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Maria Inês Alves
Sandra Jacobs

CLINICAL PRACTICE RECOMMENDATIONS

Medulloblastoma

Moderation: Simon Bailey

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COI declaration

The presenters have no conflict of interest to disclose

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WHO classification

2016

Medulloblastoma, genetically defined

- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and *TP53*-mutant
- Medulloblastoma, SHH-activated and *TP53*-wildtype
- Medulloblastoma, non-WNT/non-SHH Medulloblastoma (encompassing Group 3 and Group 4)

Medulloblastoma, histologically defined

- Classic medulloblastoma,
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large-cell / anaplastic medulloblastoma

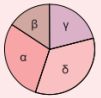
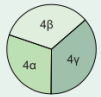
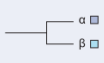
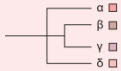
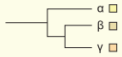
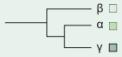
2021

- 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

Subgrouping and *TP53* status!

Louis et al., The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. 2021, Neuro-Oncology: 23(8), 1231–1251

Classification

Subgroup		WNT		SHH				Group 3			Group 4		
Subtype		WNT α	WNT β	SHH α	SHH β	SHH γ	SHH δ	Group 3α	Group 3β	Group 3γ	Group 4α	Group 4β	Group 4γ
Subtype proportion													
Subtype relationship													
Clinical data	Age												
	Histology			LCA Desmoplastic	Desmoplastic	MBEN Desmoplastic	Desmoplastic						
	Metastases	8.6%	21.4%	20%	33%	8.9%	9.4%	43.4%	20%	39.4%	40%	40.7%	38.7%
	Survival at 5 years	97%	100%	69.8%	67.3%	88%	88.5%	66.2%	55.8%	41.9%	66.8%	75.4%	82.5%
Copy number	Broad	6^-		$9q^-$, $10q^-$, $17p^-$		Balanced genome		7^+, 8^-, 10^-, 11^-, i17q		8^+, i17q	$7q^+$, $8p^-$, i17q	i17q	$7q^+$, $8p^-$, i17q (less)
	Focal			*MYCN* amp, *GLI2* amp, *YAP1* amp	*PTEN* loss		$10q22^-$, $11q23.3^-$		*OTX2* gain, *DDX31* loss	*MYC* amp	*MYCN* amp, *CDK6* amp	*SNCAIP* dup	*CDK6* amp
Other events				*TP53* mutations			*TERT* promoter mutations		High *GFI1/1B* expression				

Age (years): 0-3 >3-10 >10-17 >17

Cavalli et al., Intertumoral Heterogeneity within Medulloblastoma Subgroups. 2017, Cancer Cell: 31, 737–754

Biological and clinical risk groups

Key points:

- Childhood WNT patients (<16 years at diagnosis) consistently show a favourable prognosis (>90% survival)
- TP53 mutations associate with a poor outcome in SHH

(somatic mutation vs germline mutation …)

- MYC or MYCN amplification - but … its prognostic significance and histology is likely to be relevant only in the context of molecular subgrouping !
- Familial disease/germline mutations - important for therapy selection!

Emerging biological risk factors → Understand disease heterogeneity
Improve the stratification of risk

Residual disease

Extent of resection – a prognostic variable

< 1.5 cm^2 vs ≥ 1.5 cm^2

It is probable that the prognostic benefit of a total resection is attenuated after accounting for molecular subgroup affiliation.(3) Considering all these data it was felt that there is a paucity of supportive evidence that intensifying therapy to the craniospinal axis improves local control in the setting of subtotal resection.

It is recommended that residual tumour where second look surgery is not considered appropriate without any other high-risk factors should be treated as standard risk disease.

Risk stratification

Table 1. Risk groups for children age 3-5 years old and over.

	Molecular features	Histology	Residual	Metastatic disease
Low Risk	WNT subgroup under 16 years old TP53 wild type, MYCN not amplified	Classic, Nodular Desmoplastic	<1.5cm^2	M0
Standard Risk	TP53 wild type, MYCN not amplified (unless group 4 MYCN amplified)	Classic, Nodular Desmoplastic	<1.5cm^2	M0
	WNT subgroup any age and not low risk	Any	Any	M+ if under 16 M0 if over 16
	No biological high-risk features non- WNT subgroup	Classic, Nodular Desmoplastic	≥1.5 cm^2	M0
High Risk	TP53 mutant and /or MYCN / MYC amplified (unless group 4 MYCN amplified)	Classic, Nodular Desmoplastic,	Any	Any
	Any	Classical	≥1.5cm2	M+
	Any non-WNT and WNT > 16 years	Any	<1.5cm2	M+
	MYC amplified	Any	Any	Any
	Any non-WNT	Anaplastic Large Cell	Any	Any

Risk stratification

Table 2. Risk groups for children < 3-5 years

	Molecular features	Histology	Residual	Metastatic disease
Low Risk	SHH - TP53 wild type MYC/ MYCN not amplified	DN/MBEN	Any	Any
Standard Risk	Not high risk, non- SHH, non WNT	Classical	<1.5cm2	M0
High Risk	TP53 mutant and/or MYC/ MYCN amplified	DN/MBEN	Any	Any
	non- SHH, non WNT	Classical	≥1.5cm2	Any
	non- SHH, non WNT	Classical	<1.5cm2	M+
	MYC amplified	Classical	Any	Any
	Any	Anaplastic Large Cell	Any	Any

Late effects

Toxicity		Investigation
Endocrine		
	Hypothyroidism Primary Secondary	Serum Free T4/TSH
	Growth Hormone insufficiency	Growth chart showing crossing of growth centiles, IGF-1 and stimulation testing
	Hypoadrenalism	Early morning (pre-9.30 am) Cortisol Synacthen testing
	Delayed puberty	Clinical examination, serum LH/FSH, testosterone or oestradiol
	Infertility	Clinical examination, serum LH/FSH, testosterone or oestradiol, sperm testing when required or more specialised testing
Neurocognitive dysfunction		Neurocognitive assessment
Hearing loss		Auditory assessment
Neurological sequelae		Clinical examination
Diplopia		Clinical examination
Cataracts		Clinical examination
Optic Atrophy		Fundoscopy, visual acuity
Vascular problems	e.g. Moya-Moya, arteritis, cavernoma	Usually manifests as a CVA (cerebro-vascular accident) or MRI follow up
Secondary Tumours		Suspicion on clinical examination or MRI follow up.

Table 8. Table of late effects which may be seen in children and young people treated for medulloblastoma

Individual End of Treatment Summary

- The late effects risks
- Schedule of suggested follow-up monitoring

Diagnostic Criteria

Imaging – Appendix 2: SCPR Imaging Working Group

Must have
All imaging studies must be performed according to the SIOPE-BTG neuroimaging protocol
Pre-OP MRI plus contrast must be available for all patients
Pre-OP 3D imaging acquisition should be done for surgery and RT purposes
Early post-OP MRI plus contrast must be available for all patients within 72h post-OP even in ventilated patients
Scans must be reported according to protocol guidelines by designated specialists with experience in paediatric neuroimaging
Desirable
Baseline spine MRI is recommended before surgical resection or biopsy, or 10-14 days after surgical resection or biopsy (to minimise postsurgical blood products and dural enhancement that might confound imaging interpretation).
During the study, at each examination, the same Tesla-strength is recommended
During the study, at each examination, comparable sequences on consecutive scans are recommended
If post-OP imaging shows extensive post-surgical changes that decrease the ability to assess residual disease, or that mimic tumour infiltration, a second follow-up MRI is recommended within 2-3 weeks after surgery.
Don't do
Do not use CT for standard brain imaging in any childhood cancer tumour

Whole brain and spine MRI including the entirety of the dural sac

Diagnostic Criteria

Histopathology

A histopathological diagnosis of medulloblastoma group of tumours should be ideally made by neuropathologists experienced in reporting paediatric brain tumours. This can be achieved in the context of central pathology review. If available whereby samples are assessed by HE and a CNS embryonal tumour immunohistochemical panel including synaptophysin, GFAP, INI1, YAP1, GAB1, LIN28A, beta catenin etc. Once the histological diagnosis of medulloblastoma (including histological subtype and molecular group prediction if appropriate) is confirmed, the molecular diagnostic panel is activated as soon as feasible.

Medulloblastoma, histologically defined

- Classic medulloblastoma,
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large-cell / anaplastic medulloblastoma

Diagnostic Criteria

Molecular pathology

Subgrouping

At least two independent validated methods

Based on DNA methylation or transcriptomic profiling, and DNA sequencing

Further SHH subtypes and non-WNT/non-SHH subtypes may be optionally assigned

Assessment of specific genetic defects (MYC, MYCN, monosomy ch 6)

iFISH as “gold standard”

Diagnostic Criteria

Molecular pathology

Mutation analysis

Tumour samples

CTNNB1: Analysis should encompass the mutation cluster region in exon 3, including sequences encoding amino acids 30 to 45. Positive results are those cases displaying confirmed non-synonymous missense mutations in this mutation cluster region.

TP53, SMO, PTCH1, SUFU (all essential), ELP1, GPR161 (both optional): Analysis of the whole coding sequence and splice sites to be undertaken in SHH activated tumours. Positive results are those cases displaying confirmed non-synonymous variations to the coding sequence.

APC: Analysis of the whole coding sequence and splice sites to be undertaken in cases of *CTNNB1*-wildtype WNT MB patients. Positive results are those cases displaying confirmed non-synonymous variations to the coding sequence.

BRCA2, PALB2: Fanconi-type mutations should be assessed in all patients' tumours by analysis of the whole coding region and splice sites. Positive results are those cases displaying confirmed non-synonymous variations to the coding sequence.

Germline alterations

In all cases with SHH medulloblastomas or *CTNNB1*-wt WNT medulloblastomas, urgent genetic counselling of the patients and their families should be offered immediately and germline testing performed in a laboratory certified for genetic testing of germline material.

In cases with somatic *TP53, PTCH, SUFU, APC, PALB2, BRCA2, ELP1* or *GRP161* mutations, these mutations should be indicated to the human genetics department responsible for genetic counselling and testing. The presence in the germline can be tested, using DNA extracted from the matching patient blood sample.

Reporting variants

Diagnostic Criteria

Cerebrospinal Fluid

CSF via a lumbar spinal tap should be collected and the presence of medulloblastoma cells looked for. This should ideally be performed at 14 days post operatively but if performed before this date with no evidence of malignant cells it need not be repeated. However, if positive prior to 14 days post-surgery the sample will need to be repeated at a minimum of 14 days post-surgery.

Chang Criteria for staging of Medulloblastoma

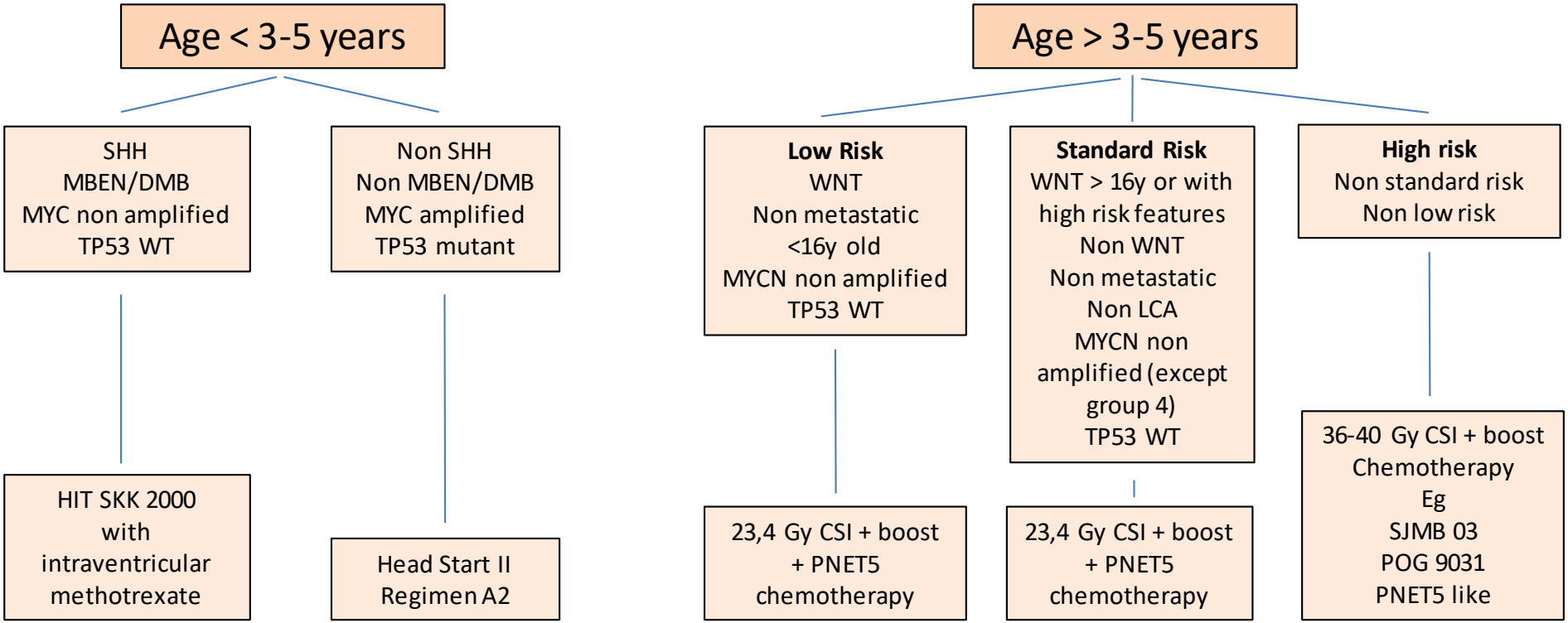
M0	No evidence of gross subarachnoid or hematogenous metastasis.
M1	Microscopic tumour cells found in cerebrospinal fluid.
M2	Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M3	Gross nodular seeding in spinal subarachnoid space.
M4	Metastasis outside the cerebrospinal axis.

Treatment details

Surgery

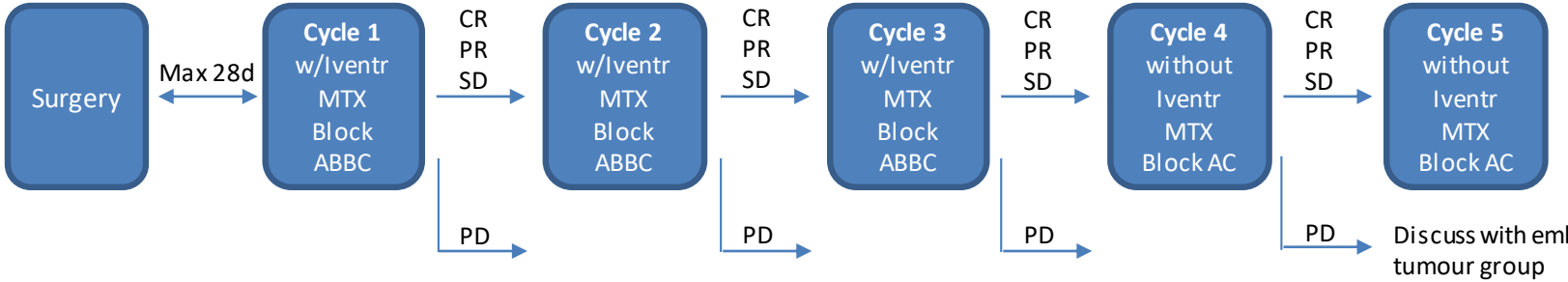
- Surgical resection remains the **mainstay** of the initial management of medulloblastoma
- need for **urgent CSF diversion** is dictated by the severity of the hydrocephalus on imaging and the clinical condition of the child
- pre-operative insertion of a ventriculoperitoneal shunt is not recommended
- achieve **complete resection or near complete resection**
- in case of **residual disease** (>1.5 cm^2) -> consider **second look surgery**
- **Posterior fossa syndrome** occurs in up to 29% of medulloblastoma patients after surgery
- **small residual (<1.5 cm^2)** to protect against post-operative neurological damage preferable

Treatment details



Treatment details

<3-5 years	Molecular Features	Histology	Residual	Metastatic disease	Treatment
Low Risk	SHH TP53 WT MycN non amplified	DM/MBEN	Any	Any	HIT SKK 2000*



Block A**
Cyclophosphamide IVI 800 mg/m² D1-3
Vincristine IV 1,5 mg/m² D5
MTX Iventr 2 mg D1-4 during cycle 1, 2 & 3

Block B**
Methotrexate IVI 5g/m² D1
Vincristine IV 1,5 mg/m² D3
MTX Iventr 2 mg D1-2 during cycle 1, 2 & 3

Block C**
Carboplatin IVI 200 mg/m² D1-3
Etoposide IVI 150 mg/m² D1-3
MTX Iventr 2 mg D1-4 during cycle 1, 2 & 3

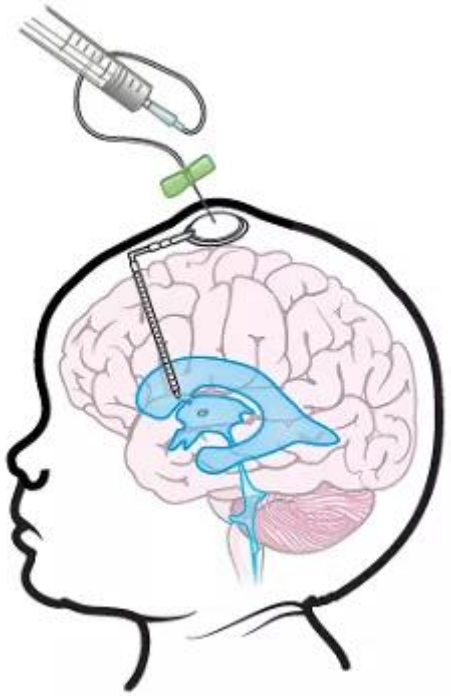
* Rutkowski S. *et al*. NEJM 2005

** Administration details and dose modifications for age and/or toxicity are described in the ESCP guidelines

Treatment details

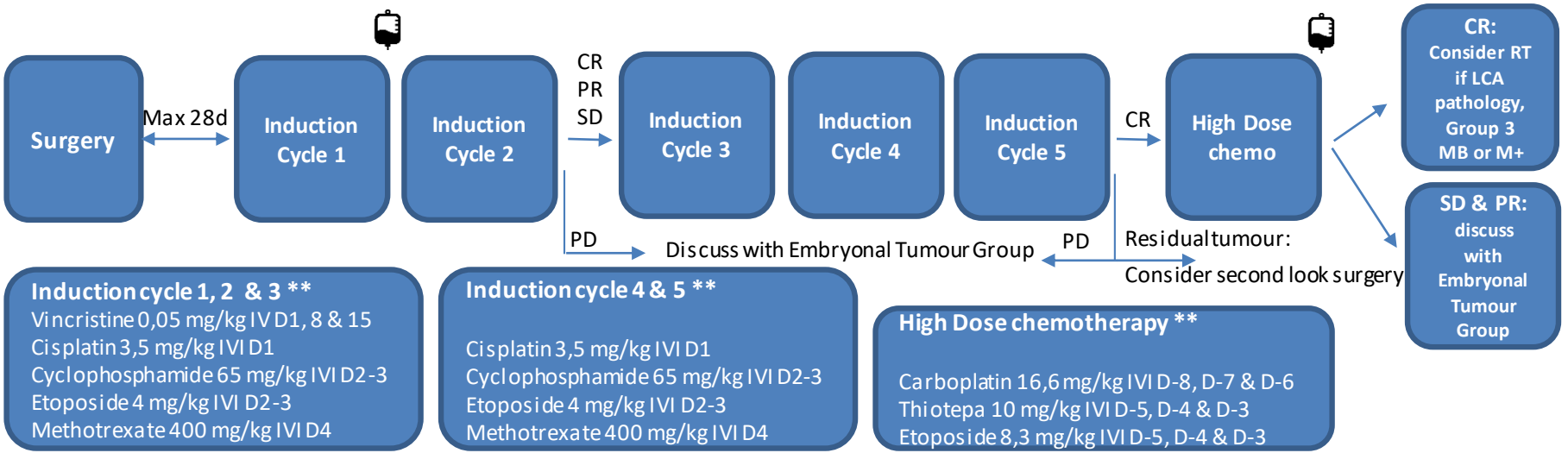
Rickham/Ommaya reservoir

- Intraventricular chemotherapy will be administered via an Ommaya/Rickham reservoir
- SIOPE does not support the routine use of intrathecal methotrexate administered by lumbar puncture/port
- Preventive measures must be established to **exclude the intraventricular application of any other drug** other than methotrexate



Treatment details

<3-5 years	Molecular Features	Histology	Residual	Metastatic disease	Treatment
Standard & High risk	non SHH SHH MycN/Myc Amplified TP53 mutant	Non DM/MBEN	Any	Any	Head Start II*



* Chi *et al*. JCO 2004

** Administration details and dose modifications for age and/or toxicity are described in the ESCP guidelines

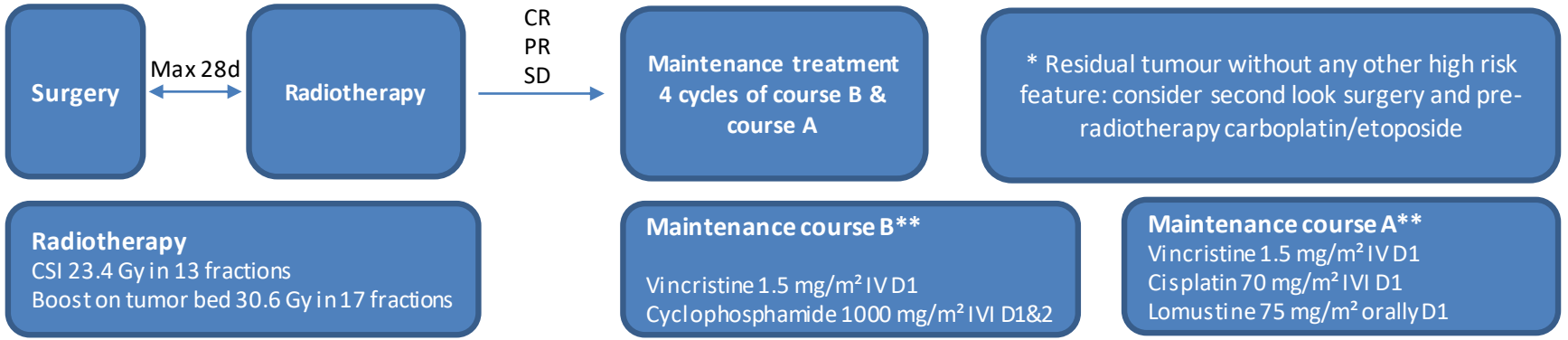
Treatment details

Autologous stem cell collection

- should be undertaken by an accredited stem cell transplantation program by an experienced paediatric team
- Use G-CSF 5-10 micrograms/kg/day subcutaneously to prime bone marrow for stem cell collection
- Target >6 x 10^6 CD34+ cells/kg should be collected and stored in different aliquots (3x10^6 CD34+ cells/kg) as per local policy

Treatment details

>3-5 years	Molecular Features	Histology	Residual	Metastatic disease	Treatment
Low Risk	Wnt (<16y old) Myc & MycN non amplified, TP53 WT	Classic, Nodular desmoplastic	< 1.5 cm^2	M0	23,4 Gy + BABABABA
Standard Risk	No high risk biology: Myc & MycN non amplified, TP53 WT	Classic, Nodular desmoplastic	< 1.5 cm^2*	M0	23,4 Gy + BABABABA
	Wnt (non LR) Unless Wnt > 16y old M+	Any	Any	Any	23,4 Gy + BABABABA

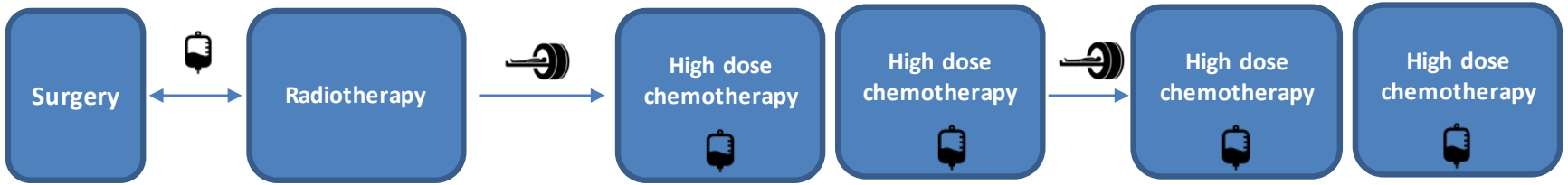


**Administration details and dose modifications for age and/or toxicity are described in the ESCP guidelines

Treatment details

>3-5 years	Molecular Features	Histology	Residual	Metastatic disease	Treatment
High Risk	Myc & MycN amplified TP53 somatic mutation	Any	Any	Any	36Gy + SJMB03 or + POG 9031 or + BABABABA
	Any	Any	Any	M+	

SJMB03*



Radiotherapy
CSI 36 Gy in 20 fractions
Tumour bed boost 18 Gy in 10 fractions
Macroscopic metastatic disease (M2&3) boost to 50.4 Gy

High dose chemotherapy**
Vincristine 1.0 mg/m² IV D-4 & D+6
Cisplatin 75 mg/m² IVI D-4
Cyclophosphamide 2000 mg/m² IVI D-3 & D-2

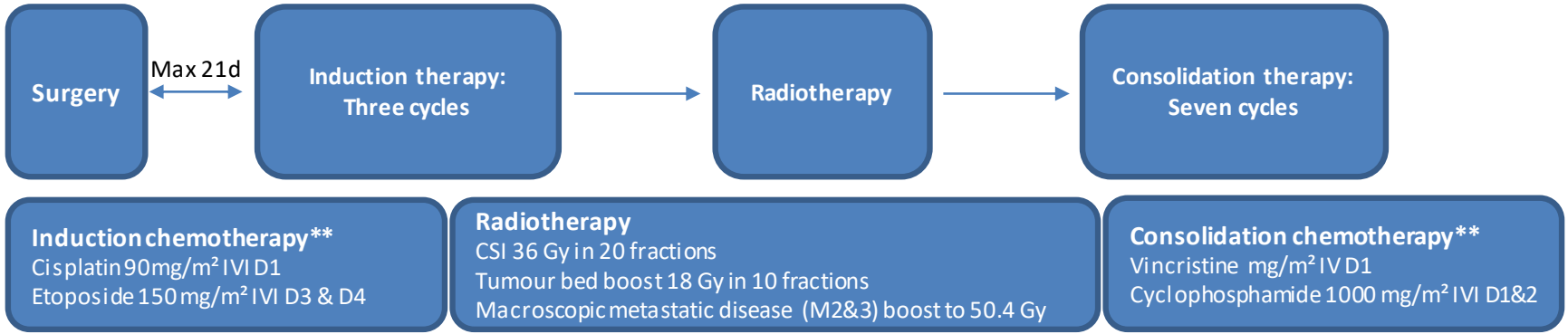
* Gajjar *et al.* JCO 2021

**Administration details and dose modifications for age and/or toxicity are described in the ESCP guidelines

Treatment details

>3-5 years	Molecular Features	Histology	Residual	Metastatic disease	Treatment
High Risk	Myc & MycN amplified TP53 somatic mutation	Any	Any	Any	36Gy + SJMB03 or + POG 9031 or + BABABABA
	Any	Any	Any	M+	

POG 9031*

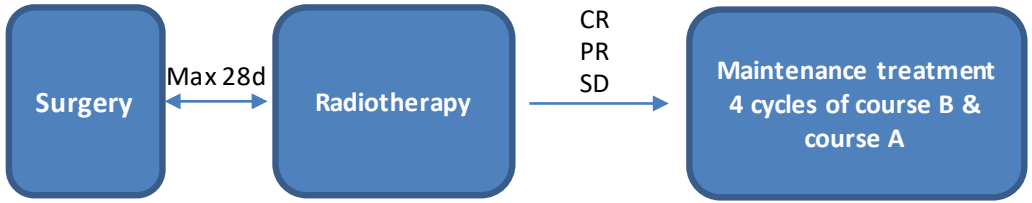


* Tarbell *et al*. JCO 2013

**Administration details and dose modifications for age and/or toxicity are described in the ESCP guidelines

Treatment details

>3-5 years	Molecular Features	Histology	Residual	Metastatic disease	Treatment
High Risk	Myc & MycN amplified TP53 somatic mutation	Any	Any	Any	36Gy + SJMB03 or + POG 9031 or + BABABABA
	Any	Any	Any	M+	



Radiotherapy
CSI 36 Gy in 20 fractions
Tumour bed boost 18 Gy in 10 fractions
Macroscopic metastatic disease (M2&3) boost to 50.4 Gy

Maintenance course B**
Vincristine 1.5 mg/m² IV D1
Cyclophosphamide 1000 mg/m² IVI D1&2

Maintenance course A**
Vincristine 1.5 mg/m² IV D1
Cisplatin 70 mg/m² IVI D1
Lomustine 75 mg/m² orally D1

**Administration details and dose modifications for age and/or toxicity are described in the ESCP guidelines

Treatment details

Radiotherapy

- Children aged less than 3 years are generally managed with a chemotherapy only approach
- Despite advances in systemic therapy and neurosurgical techniques, craniospinal irradiation remains the standard radiotherapy technique

DOSE

<u>High risk Medulloblastoma</u>

CSI dose will be 36Gy in 20 fractions. Tumour bed boost 18Gy in 10 fractions

Total dose to boost PTV will be 54Gy

Sites of brain or spinal metastasis (M2 & M3) to boost also to 50.4Gy (if felt appropriate).

<u>Standard risk Medulloblastoma</u>

CSI dose will be 23.4Gy in 13 fractions. Tumour bed boost 30.6Gy in 17 fractions

Total dose to boost PTV will be 54Gy

Thank you for your attention!