et al, Clinical Oncology, 2018

Systematic review and meta-analysis of re-irradiation in DIPG

Study	Cohort size (*n*)	Median time from initial RT to reRT (months)	reRT regimen		Additional systemic therapy at reRT	reRT complications (grade 3+)	Radiation necrosis (*n*)	Median OS from initial diagnosis (months)
			Dose (Gy)	Fractions (*n*)				
Amsbaugh et al. 2019	12	12.3	24–30.8	10–12	N	1 x hypoxia	NR	19.5
Kline et al. 2018	12	11.8	24	10–12	Y	N	NR	20.8
Lassaletta et al. 2018	16	13	21.6–30.6	10–17	Y	1 x pontine necrosis	2	19.3
Freese et al. 2017	3	14	20	10	N	N	NR	17.3
Janssens et al. 2017	31	NR	18–30	10–11	Y	N	0	13.7
Massimino et al. 2014	11	NR	19.8	11	Y	N	NR	16
Fontanilla et al. 2012	5	12.5	18–20	10	Y	N	0	NR

Re-RT in DIPG: Outcomes (N=90)

- Clinical improvement – **87%**
- Radiological response – **69% (40 patients)**
- Steroid weaning – **76% (42 patients)**
- Median PFS (from time of reRT) **– 4.2 months**
- Median OS (from time of reRT) **– 6.2 months**
- Median OS (from diagnosis) – **18 months**



Lu et al, CNS 2019

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2021, 1–8
doi: 10.1093/jjco/hyab006
Original Article

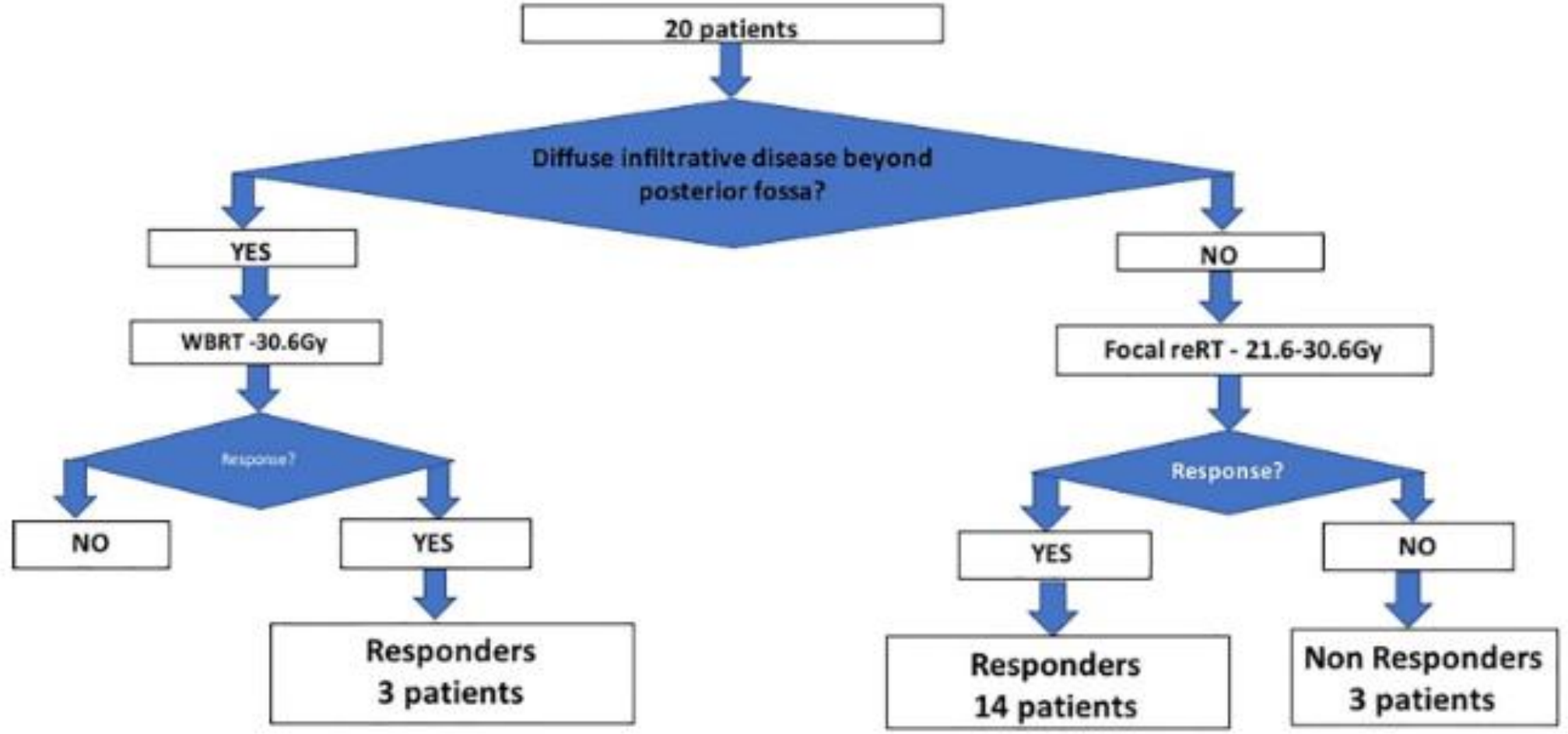


Figure 1. Institutional pragmatic clinical scenario and response-based dose and volume approach.

Table 1. General characteristics of the study cohort

Age—median (IQR)	7.5 years (6–13.2)
Male: Female	12:8
LPS at diagnosis—median (IQR)	70 (50–77.5)
Clinical diagnostic criteria	
Two	75% (15 pts)
Three	25% (5 pts)
Radiological criteria	100%
Initial treatment details	
RT dose	54 Gy (19 patients), 60 Gy (one patient)
Concurrent therapy	20% (4 pts)
Adjuvant chemotherapy	40% (8pts)
Median PFS (IQR)	8.4 months (6.6–9.7)
LPS at reRT—median (IQR)	50 (50–60)
reRT details	
Median dose (IQR)	41.4 Gy (33.8–43.2)
Technique-3DCRT: IMRT	17:3
Adjuvant therapy	10% (2 pts)
Salvage therapy	
Pre reRT	15% (3 pts)
Post reRT	5% (1 pt)
Median RT interval (IQR)	8.9 months (7.3–9.9)

IQR, inter-quartile range; LPS, Lansky performance score; RT, radiotherapy; reRT, re- irradiation; Gy, Gray.

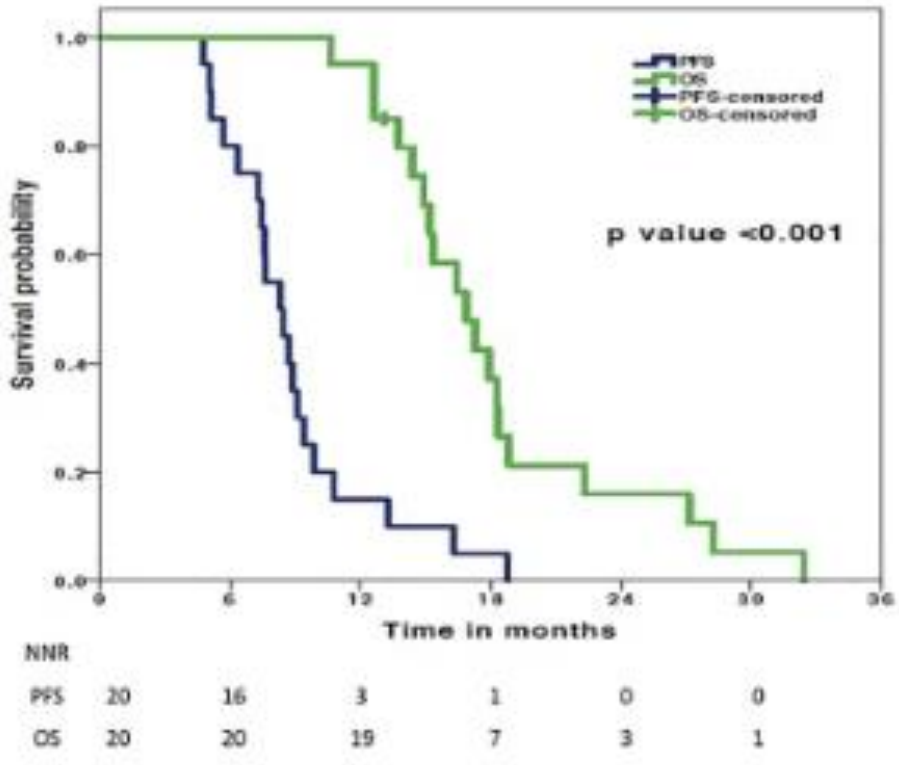


Figure 2. Initial progression-free survival compared with cumulative overall survival for the whole cohort

Conclusions: Higher doses of re-irradiation based on a clinical-response-based approach show improvement in survival and steroid dependence rates with acceptable toxicity. Steroid independent status at 1-month post-re-irradiation predicts better outcomes. Prospective studies may validate this with quality of life data.

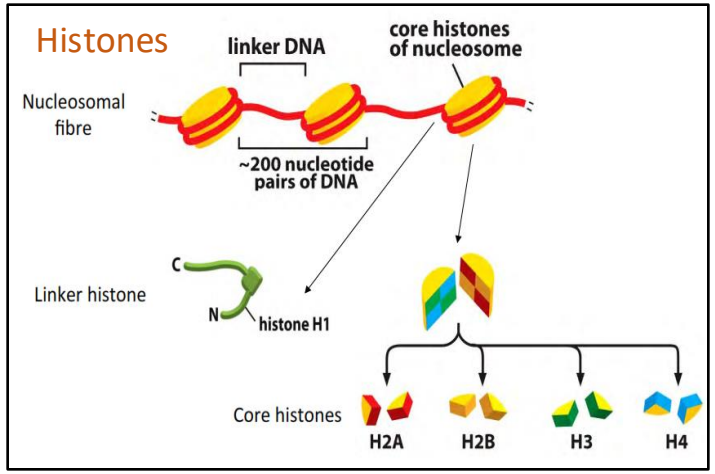
Molecular Biology of DIPG

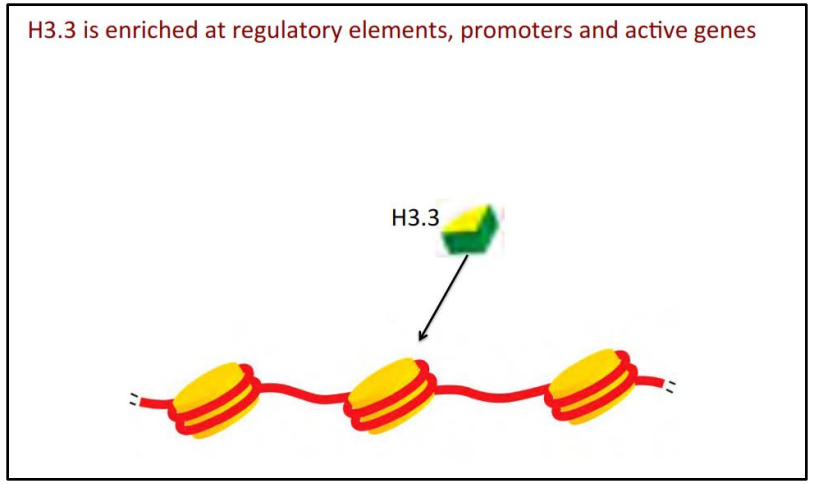
Table 1 Summary of genetic, epigenetic and immune check abnormalities in DIPG with their pathways and main drivers

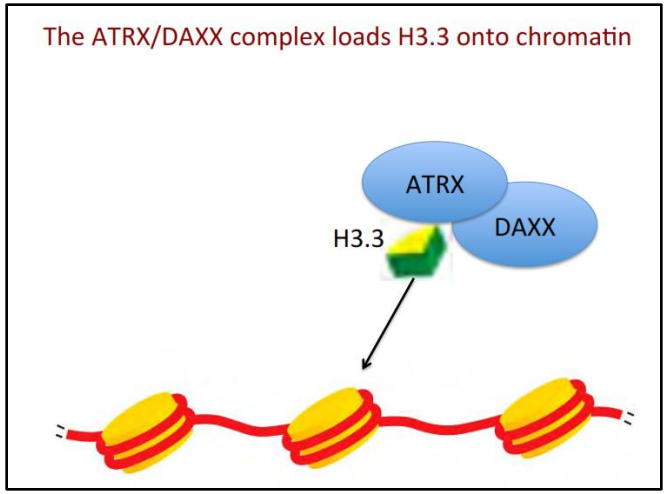
Abnormality classification	Pathway	Main driver	References
1-Epigenetic Aberrations	H3 mutation	H3K27M mutation	[45]
		G3R/V mutation	[39]
	Polycomb Repressive Complex (PRC)	PRC1 downregulation	[47]
2-Gene Aberrations			
I-Cellular Proliferation pathway aberrations	ACVR1	ACVR1 somatic mutation	[48-50,52]
	Receptor Tyrosine Kinase Pathways	PDGFA amplification and PDGFR alpha overexpression	[54]
		EGFR mutation and amplification	[55,60]
	MYC-N abnormalities	MYC-N amplification	[2,38,63]
II-Cell Cycle Regulation Pathways aberrations	The P53 pathway	*TP53* mutation	[38,64-65]
		PPM1D mutation	
	The RB pathway	Cdk2A and CDK2B Deletions Cdk4, cdk6 and cyclin D1 amplification	[60,69,70]
	The Aurora Kinase signaling pathway	AURB overexpression	[74]
	The WEE1 kinase pathway	WEE1 overexpression	[76-78]
	Poly (ADP-ribose) polymerase (PARP)-1 overexpression	PARP1 overexpression	[80]
3-Immune Check Abnormalities	B7-H3 as a part of B7-CD28 family	B7-H3 overexpression	[83]

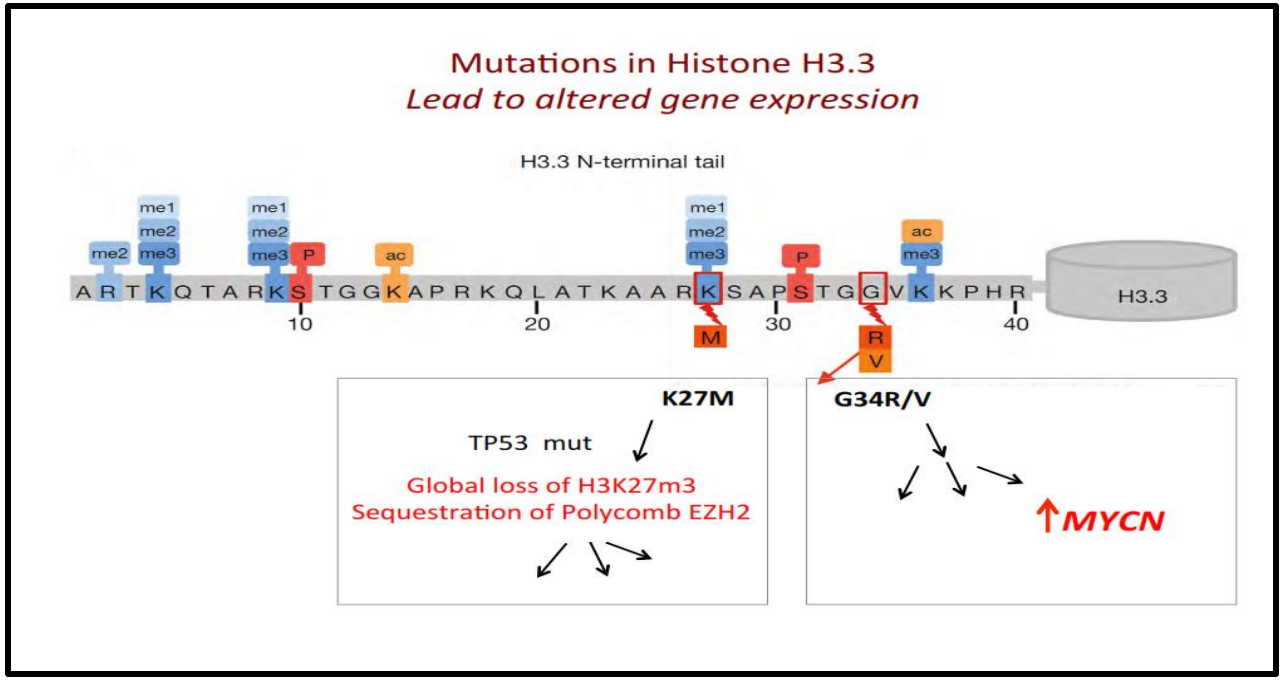
Rashed et al, CMR 2019

Alterations in histones predominant driver in pediatric glioblastoma including DIPG









Pathogenesis of DIPG via Histone Alterations

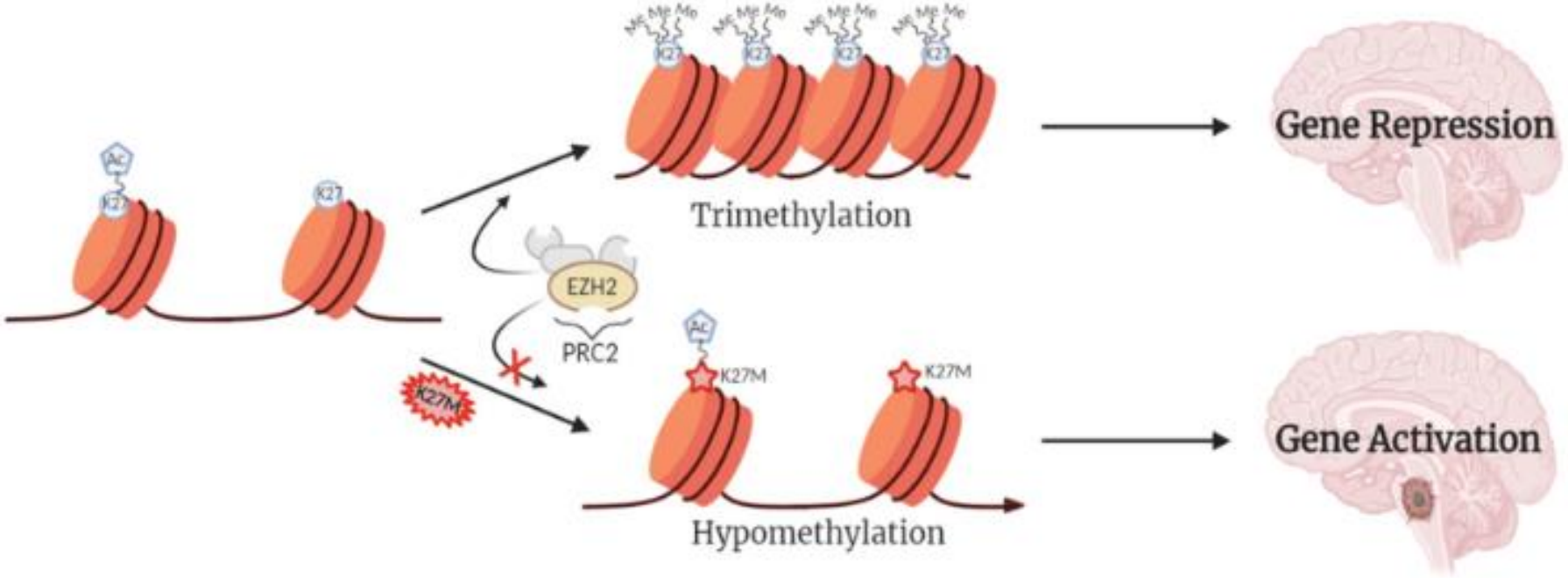


Fig. 1 Overview of H3K27 and its Epigenetic Modification. In normal neurological development, genes that regualte stem cell differentiation are silenced by the polycomb repressor complex 2 (PRC2). To repress these genes, the EZH2 subunit catalyzes the PCR2-mediated H3K27 trimethylation by binding to histone H3 tail, a common site for post-translational modification. However, in the H3K27M, the lysine substitute inhibits EZH2 binding which prevents PCR2-dependent methylation and results in aborrant gene activation

Newer Therapeutic Avenues in DIPG

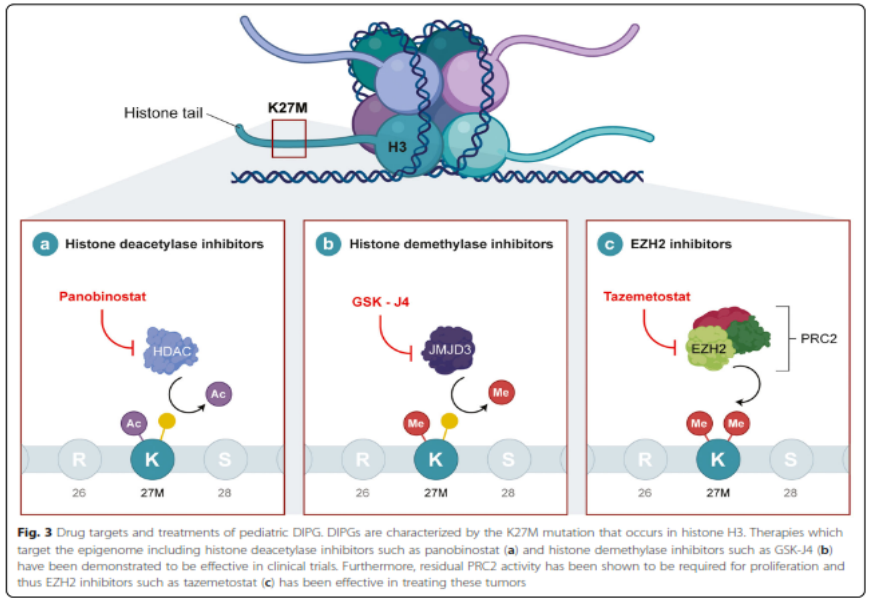


Fig. 3 Drug targets and treatments of pediatric DIPG. DIPGs are characterized by the K27M mutation that occurs in histone H3. Therapies which target the epigenome including histone deacetylase inhibitors such as panobinostat (**a**) and histone demethylase inhibitors such as GSK-J4 (**b**) have been demonstrated to be effective in clinical trials. Furthermore, residual PRC2 activity has been shown to be required for proliferation and thus EZH2 inhibitors such as tazemetostat (**c**) has been effective in treating these tumors

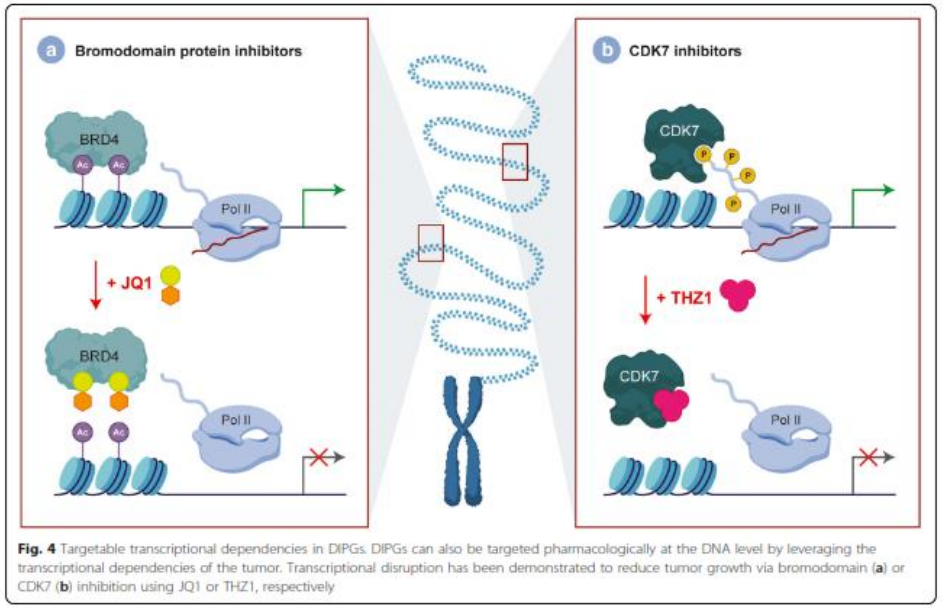


Fig. 4 Targetable transcriptional dependencies in DIPGs. DIPGs can also be targeted pharmacologically at the DNA level by leveraging the transcriptional dependencies of the tumor. Transcriptional disruption has been demonstrated to reduce tumor growth via bromodomain (**a**) or CDK7 (**b**) inhibition using JQ1 or THZ1, respectively

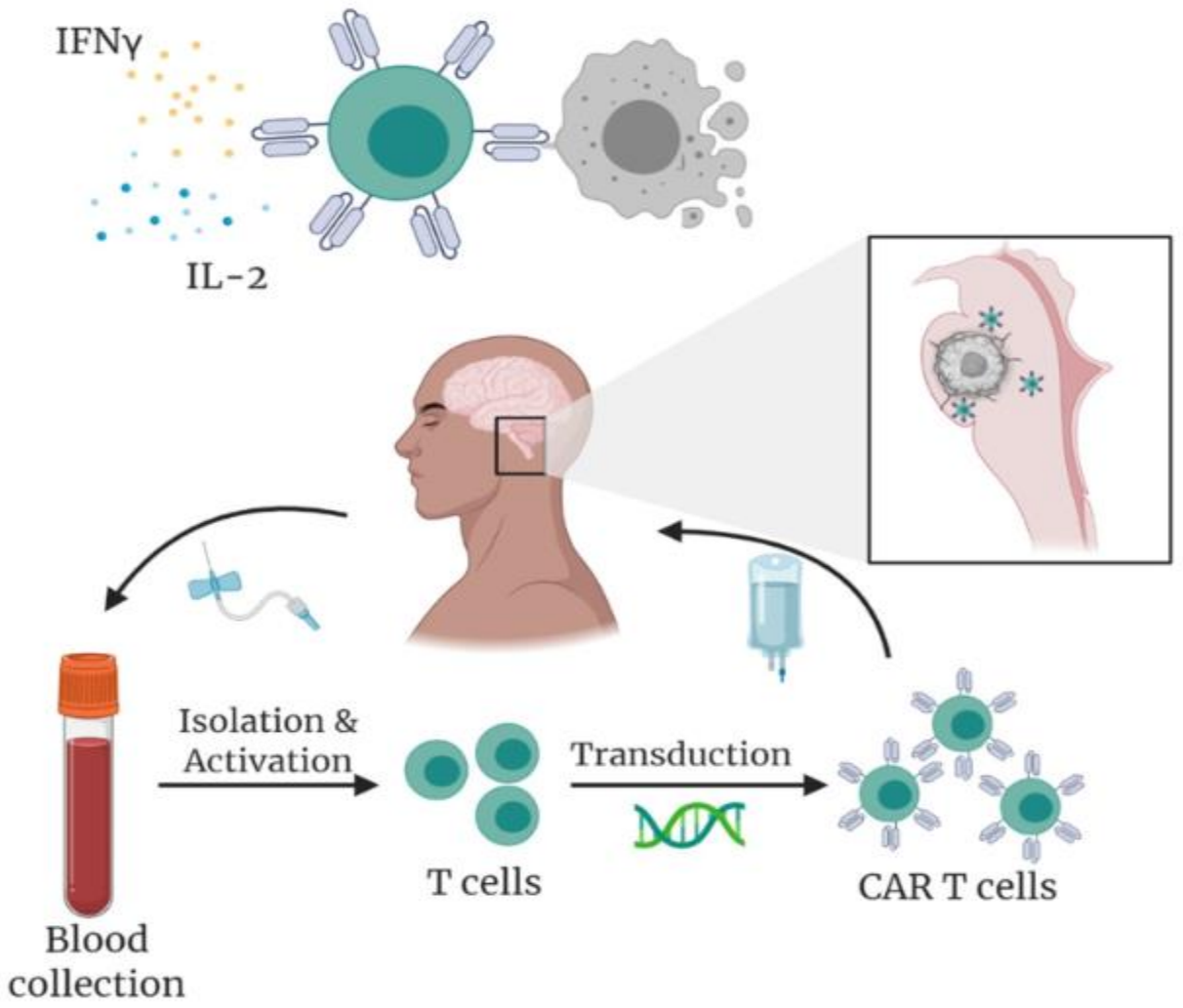
Table 2 Potential targetable secondary mutations in pediatric DIPG. Summary table which outlines key secondary genes that are altered in DIPGs and their subsequent result which increases tumorigenesis. We suggest that these secondary mutations can be complimentarily targeted in order to effectively treat DIPGs

Gene	Alteration	Impact	Result
ACVR1	Missense	Loss of function	Arrests glial cell differentiation and drives tumourigenesis
PDGFRA	Amplification	Gain of function	Upregulation of PI3K/AKT/mTOR pathway, increased proliferation
CDK4/6	Amplification	Gain of function	Upregulation of the cell cycle, increased proliferation
PTEN	Deletion	Loss of function	Loss of inhibition of PI3K/AKT/mTOR signaling network, increased proliferation
PPM1D-p53	Truncation	Loss of function	Impairs DNA repair mechanisms, evasion of apoptosis

Srikanthan et al CNJ 2021

Chimeric Antigen Receptor (CAR)- T cells targeting DIPG

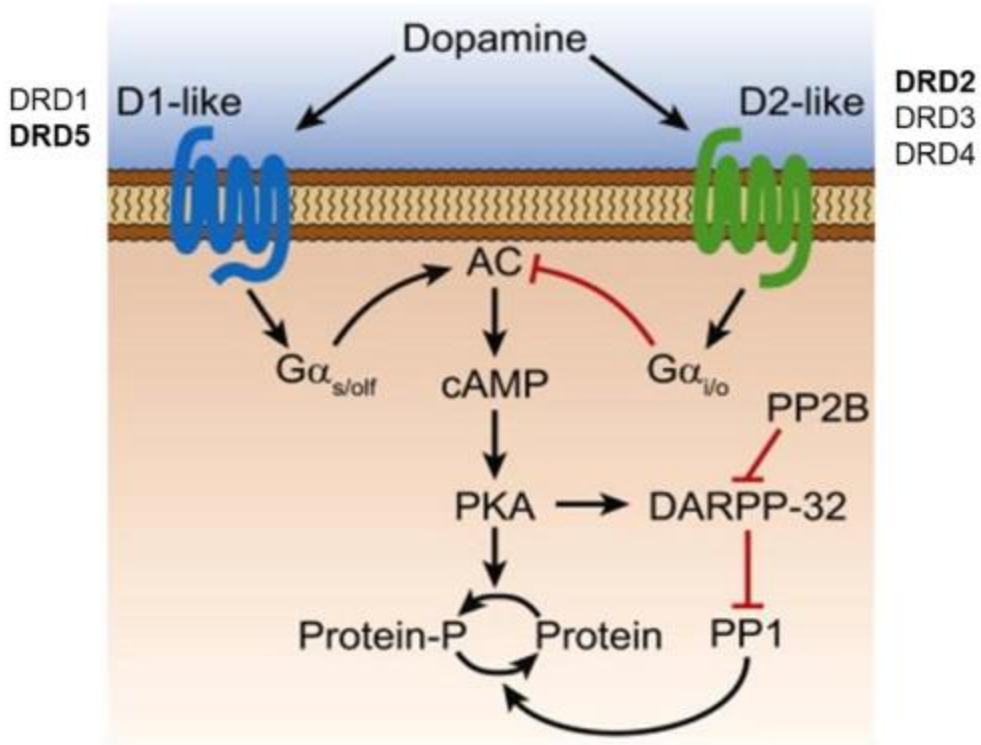
Fig. 2 Generation of CAR T cells targeting BSGs. The develoopment of CAR T cell therapy begins with the collection of a patient's peripheral blood mononuclear cells. The cells are enriched for a T cell susbset, such as a $CD3^+$ population, and subseqently expanded and activated ex vivo using costimulatory ligands such as CD28. Activated T cells are then genetically modified by electroporation or viral vectors, such as lentiviral or retroviral vectors, to deliver the CAR gene. Then, the CAR T cells are actived against the specific tumor target and expanded ex vivo using costimulatory ligands before administration to the patient



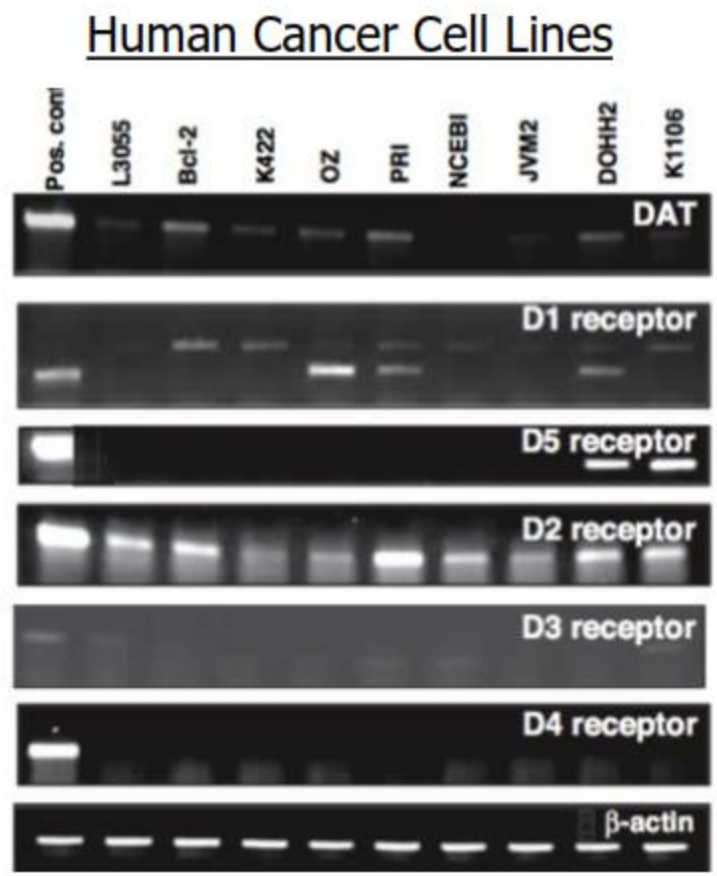
Wummer et al, JNO2021

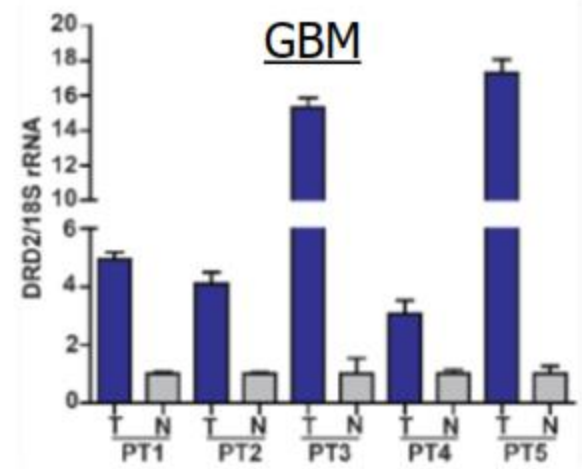
Dopamine Receptor D2 Promotes Tumor Growth in High Grade Glioma

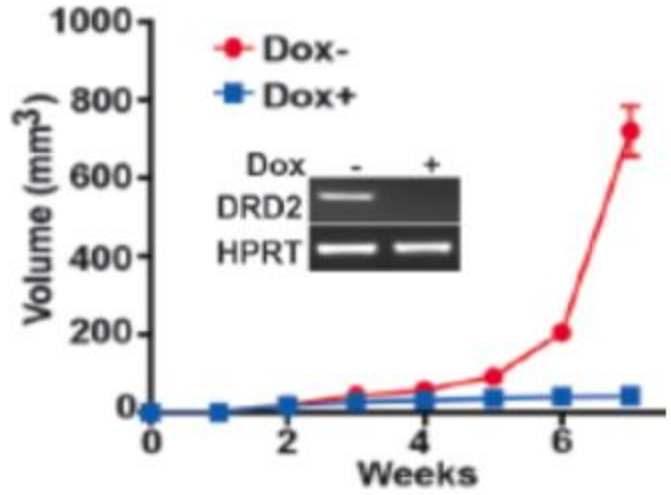
Dopamine receptors are GPCRs divided into two functionally opposing subfamilies



DRD2 is a selectively overexpressed GPCR target for oncology

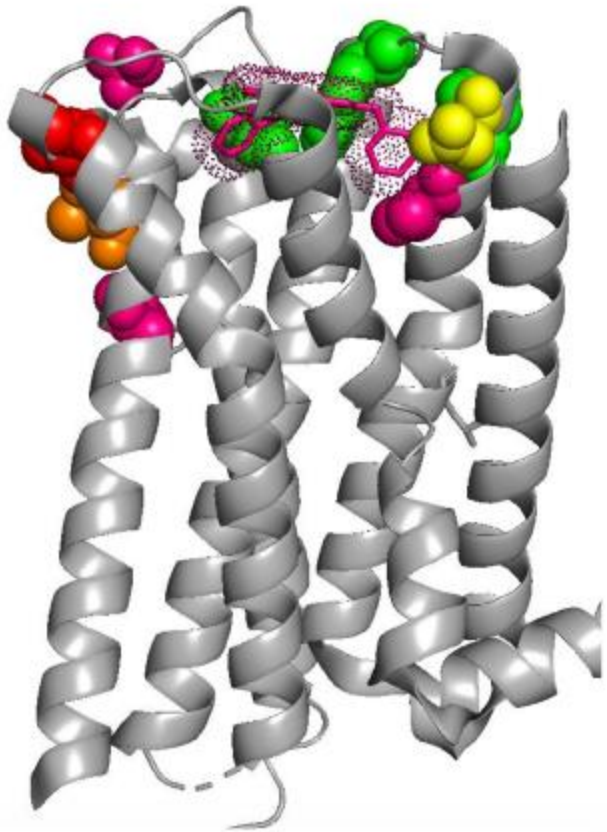






ONC201: First Clinical Bitopic DRD2 Antagonist

ONC201 selectivity antagonizes DRD2 via orthosteric and allosteric residues



DRD2

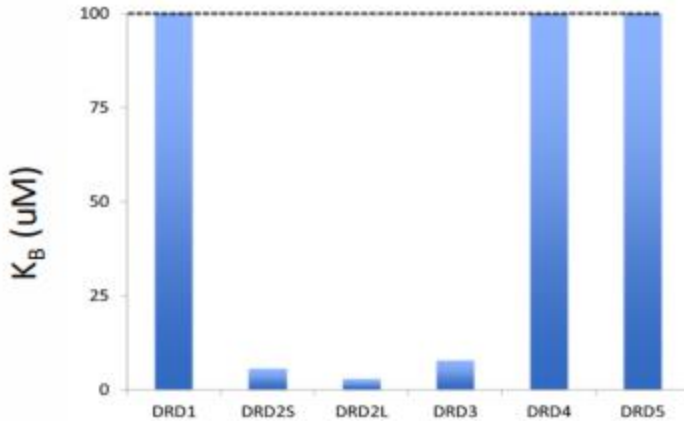
ONC201

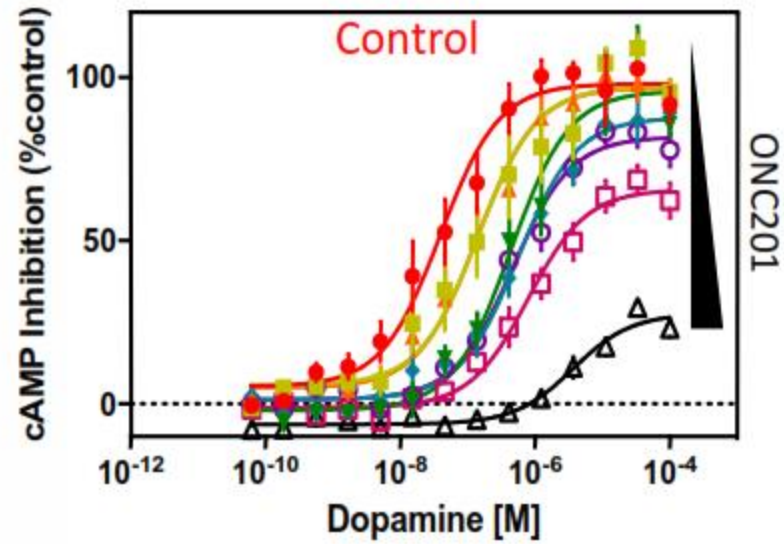
Orthosteric Residues

DR Conservation of ONC201-critical residues

20% 40% 60% 80% 100%

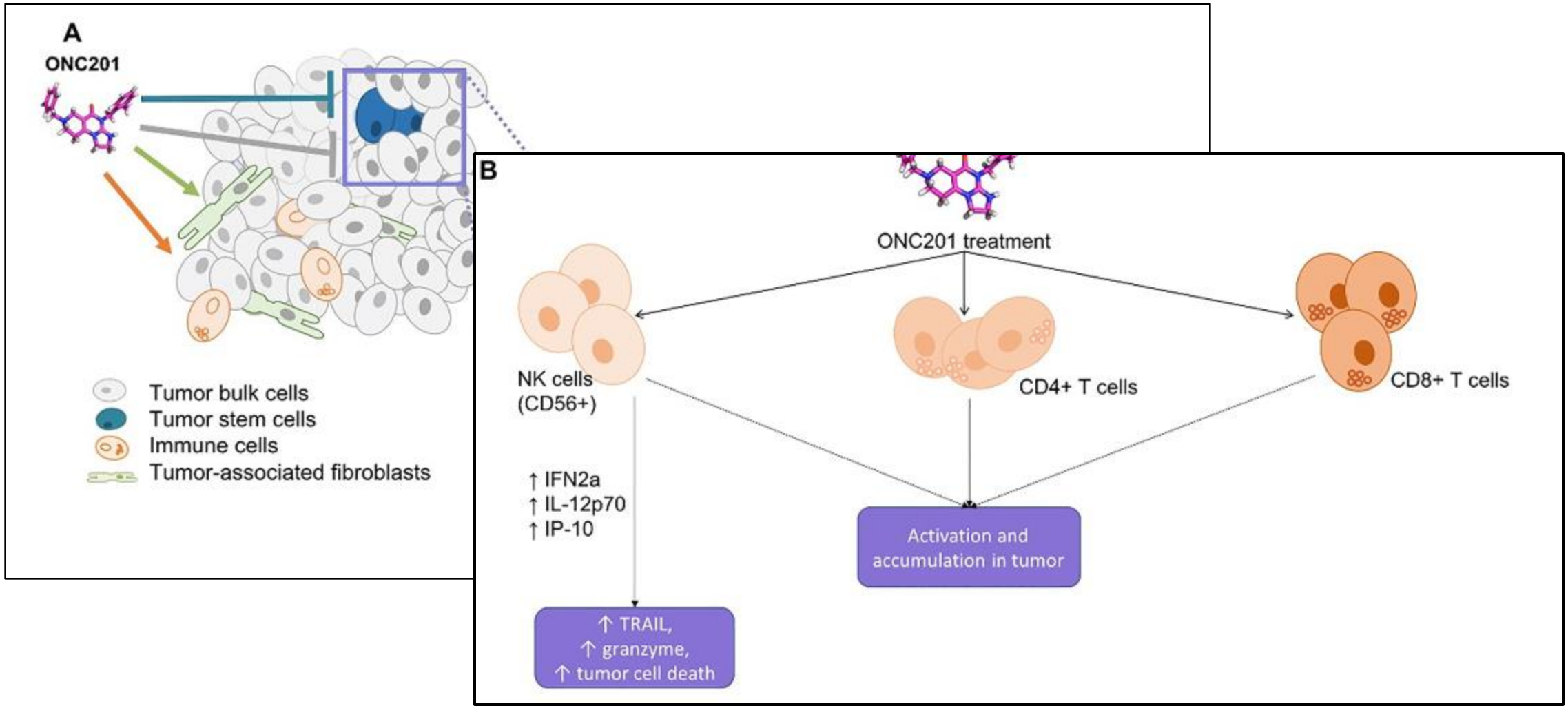
Enables selective and unique DRD2 antagonism





Prabhu et al, Neoplasia 2020

ONC201: is this the magic bullet?



Prabhu et al, Neoplasia 2020

Phase I Pediatric DIPG and H3 K27M-mutant Glioma Trial: Endpoints

Open-label, multi-arm, multi-center, Phase I dose escalation and dose expansion trial (NCT03416530) in pediatric H3 K27M-mutant glioma and/or DIPG

List of Clinical Trial Sites	
New York University	Children's Healthcare of Atlanta / Emory University School of Medicine
MD Anderson Cancer Center	University of California, San Francisco
Miami Cancer Institute	Cincinnati Children's Hospital
University of Michigan	

Primary Endpoint:

Determine RP2D of ONC201 (single agent and + RT)

Secondary Endpoints:

- Safety/tolerability
- PK, PD, CSF Tumor DNA
- PFS, ORR, Duration of Response, Overall Survival
- Cranial nerve palsy scoring
- Clinical benefit/symptom scores

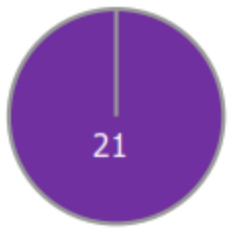
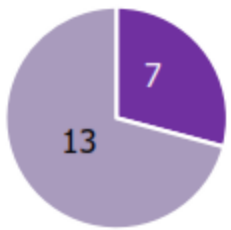
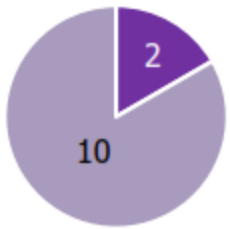
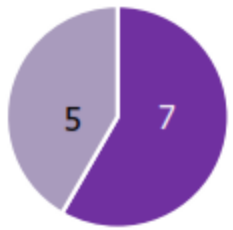
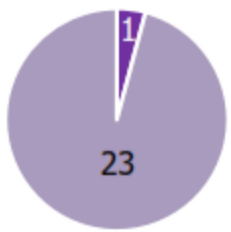
Exploratory Endpoints:

- Association of outcomes w/ tumor markers
- Association of outcomes w/ circulating markers
- Correlation between H3 K27M in tumor and CSF

Cranial palsy score developed based on first DIPG patient treated 6 weeks post-RT treated on compassionate use

Allen et al, SNO 2019

Phase I Pediatric DIPG and H3 K27M+ Glioma Trial: Arms and Accrual

Arm A	Arm B	Arm C	Arm D	Arm E
Post-radiation H3 K27M+ Glioma	Newly Diagnosed DIPG	DIPG Tumor Biopsy	Post-radiation H3 K27M+ Glioma CSF	Post-radiation H3 K27M+ Glioma OraSweet Formulation
ONC201	ONC201 + RT	ONC201 -/+ RT	ONC201	ONC201
Enrollment				
				
Level 2: n=6 → n=12	Level 2: n=6 → n=12	Level 2: n=12	Level 2: n=12	Level 2: n=6 → n=12
Level 1: n=3	Level 1: n=3			Level 1: n=3
Level -1	Level -1: n=3			Level -1: n=3

Allen et al, SNO 2019

Table 1 Summary of our current knowledge of pediatric DIPG. Summary table which details key clinical, pathological, and genetic features of pediatric diffuse intrinsic pontine glioma. *LGG*: low-grade glioma; *PNET*: primitive neuroectodermal tumor

Location	Pons - diffuse
Prognosis	Median overall survival (OS) 8-12 months
Median Age of Diagnosis	6-7 years
Prevalence	10-20% of all pediatric brain tumors, 80% of all pediatric brainstem tumors
Clinical Presentation	>50% 'classic triad' 1. Cranial nerve palsies *(facial asymmetry and diplopia)* 2. Long tract signs *(hyperreflexia, upgoing Babinski)* 3. Cerebellar signs *(ataxia, dysmetria)* Cranial nerve VI and VII dysfunction Obstructive hydrochephalus *(<10% at diagnosis, common at end-stage)*
Diagnostic Tools	Clinical presentation MRI (common) - T1-hypointensity with ill-defined margins - T2-hyperintensity - tumor core centered in pons *(often >50% axial diameter, engulfing basilar artery)* Stereotactic biopsy and histological review, molecular testing
Differential Diagnoses	Non-malignant brainstem entities (rare): LGG, PNET, vascular malformations, encephalitic parenchymal lesions, cysts, demyelinating disorders
Symptom Onset	Rapid, symptoms typically present ≤1 month before medical attention

Histology	Common: high-grade astrocytic, increased mitotic activity, microvascular proliferation and/or necrosis Rare: lower-grade histology, overall bland cytology
Immunohistochemistry	GFAP, ATRX, p53, neurofilament, ki-67 immunostains Targeted antibodies for H3K27M, IDH1R132H
Molecular Testing	Next generation sequencing, DNA microarrays *(confirm presence/absence of H3 mutation/isoform)*
Molecular Subgroups	H3K27M, MYCN and silent
Mutations	Histone 3 (H3) - 80% - significantly worse outcomes *vs.* H3 wild-type H3K27M - isoforms H3.1 *(HIST1H3B)* - reduced metastasis, better median overall survival H3.3 *(H3F3A)* ACVR1 - 30% - co-segregates with H3.1, facilitates early tumor progression TP53 - 22-40% - often coincident with PDGFRA amplification PDGFRA amplification - 33%, RTY-RAS-PI3K-Akt signaling pathway, co-segregates with H3.3 PIK3R1 and PIK3CA - PI3K pathway oncogenes MYC and MYCN aberrations - transcriptional regulators, enhance overall gene expression
Current Treatment	Standard fractionated radiation alone, to a dose of 54-59 Gy
Treatment Roadblocks	Monotherapy and combination chemotherapy - no substantial benefit Location - does not allow for meaningful surgical resection Lack of effective drug delivery across intact blood brain barrier (BBB)
Ongoing Trials	Histone deacetylase (HDAC) and demethylase inhibitors Transcriptional regulators Immunotherapy - recruitment/introduction of immune cells to tumor Drug delivery enhancement

MISSION

SERVICE

EDUCATION

RESEARCH