Rare CNS embryonal tumors

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XLVIII CONGRESSO NAZIONALE AIEOP

Bologna
2-4 Ottobre 2023

La sottoscritta Elisabetta Schiavello

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

☒ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*

- 16% of CNS tumors: MBL, ATRT, ETMR and others rarer entities
- infants/ young children
- highly cellular tumors: small, blue, round cells
- with tendency for dissemination

HISTORY

- 1993-97 PNET: descriptive diagnosis
- 2000 supratentorial PNET
- 2007 CNS-PNET : heterogeneous group with descriptive- morphological characteristics but lacking specific diagnostic criteria

- WHO 2016: ~~PNET~~→ introduction of genome wide molecular diagnostics unveiled molecular heterogeneity
- **WHO 2021: incorporation of specific molecular-genetic alterations into the diagnostic criteria**

rare CNS embryonal tumors

World Health Organization Classification of Tumors of the Central Nervous System, fifth edition
Choroid plexus tumors
Choroid plexus papilloma
Atypical choroid plexus papilloma
Choroid plexus carcinoma
Embryonal tumors
Medulloblastoma
Medulloblastomas, molecularly defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and *TP53*-wildtype
Medulloblastoma, SHH-activated and *TP53*-mutant
Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined
Other CNS embryonal tumors
Atypical teratoid/rhabdoid tumor
Cribriform neuroepithelial tumor
Embryonal tumor with multilayered rosettes
CNS neuroblastoma, *FOXR2*-activated
CNS tumor with *BCOR* internal tandem duplication
CNS embryonal tumor

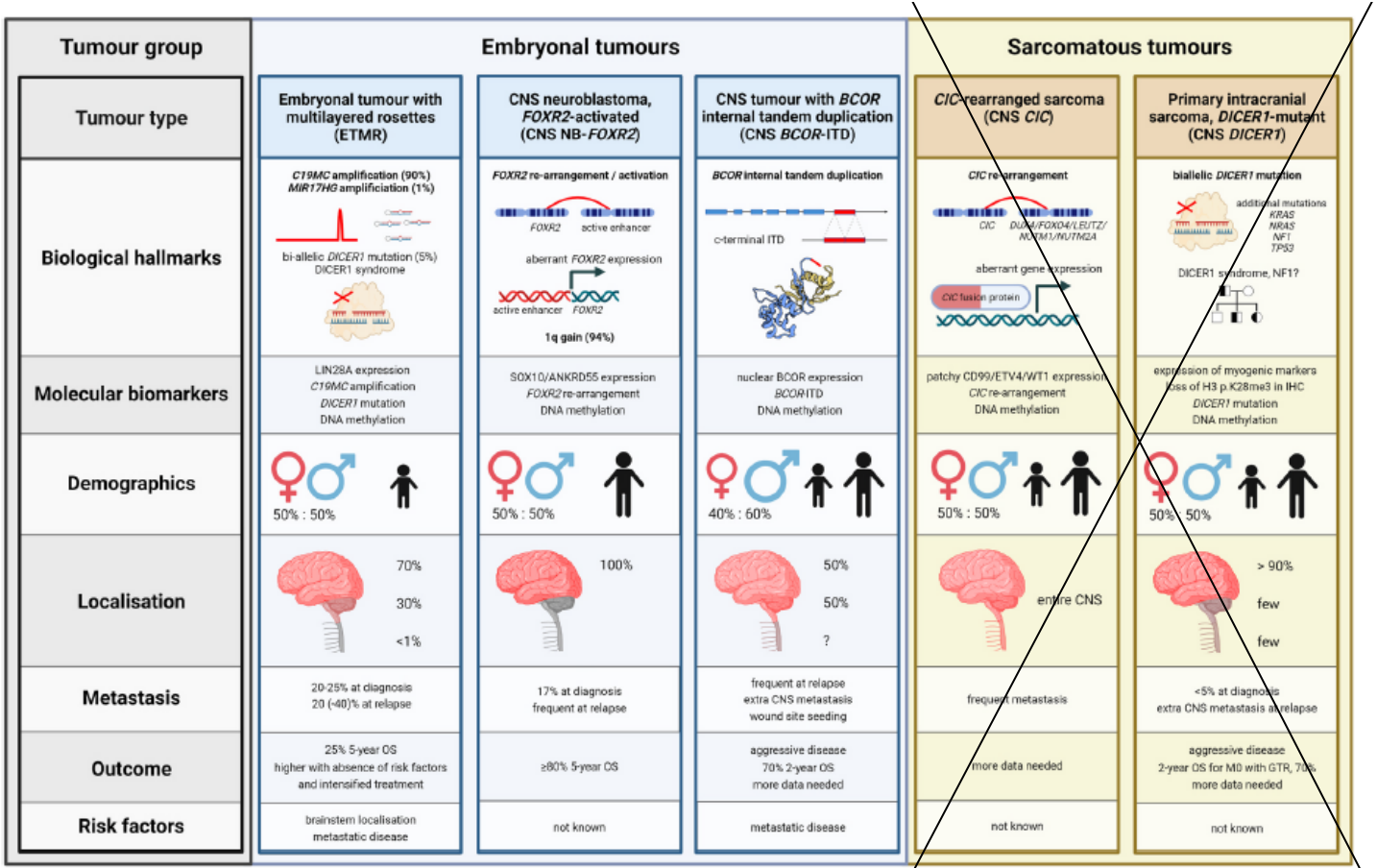
Louis et al

Neuro-Oncology

The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

Rare embryonal and sarcomatous central nervous system tumours: State-of-the art and future directions

European Journal of Medical Genetics 66 (2023) Gojo J. et al



Tumour group	Embryonal tumours			Sarcomatous tumours	
Tumour type	**Embryonal tumour with multilayered rosettes (ETMR)**	**CNS neuroblastoma, *FOXR2*-activated (CNS NB-*FOXR2*)**	**CNS tumour with *BCOR* internal tandem duplication (CNS *BCOR*-ITD)**	***CIC*-rearranged sarcoma (CNS *CIC*)**	**Primary intracranial sarcoma, *DICER1*-mutant (CNS *DICER1*)**
Biological hallmarks	*C19MC* amplification (90%) *MIR17HG* amplification (1%); bi-allelic *DICER1* mutation (5%) DICER1 syndrome	*FOXR2* re-arrangement / activation; *FOXR2* active enhancer; aberrant *FOXR2* expression; active enhancer *FOXR2*; 1q gain (94%)	*BCOR* internal tandem duplication; c-terminal ITD	*CIC* re-arrangement; *CIC* DUX4/FOXO4/LEUTZ/ NUTM1/NUTM2A; aberrant gene expression; *CIC* fusion protein	biallelic *DICER1* mutation; additional mutations *KRAS* *NRAS* *NF1* *TP53*; DICER1 syndrome, NF1?
Molecular biomarkers	LIN28A expression *C19MC* amplification *DICER1* mutation DNA methylation	SOX10/ANKRD55 expression *FOXR2* re-arrangement DNA methylation	nuclear BCOR expression *BCOR*-ITD DNA methylation	patchy CD99/ETV4/WT1 expression *CIC* re-arrangement DNA methylation	expression of myogenic markers loss of H3 p.K28me3 in IHC *DICER1* mutation DNA methylation
Demographics	50% : 50%	50% : 50%	40% : 60%	50% : 50%	50% : 50%
Localisation	70% 30% <1%	100%	50% 50% ?	entire CNS	> 90% few few
Metastasis	20-25% at diagnosis 20 (-40)% at relapse	17% at diagnosis frequent at relapse	frequent at relapse extra CNS metastasis wound site seeding	frequent metastasis	<5% at diagnosis extra CNS metastasis at relapse
Outcome	25% 5-year OS higher with absence of risk factors and intensified treatment	≥80% 5-year OS	aggressive disease 70% 2-year OS more data needed	more data needed	aggressive disease 2-year OS for M0 with GTR, 70% more data needed
Risk factors	brainstem localisation metastatic disease	not known	metastatic disease	not known	not known

- ETMR
- CNS neuroblastoma, *FOXR2*-activated (CNS NB-*FOXR2*)
- CNS tumour with *BCOR*-ITD (CNS *BCOR*-ITD)

- primary intracranial sarcoma, *DICER1*-mutant(CNS *DICER1*)
- *CIC*-rearranged sarcoma (CNS *CIC*)

} are now listed in the group of mesenchymal tumours of uncertain differentiation

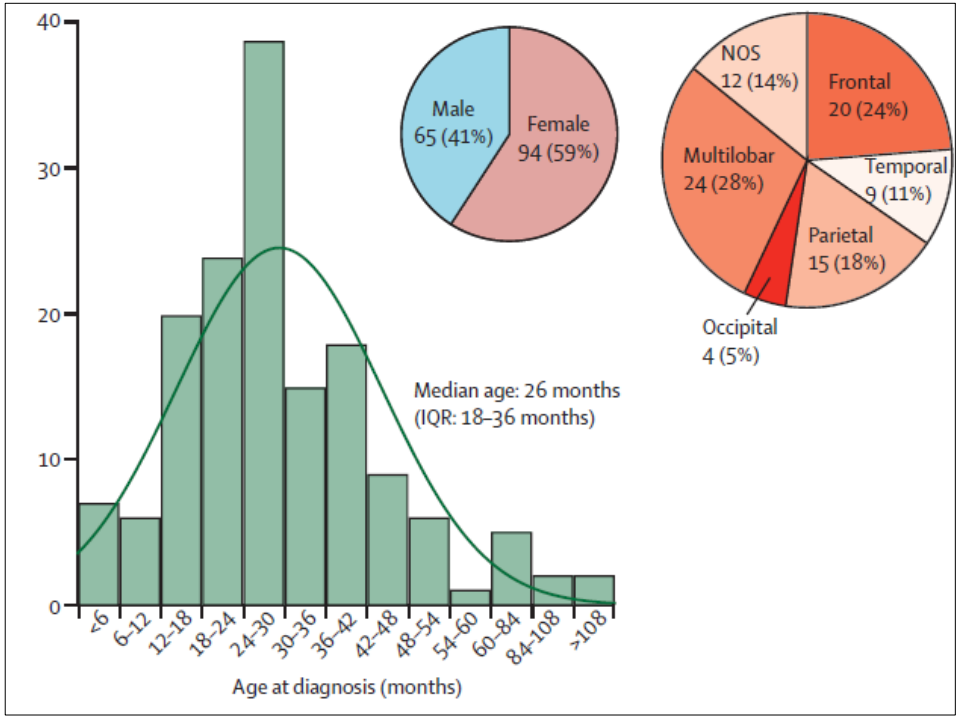
- Pineoblastoma
- Astroblastoma MN1 altered (glioma sub-type??)

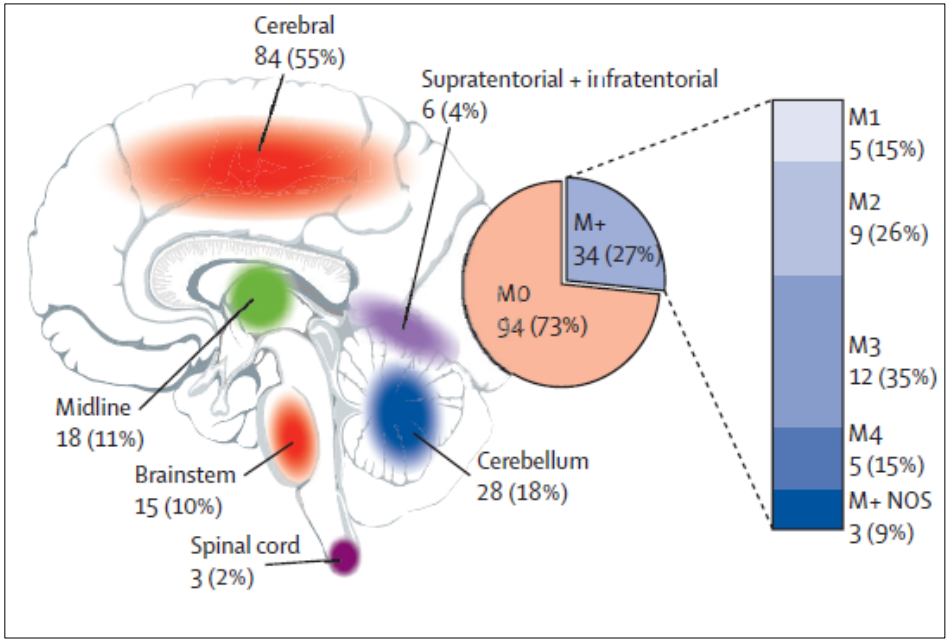
→ other novel tumour types with distinct molecular features such as gene fusions involving *PATZ1, BCOR/BCORL1* or *PLAGL1* have recently been described and are **not included** in the 5th edition of the WHO classification of CNS tumours, yet

→the classification is expected to undergo constant evolution and refinement in the coming years…

Tumour type	Embryonal tumour with multilayered rosettes (ETMR)
Biological hallmarks	*C19MC* amplification (90%) *MiR17HG* amplificiation (1%)  bi-allelic *DICER1* mutation (5%) DICER1 syndrome 
Molecular biomarkers	LIN28A expression *C19MC* amplification *DICER1* mutation DNA methylation
Demographics	 50% : 50% 
Localisation	 70% 30% <1%
Metastasis	20-25% at diagnosis 20 (-40)% at relapse
Outcome	25% 5-year OS higher with absence of risk factors and intensified treatment
Risk factors	brainstem localisation metastatic disease

embryonal tumour with multilayered rosettes- ETMR



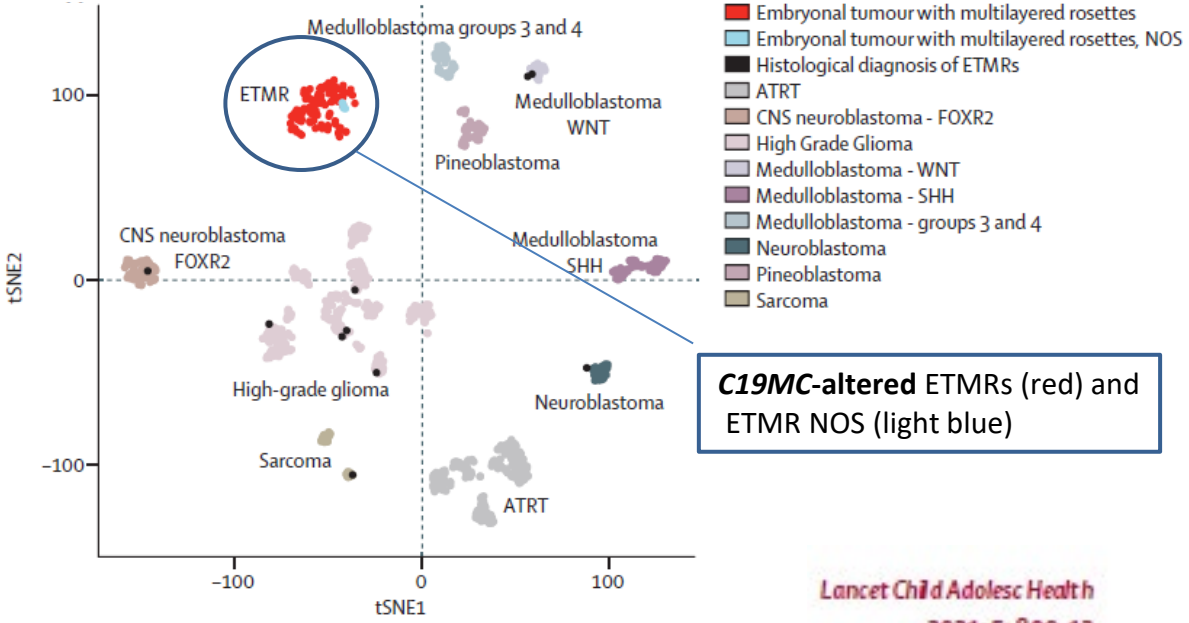


Clinical phenotypes and prognostic features of embryonal tumours with multi-layered rosettes: a Rare Brain Tumor Registry study Khan S. et al

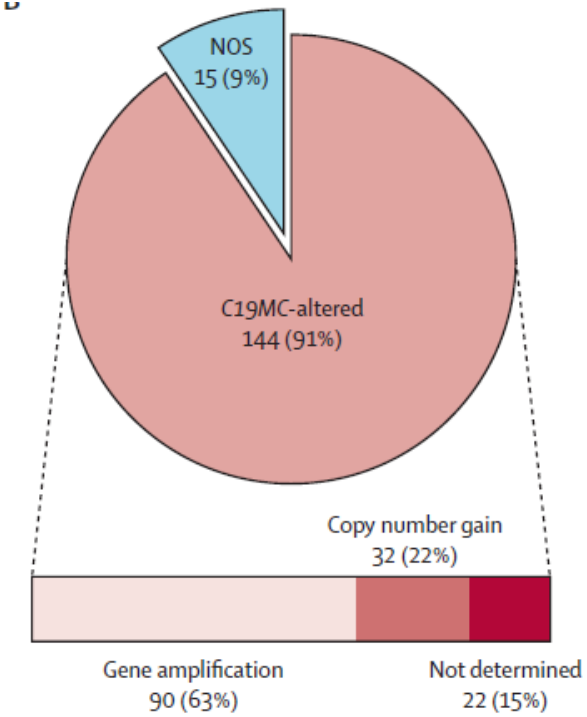
Lancet Child Adolesc Health
2021; 5: 800–13

Clinical phenotypes and prognostic features of embryonal tumours with multi-layered rosettes: a Rare Brain Tumor Registry study

159 pts, centrally reviewed



***C19MC*-altered** ETMRs (red) and ETMR NOS (light blue)

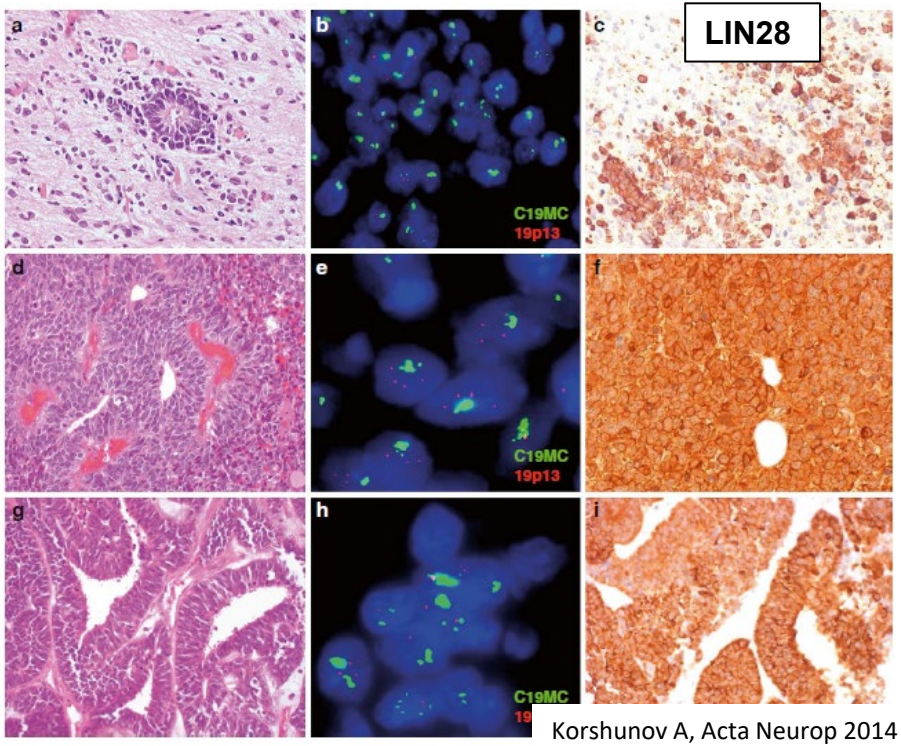


Lancet Child Adolesc Health
2021; 5: 800–13

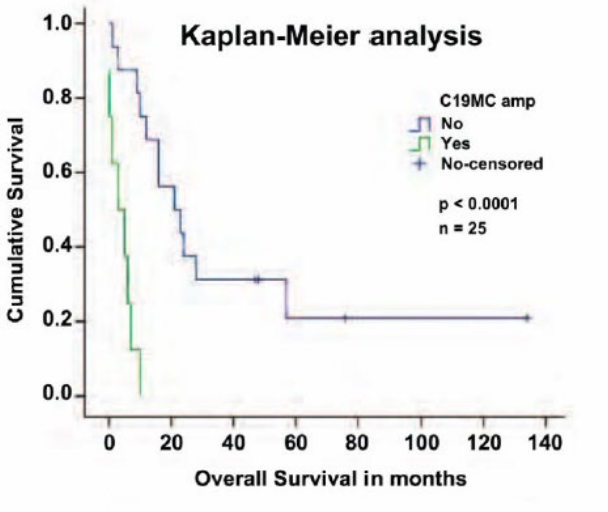
ETMR, essential diagnostic criteria

- typical morphological pattern: ETANTR, EBL, MEPL
- IHC: LIN28A expression, is supportive but not specific (also in HGG/ATRT)

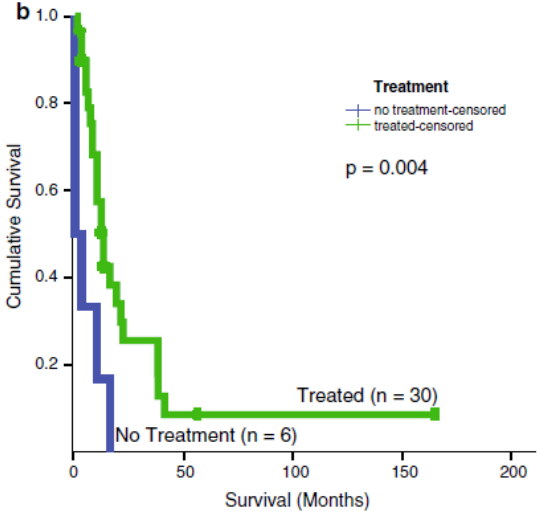
- 90%: recurrent amplification of **C19MC** (by FISH or methylation)- chr19 miRNA cluster
- 5%: **DICER1** mutation (→genetic counselling)
- rare negative C19MC/DICER1**: miR-17-92** microRNA amplification, chr13



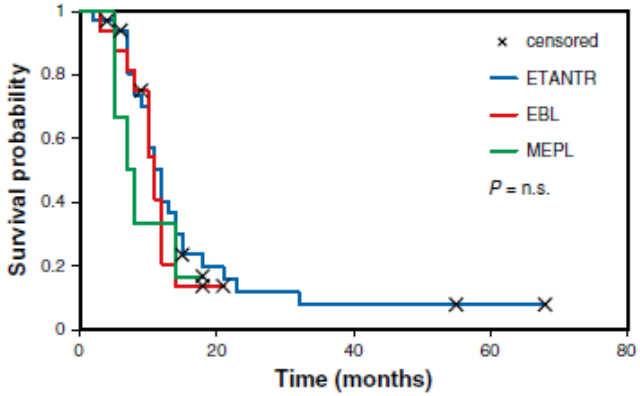
Korshunov A, Acta Neurop 2014
N=97



Li C, Cancer Cells 2009
N=11



Spencer T, Acta Neurop 2014
N=54



Korshunov A, Acta Neurop 2014
N=97

ETMR- previous retrospective series

159 pts
108 pts with curative intent:
2yrs EFS 31%; OS 29%

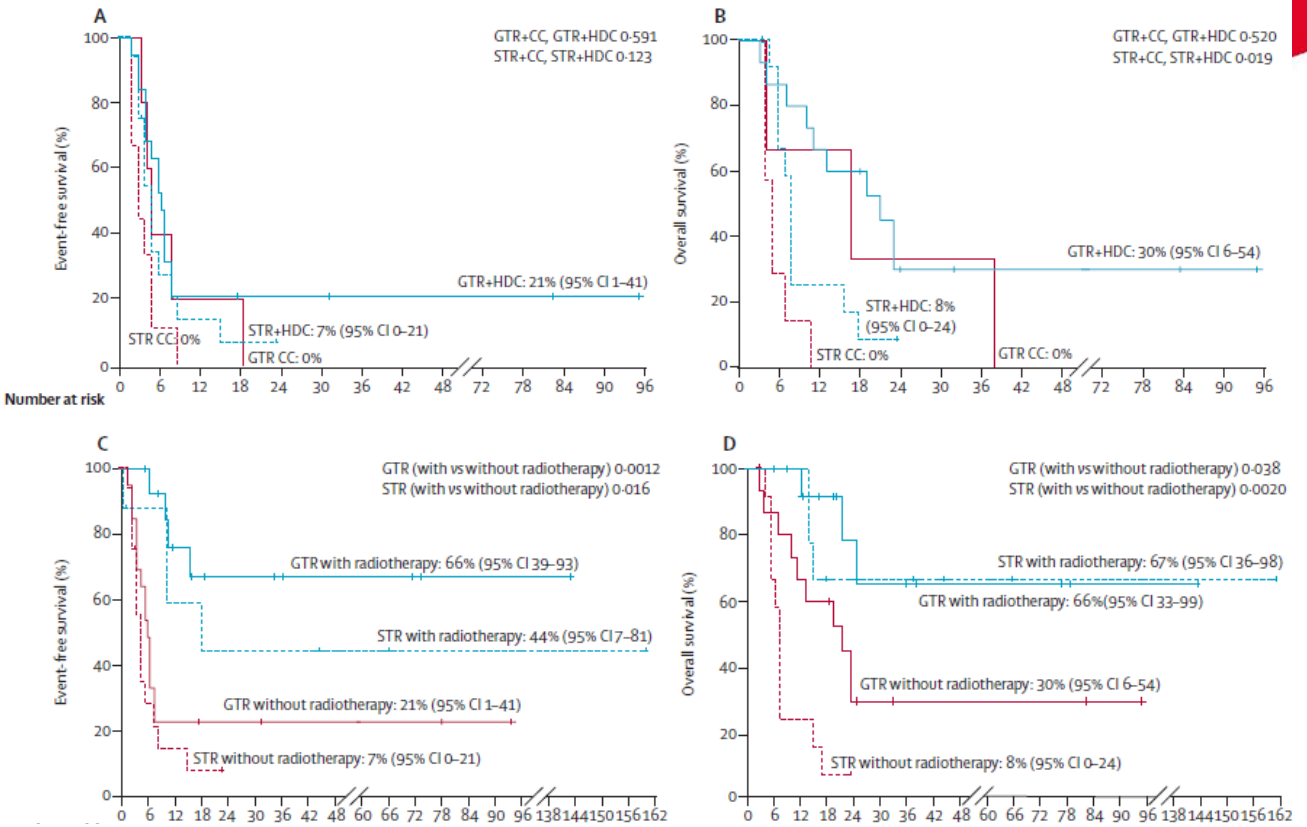
EFS(n=57) and OS(n=51) for pts treated **HD CT with or without RT**

better OS associated with :
- NON METASTATIC
- NON-BRAINSTEM

} univariate analysis

- GTR
- HD-CT
- RT

} multivariable analysis



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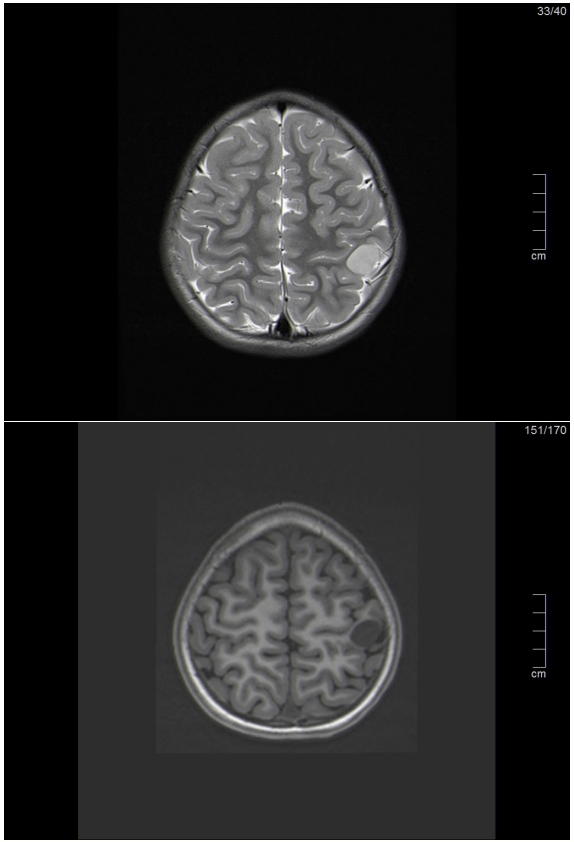
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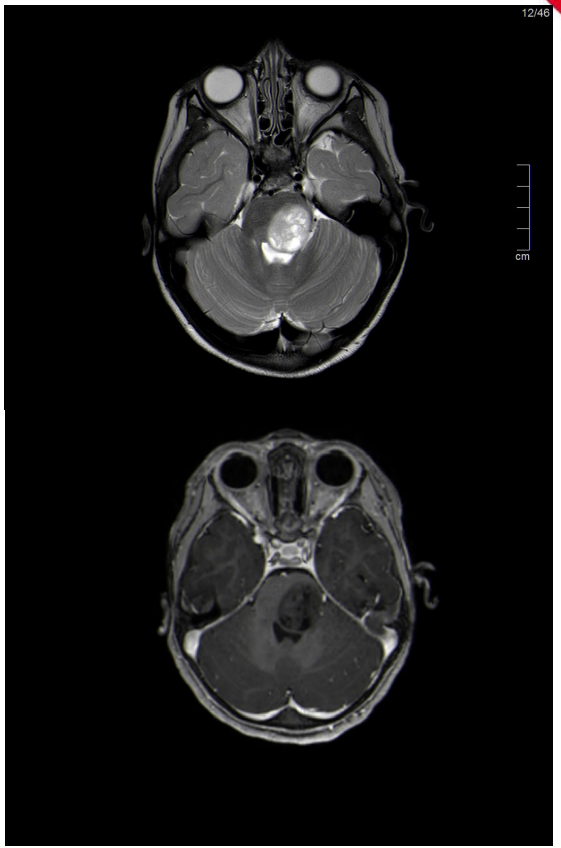
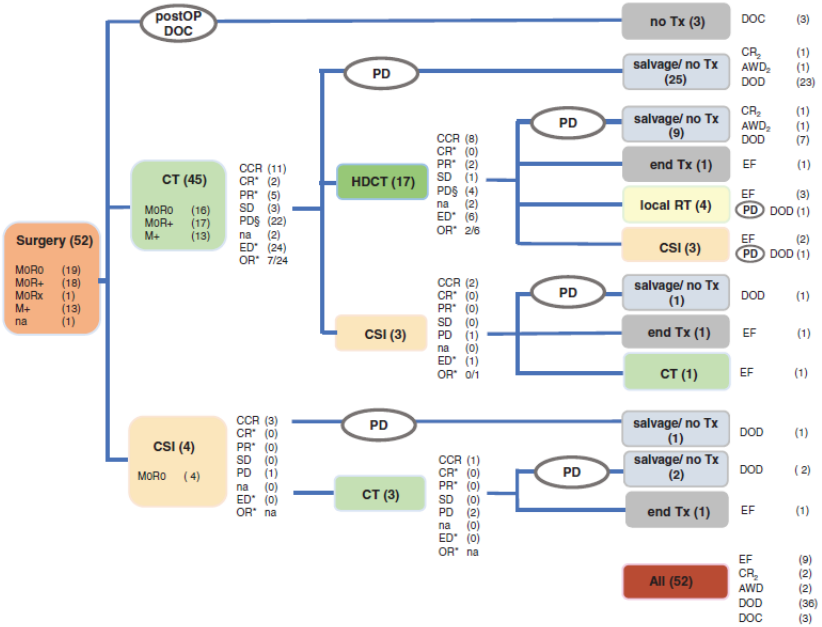

12/46
cm

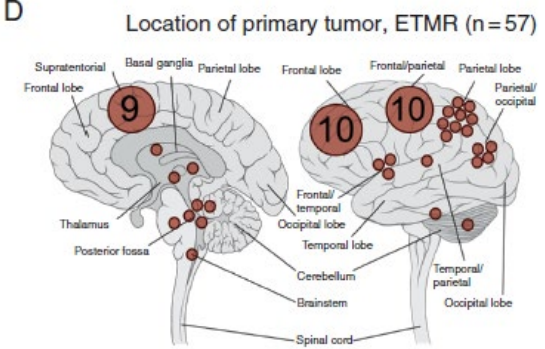
Neuro-Oncology
23(6), 1582–1611, 2021 | doi:10.1093/neuonc/noab136 | Advance Access date 2 June 2021

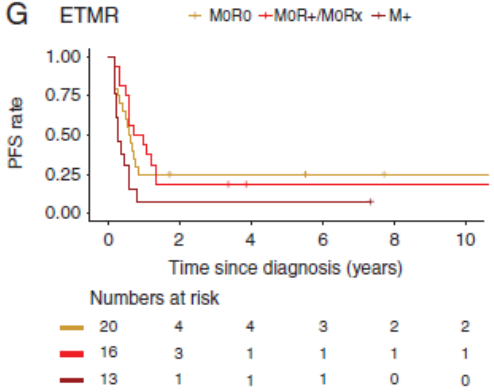
Therapeutic implications of improved molecular diagnostics for rare CNS embryonal tumor entities: results of an international, retrospective study

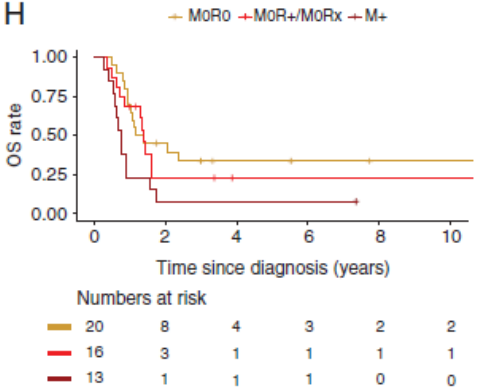
von Hoff, 2021

Clinical data on 52 ETMR patients:







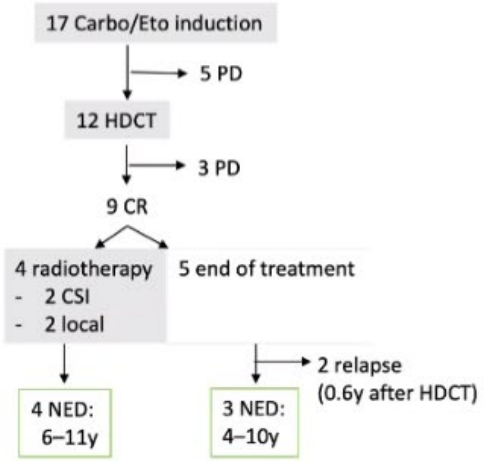


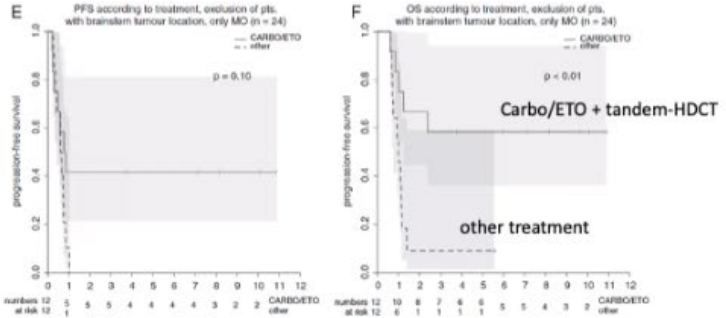
despite response rates on CT of 30%
38/40 (95%) relapse/progressions occurred on treatment

Neuro-Oncology
24(1), 127–137, 2022 | doi:10.1093/neuonc/noab100 | Advance Access date 28 April 2021

Treatment of embryonal tumors with multilayered rosettes with carboplatin/etoposide induction and high-dose chemotherapy within the prospective P-HIT trial

B.-Ole Juhnke, Marco Gessi, Nicolas U. Gerber, Carsten Friedrich, Martin Mynarek, André O. von Bueren, Christine Haberler, Ulrich Schüller, Rolf-Dieter Kortmann, Beate Timmermann, Brigitte Bison, Monika Warmuth-Metz, Robert Kwiecien, Stefan M. Pfister, Claudia Spix, Torsten Pietsch, Marcel Kool, Stefan Rutkowski, Katja von Hoff





5-year PFS (CARBO/ETO, n=17):
35% (95%CI: 19-67%)

5-year PFS, **M0 only** (CARBO/ETO, n=12):
42% (95%CI: 21-81%)

5-year OS (CARBO/ETO, n=17):
47% (95%CI: 28-78%)

5-year OS, **M0 only** (CARBO/ETO, n=12):
58% (95%CI: 36-94%)

- median age 2.9 yrs
- 35 pts (9 M+)
- 30 pts non-brainstem:
  5-yr PFS/OS: 35/47% with CARBO/ETO + HDCT (n = 17)
- all 4 pts with brainstem tumor died within 10 months after diagnosis
- **indipendent prognostic factors** (multiv):
  - supratentorial
  - M0
  - no residual tumor
  - CBDCA/VP16+HDCT
- of 9 survivors: 6 treated with RT (CSI 4; focal 2)

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A modified IRS-III chemotherapy regimen leads to prolonged survival in children with embryonal tumor with multilayer rosettes

Hanson D, Chi S et al.

Neuro-Oncology Advances
2(1), 1–7, 2020 | doi:10.1093/noajnl/vdaa120 | Advance Access date 18 September 2020

Table 1. Summary of Case Series

Case	Age	Sex	Tumor Location	M Stage	C19MC	Surgery	IRS-III Treatment	HDC + ASCT	RT	Additional Therapy	EFS	OS	Status
1	32 months	F	R Parietal	M0	Positive	GTR	51 weeks	No	Focal RT	None	7 years 6 months	7 years 6 months	Alive, NED
2	39 months	F	R Parietal	M0	Positive	GTR	19 weeks	No	Focal Proton	Omburtamab DFMO	3 years 3 months	3 years 3 months	Alive, NED
3	5 months	F	R Posterior Fossa	M0	Negative	STR, then GTR	12 weeks	Yes	None	DFMO Everolimus ITTopotecan	3 years 2 months	3 years 2 months	Alive, NED
4	22 months	M	R Parietal	M0	Positive	GTR	12 weeks	No	Focal Proton	DFMO Vorinostat Topotecan Lorlatinib Irinotecan Olaparib Veliparib RT × 2	4 months	1 years 10 months	Alive, NED
5	26 months	F	R Frontal/Parietal	M0	Positive	GTR	50 weeks	No	Focal Proton	None	1 year 7 months	1 year 7 months	Alive, NED

DFMO, difluromethylornithine; F, female; GTR, gross-total resection; HDC + ASCT, high-dose chemotherapy plus autologous stem cell rescue; M, Male; NED, no evidence of disease; RT, radiotherapy; STR, subtotal resection.

Potential Importance of Early Focal Radiotherapy Following Gross Total Resection for Long-Term Survival in Children With Embryonal Tumors With Multilayered Rosettes

frontiers in Oncology

Mayr L, et al

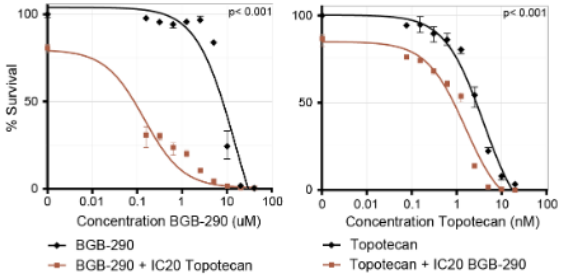
TABLE 1 | Patient characteristics, treatment and outcome.

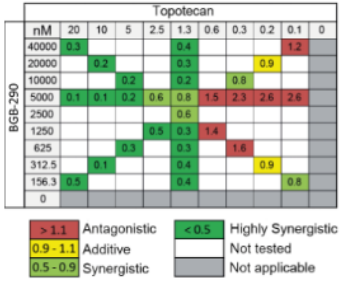
Case	Age (months)	Sex	Location	Surgery	M-Stage	Primary CT	Focal RT (months after Dx)	Intrathecal CT	HDCT (months after Dx)	Status/Follow up (months)	LIN28A	*C19MC* amplification/ *DICER1* mut	CNV Gains	CNV Losses
1	25	m	parietal	GTR	M0	HIT 2000 SKK	11.5	VP16, Depocyte MTX,	6	DOD,27	pos	19q13.42	2,5p	–
2	33	f	parietal	GTR	M0	HIT2000 SKK	7.5	VP16, Depocyte	6	DOD,14	pos	19q13.42	1q,2,4,17,20	–
3	5	f	pineal	GTR	M0	HIT2000 SKK	–	VP16, Depocyte	6	DOC,6	pos	DICER1	2	7q
4	35	f	bifrontal	GTR	M0	Doxorubicin	–	no	–	DOD,15	pos	19q13.42	2,3,4,8,11,12	–
5	16	f	pineal	GTR	M0	MUV ATRT	6.5	VP16	–	DOD,13	pos	19q13.42	–	–
6	38	f	parietal	GTR	M0	PEI/TMZ	1.5	VP16, Depocyte Topo	–	NED,56+	pos	19q13.42	–	–
7	27	f	bifrontal	GTR	M0	PEI/TMZ	1.5	VP16, Depocyte	–	NED,50+	pos	19q13.42	4	–
8	13	f	pontine	Biopsy	M0	IP-CZD	3.5	VP16	–	DOD,11	pos	19q13.42	2,7,8	–
9	19	m	pineal	PR	M0	IP-CZD	5.5	VP16, ara-C, Topo	–	DOD,14	pos	19q13.42	2	–

m, male; f, female; GTR, gross total resection; PR, partial resection; CT, chemotherapy; PEI, cisplatin, etoposide, ifosfamide; TMZ, temozolomide; IP-CZD, polish infant IP-CZD protocol; RT, radiotherapy; Dx, diagnosis; VP16, etoposide; Depocyte, liposomal cytarabine; MTX, methotrexate; Topo, topotecan, ara-C, aqueous cytarabine; HDCT, high-dose chemotherapy; DOD, dead of disease; DOC, dead of other cause; NED, no evidence of disease; CNV, copy number variations.

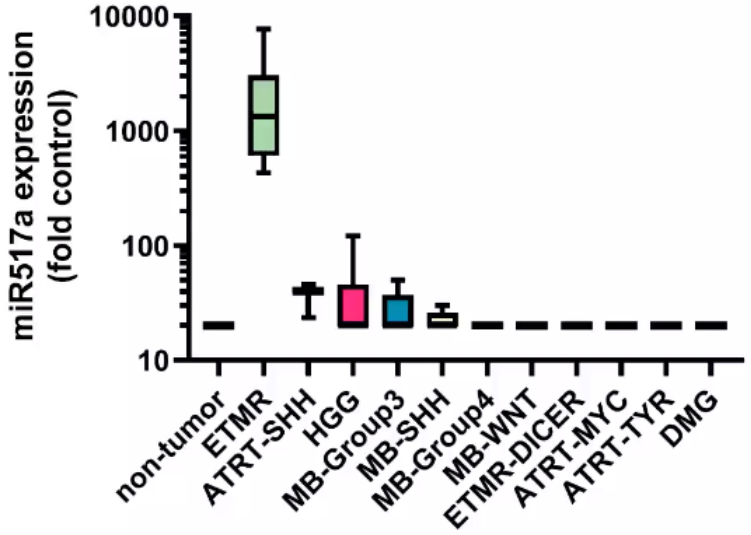
Inhibition of topoisomerase and PARP effectively kills ETMR cells

Combined inhibition with Topoisomerase and PARP inhibitors leads to a larger decrease in viability than monotherapy





Lambo *et al*. Nature 2019



Preclinical studies have identified sensivity of ETMR tumor models to topisomerase inhibitors and PARP-inhibitors→ need further evalutations (M. Kool, Heidelberg)

Clinical applicability of miR517a detection in liquid biopsies of ETMR patients (Madlener S, Wien)

ESCP Treatment recommendations

European Standard Clinical Practice Guidelines

SURGERY

- maximal safe resection
- consider re-resection

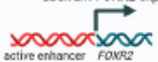
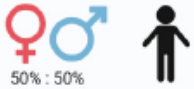
CHEMOTHERAPY (chemoresponsive tumors)

- early
- possible regimens include:
- used for AT/RT (i.e. EURHAB, IRSIII modified)
- evaluated for rare CNS embryonal tumors (i.e. P-HIT)
- evaluated for young children with high risk CNS tumors (Head start, ACNS0334)

upon detection of somatic DICER1 alterations in the tumor, CONSIDER genetic counselling

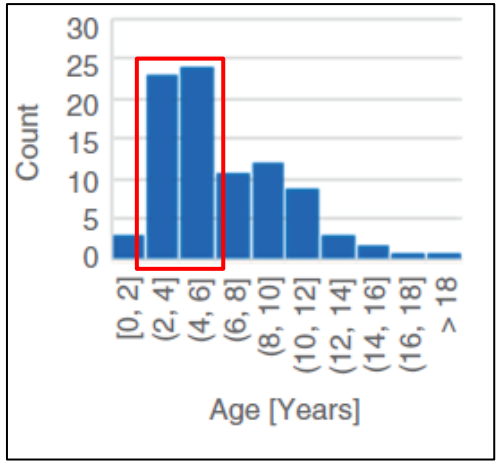
RADIOTHERAPY

- early
- decision on *fields* (focal /CSI) and irradiation *technique* (photons/protons) should be guided by age, staging and the size/ location of the tumor
- <3 yrs, M0: focal RT (tumor bed)
- >3 yrs: CSI vs focal: insufficient evidence for recommendations; on individual factors/national guidelines

Tumour type	CNS neuroblastoma, *FOXR2*-activated (CNS NB-*FOXR2*)
Biological hallmarks	*FOXR2* re-arrangement / activation  aberrant *FOXR2* expression  1q gain (94%)
Molecular biomarkers	SOX10/ANKRD55 expression *FOXR2* re-arrangement DNA methylation
Demographics	
Localisation	 100%
Metastasis	17% at diagnosis frequent at relapse
Outcome	≥80% 5-year OS
Risk factors	not known

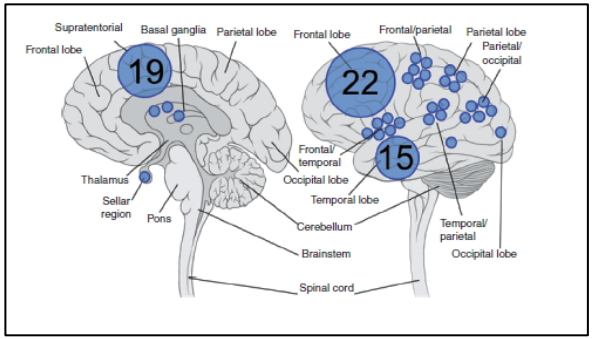
CNS neuroblastoma, *FOXR2*-activated

- arise in young children (median age 5-8 years)
- balanced across genders
- older age at presentation than ETMR



von Hoff et al, 2021

- only supratentorial



- in one study, CNS metastases were present in 17%
- 5-year OS >80% (Korshunov et al., 2021)

CNS neuroblastoma, *FOXR2*-activated

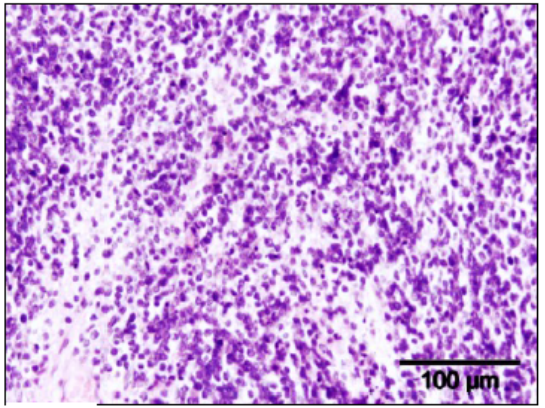
Essential diagnostic criteria:

- embryonal tumor with foci of neuroblastic or neuronal differentiation **and**
- chromosomal rearrangements that lead to increased expression

of the transcription factor *FOXR2*

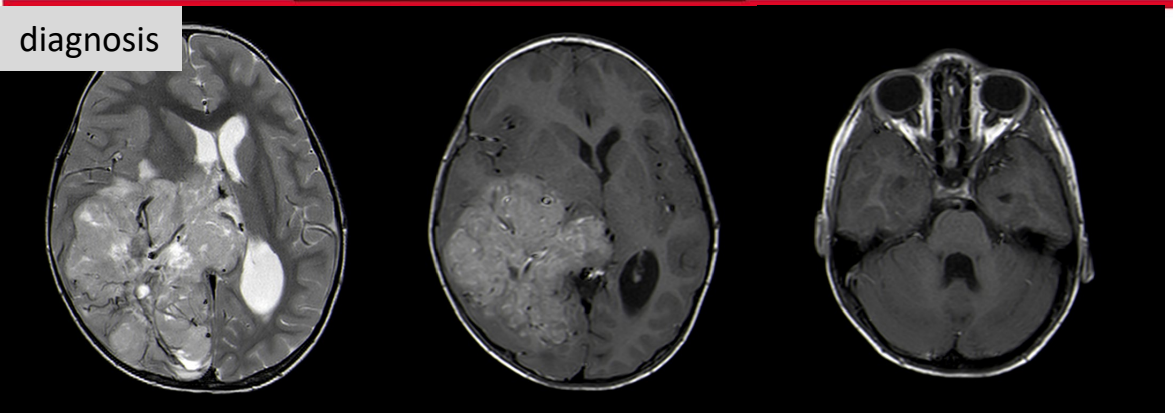
- OLIG2 and synaptophysin expression
- vimentin is usually absent

in poorly differentiated tumors exclude HGG

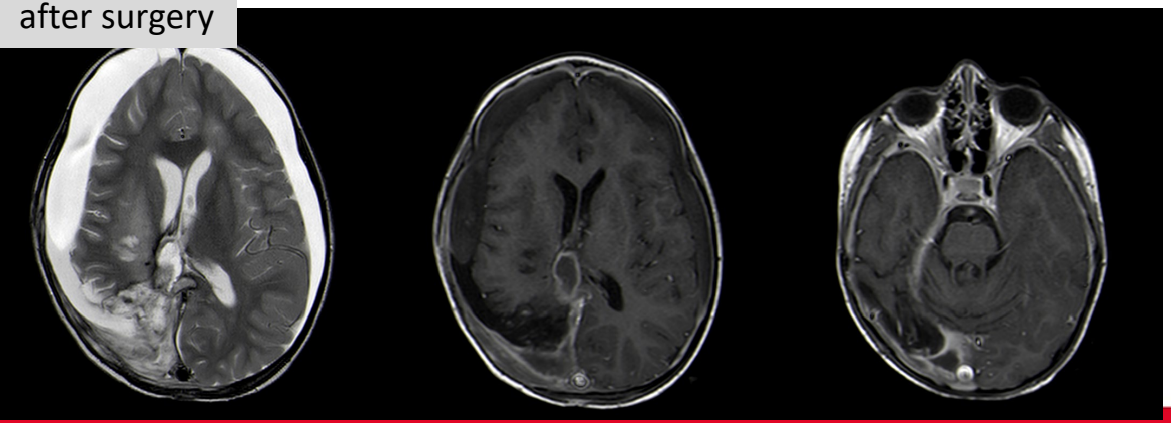


HE

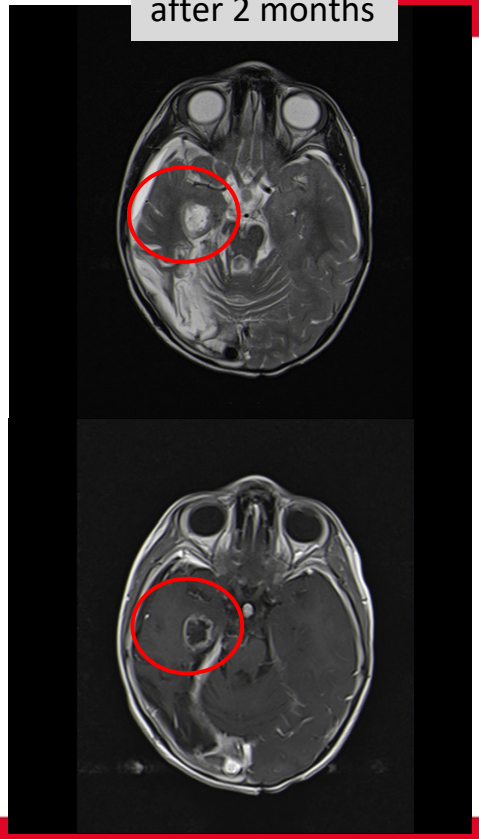
diagnosis



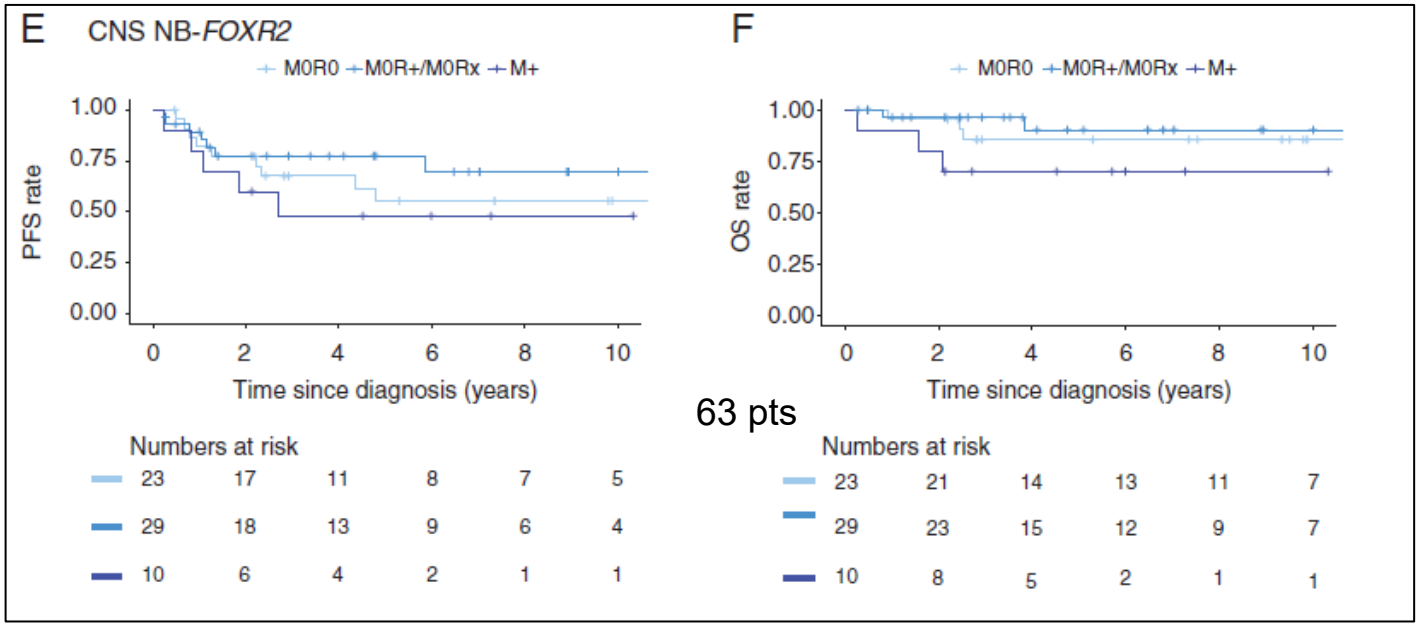
after surgery



after 2 months



- estimations for prognostic parameters are difficult to identify
- prolonged survival reported also for pts with high-risk criteria (residual tumour and M+)
- focal RT vs CSI: higher frequency of distant relapses after focal irradiation



63 pts

Von Hoff K, et al Neuroncology, 2021

LOCALIZED disease

- maximal safe resection (consider re-resection)
- focal RT cannot be recommended (distant relapses reported)-> CSI

- older children: a “MBL”-like treatment with CSI (standard risk 23.4 Gy) and maintenance CT (es BABABABA PNET5)

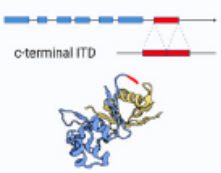
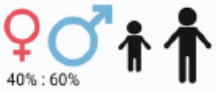
- young children: RT-omitting regimens (eventual use of salvage RT may be used)

RESIDUAL tumor

- upfront CT (i.e.CBDCA-VP16 x 2)
- second surgical opinion is recommended
- CSI and maintenance CT as localized disease

METASTATIC disease

- treatment according to MBL-HR/ CNS PNET with increased CSI dose
- upfront CT may be used with subsequent re-evaluation of re-surgery

Tumour type	CNS tumour with *BCOR* internal tandem duplication (CNS *BCOR*-ITD)
Biological hallmarks	*BCOR* internal tandem duplication 
Molecular biomarkers	nuclear BCOR expression *BCOR*-ITD DNA methylation
Demographics	
Localisation	 50% 50% ?
Metastasis	frequent at relapse extra CNS metastasis wound site seeding
Outcome	aggressive disease 70% 2-year OS more data needed
Risk factors	metastatic disease

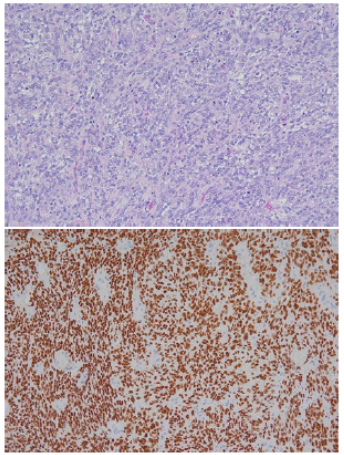
CNS tumor with *BCOR* internal tandem duplication (CNS BCOR-ITD)

CNS tumour with *BCOR* internal tandem duplication

Essential diagnostic criteria:

- Malignant primary solid CNS tumour, uniform oval or spindle shaped cells and
- Internal tandem duplication in exon 15 of *BCOR or*
- DNA methylation profile

- BCOR positive immunohistochemistry may guide diagnosis
- *BCOR* mutations present in other tumor types - not diagnostic



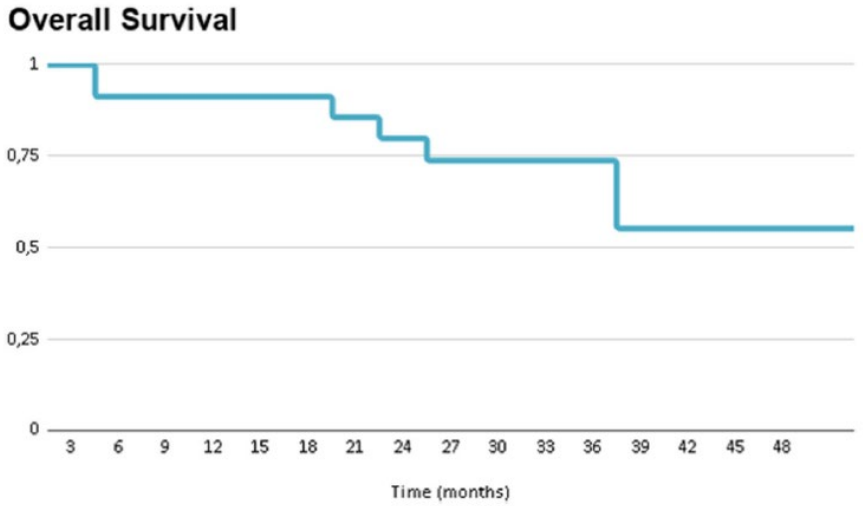
Central nervous system high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR)—case-based reviews

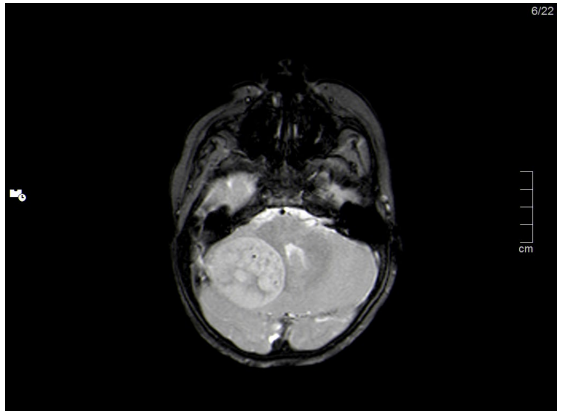
Child's Nervous System (2020)

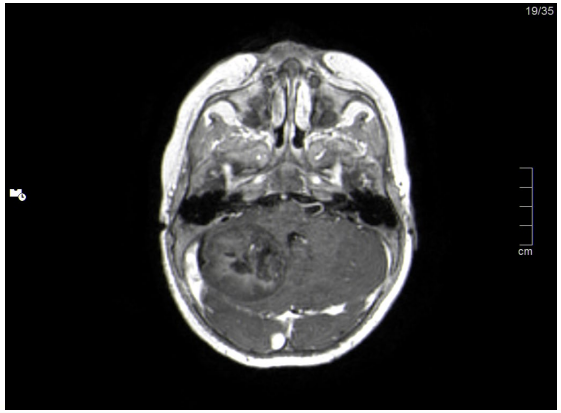
Lazaro De Lima[1] · Mehmet Beşir Sürme[1] · Marco Gessi[2,3] · Angela Mastronuzzi[4] · Evelina Miele[4] · Gianpiero Tamburrini[1,3] · Luca Massimi[1,3,5]

24 cases have been described

- young children (but also also in older/ young adults): median age 4 yrs, range 7 mos–22 yrs
- arise in both genders
- site: across entire CNS, but cerebellar hemisfere: frequently involved
- high propensity for CNS and extracranial spread
- aggressive behaviour: poor OS: 70% after 2 years and 50% after 4 years







heterogeneous data on treatment:

- gross total resection/re-resection
- benefit from RT (CSI)
- benefit from multiagent CT (regimen used for high risk embryonal tumor types or sarcoma seem to be justified)
- intrathecal chemotherapy may be used (AT/RT regimen)

CNS embryonal tumor NEC/NOS

- is a tumor arising in the CNS with embryonal /immunophenotype morphology
- but lacking an alteration that would classify it as one of the molecularly defined CNS embryonal tumors

NOS not otherwise specified

molecular analyses have not yet or could not be successfully performed

→ it is strongly recommended to refer such cases to a national/international reference centre

NEC not elsewhere classified

molecular analyses successfully performed but the results do not lead to an established WHO CNS5 diagnosis

Working group for rare CNS embryonal and sarcomatous tumors

https://paedcan.ern-net.eu/the-escp-project/.

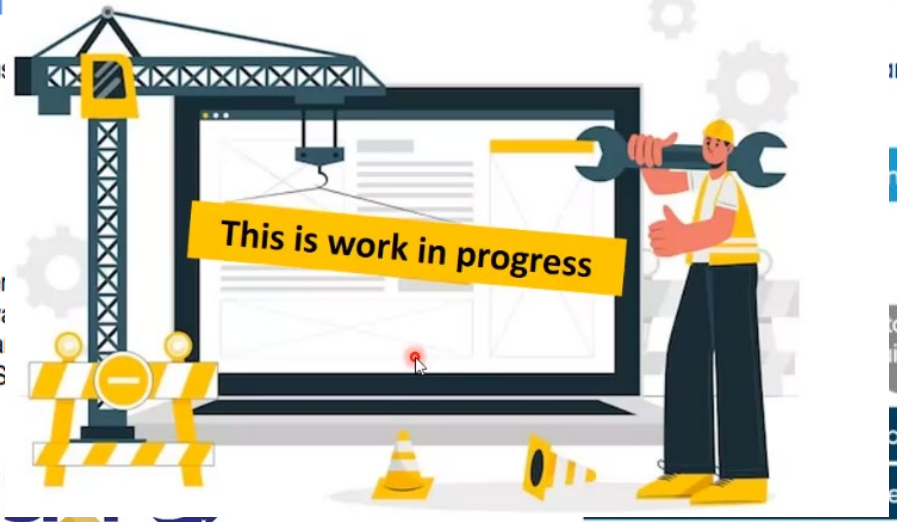
European Standard Cli

for rare embryonal and sarcomatous

Entities:

Rare CNS embryonal tumours:
- Embryonal tumours with multi-layer
- CNS neuroblastoma, *FOXR2*-activa
- CNS tumour with *BCOR* internal ta
- CNS embryonal tumour, NEC/NOS

BRAIN TUMOUR GROUP



SIOP Europe
the European Society for Paediatric Oncology

CNS InterREST Registry

International Registry for Patients with
re Embryonal or Sarcomatous CNS Tumors

nowledge on:
Treatment-associated outcome
o
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ommendations
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