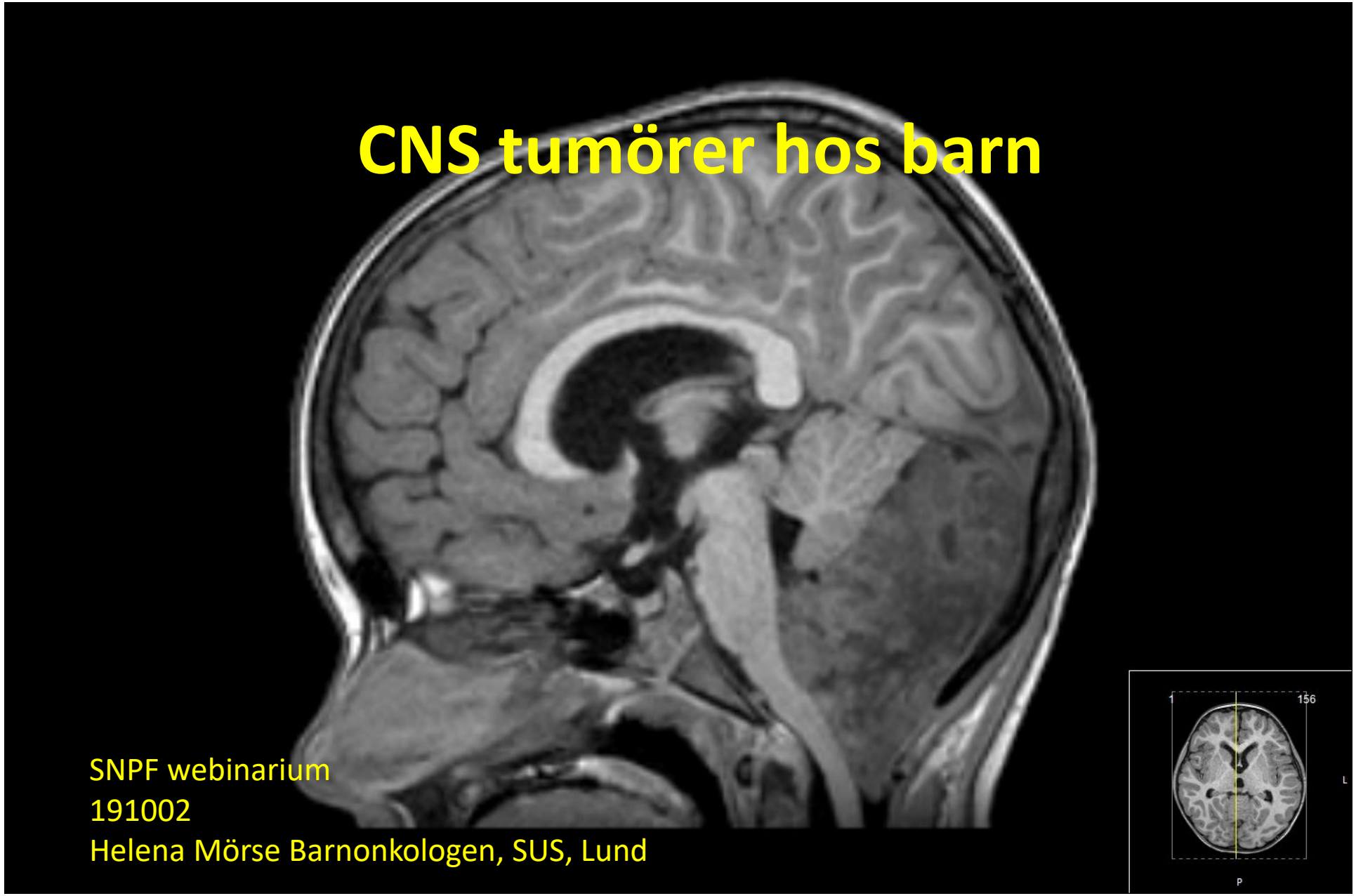
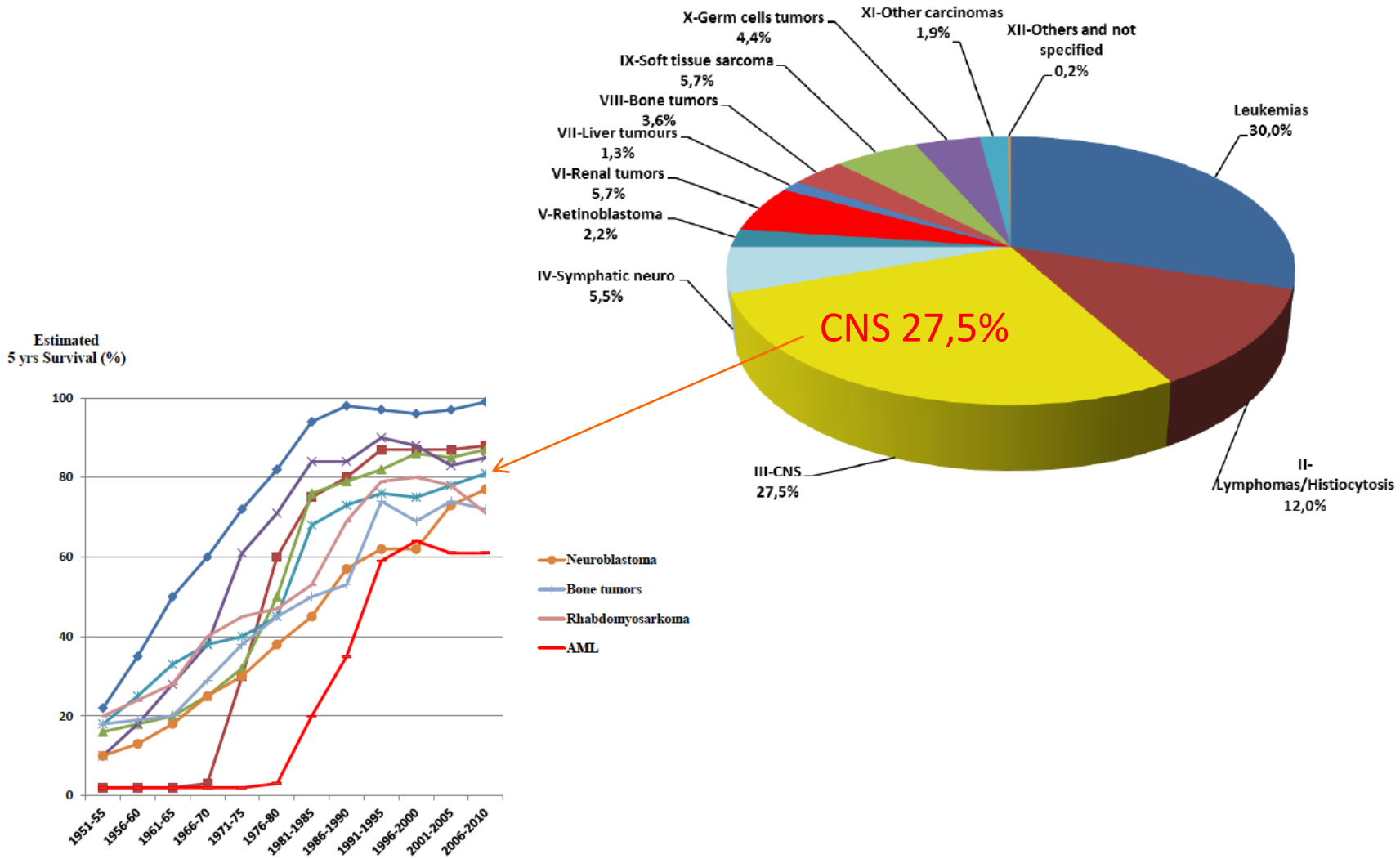
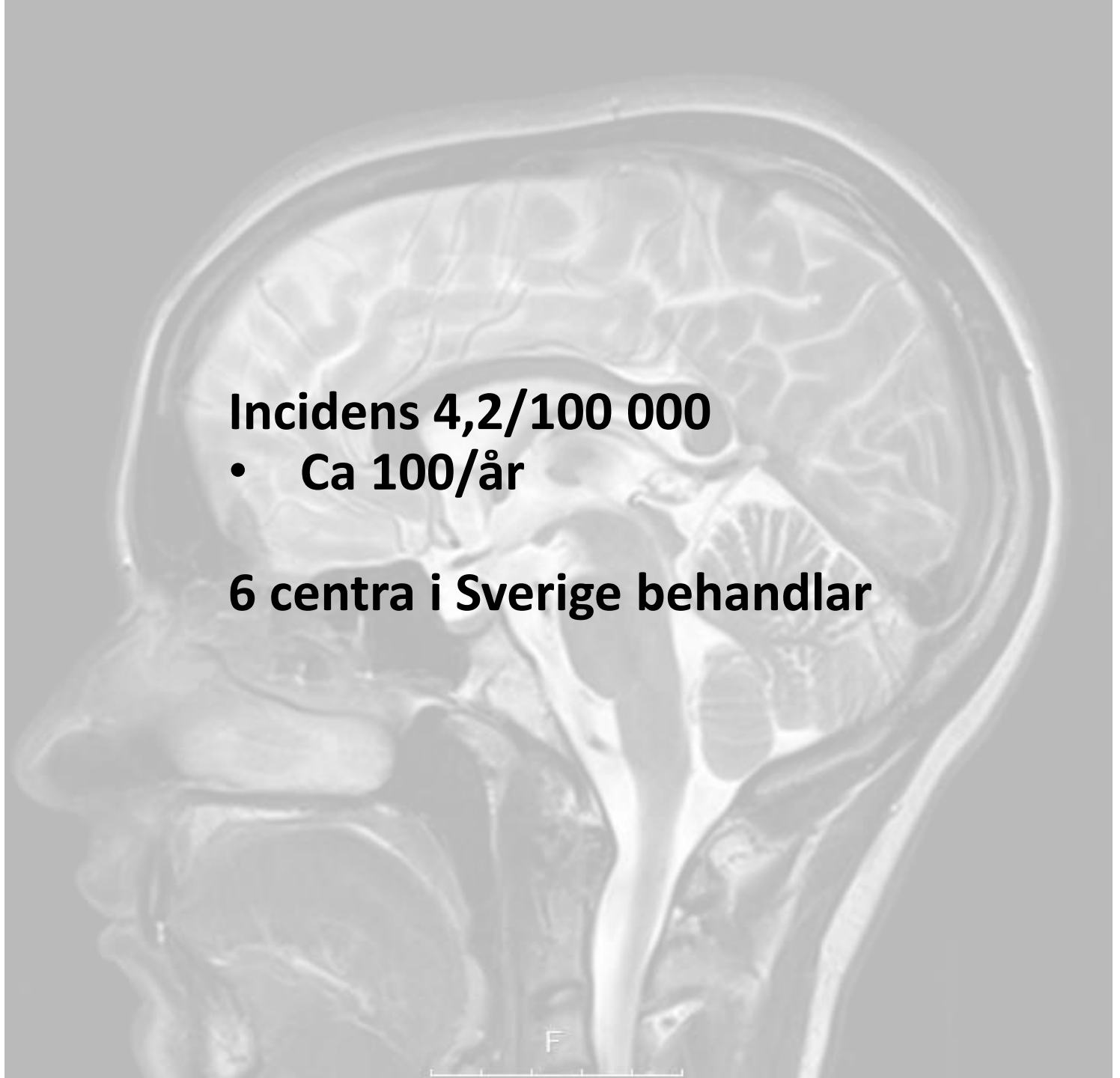
CNS tumörer hos barn



SNPF webinarium
191002
Helena Mörse Barnonkologen, SUS, Lund


X-Germ cells tumors
4,4%
XI-Other carcinomas
1,9%
XII-Others and not specified
0,2%
IX-Soft tissue sarcoma
5,7%
VIII-Bone tumors
3,6%
VII-Liver tumours
1,3%
VI-Renal tumors
5,7%
V-Retinoblastoma
2,2%
IV-Symphatic neuro
5,5%
Leukemias
30,0%
CNS 27,5%
III-CNS
27,5%
II-
Lymphomas/Histiocytosis
12,0%
Estimated
5 yrs Survival (%)
100
80
60
40
20
0
1951-55
1956-60
1961-65
1966-70
1971-75
1976-80
1981-1985
1986-1990
1991-1995
1996-2000
2001-2005
2006-2010
Neuroblastoma
Bone tumors
Rhabdomyosarkoma
AML



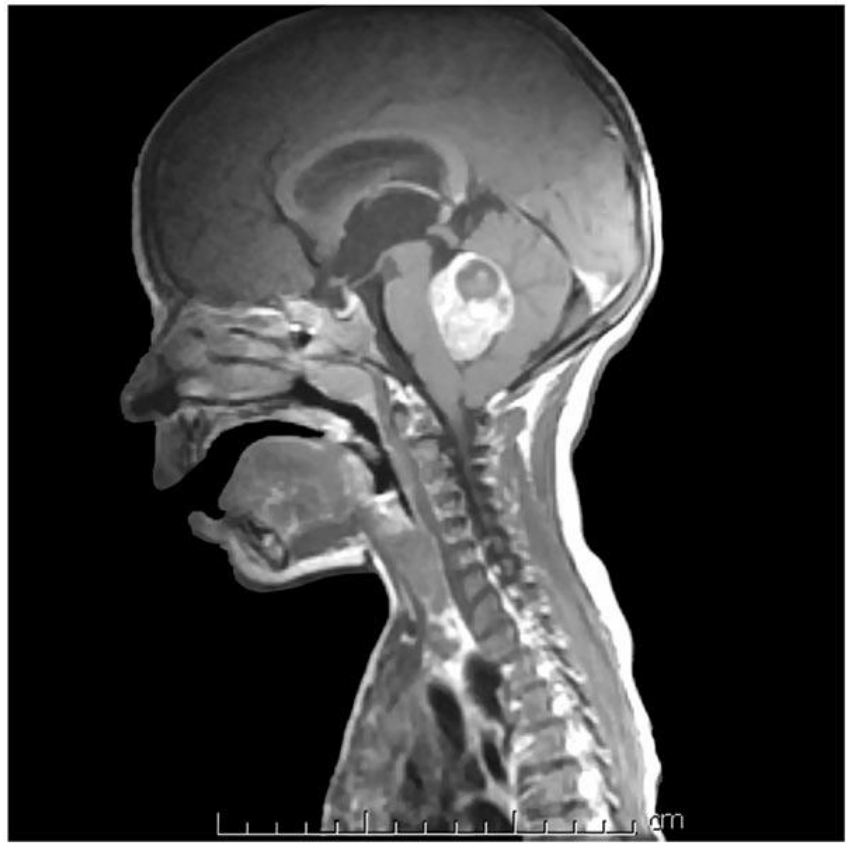
Incidens 4,2/100 000

- **Ca 100/år**

6 centra i Sverige behandlar

Hjärntumör??

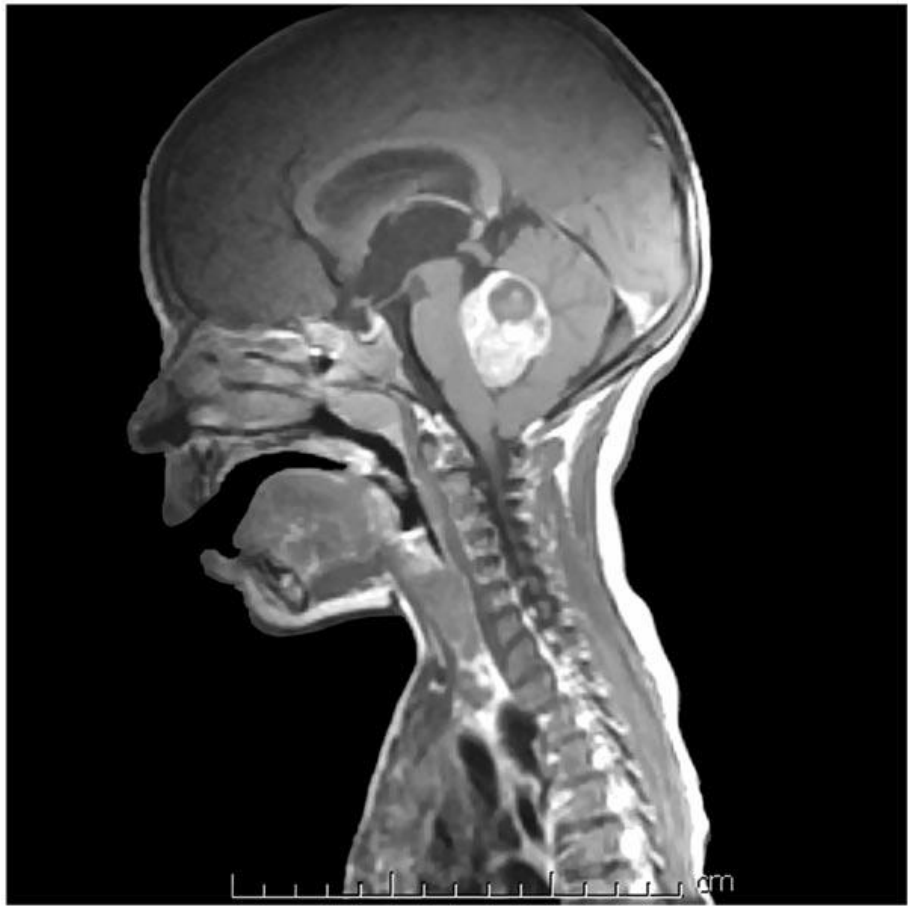
Ofta lång **”patient and doctor’s delay ”!**



Ledtider

Symptom till CT/MR diagnos 85 dgr
Symptom till behandlingsstart 96 dgr

Lokalisation?



Oftast operation primärt!

Men..

Supratentoriell tumör i medellinjen

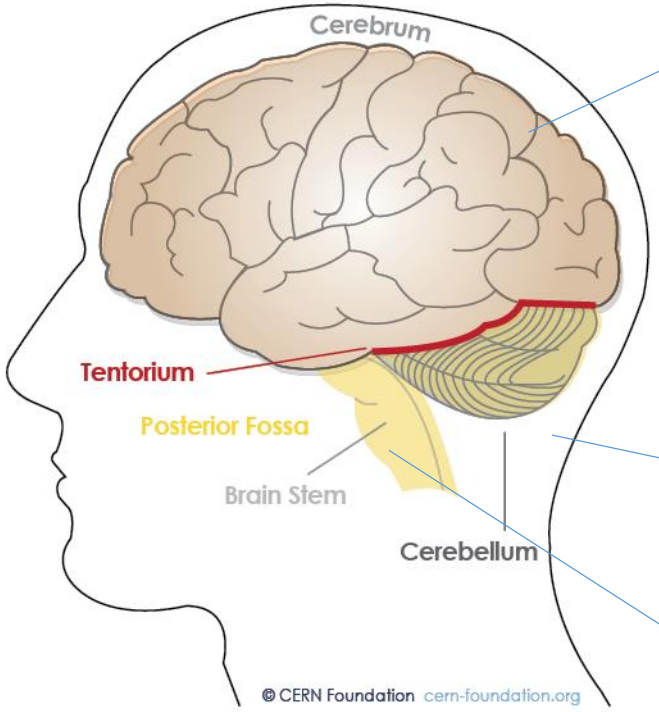
Medellinjen/ suprasellär/ bifokal: **Germ cell tumör??**

- Ta p-AFP o p-HCG!
- Lp om ej högt IC tryck för cytologi och sp-AFP och sp-beta HCG

Positiva markörer = diagnos

Start ev cytostatika alt strålbeh INNAN op eller ej op alls!

Lokalisation



Supratentoriellt

~~PNET~~

Gliom grad I-IV
Ependymom
GCT/Teratom
AT/RT
ETMR
Pineoblastom
Kraniofaryngeom

Infratentoriellt

Medulloblastom
Gliom grad I-IV
Ependymom

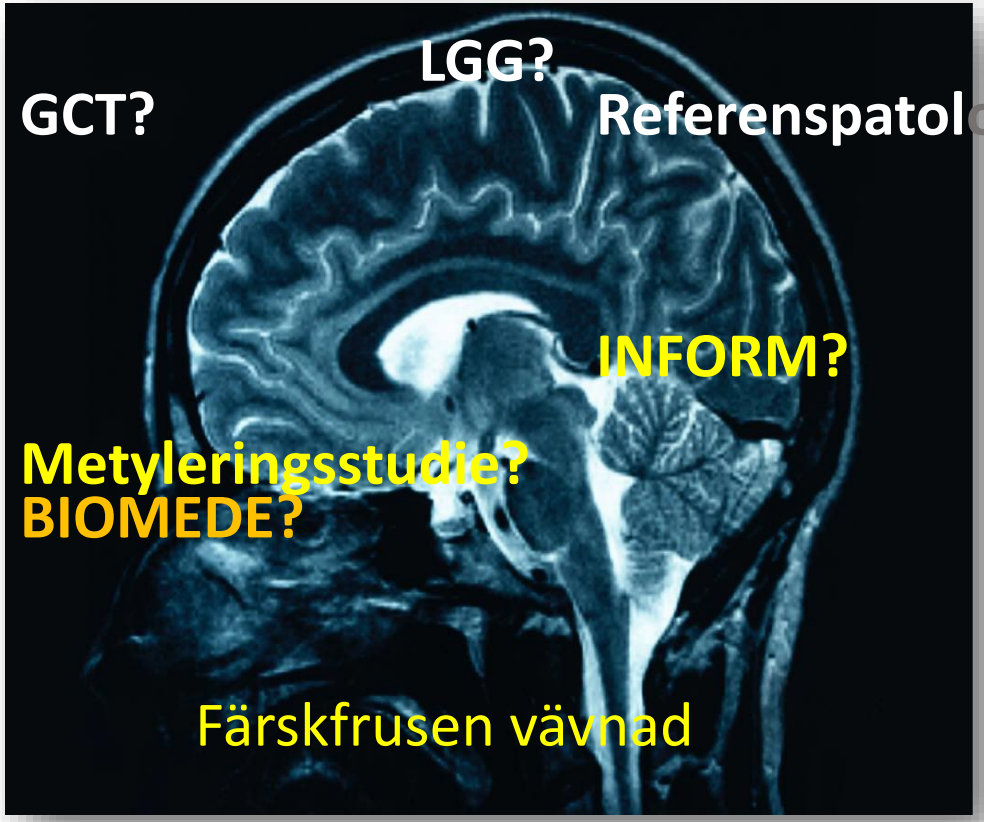
Ponsgliom

Spinala tumörer

Ofta låggradiga gliom/ependymom
Metastaser/ seeding fr tex medulloblastom

Inför operation

MR med kontrast



Barntumörbanken

- **Kirurgi – Radikalt om möjligt – Färsk fruset material**

- Postop MR – resttumör?
- Lp – Cytologi (ev. AFP och HCG)
- Ögonundersökning
- Audiogram
- Neuropsykologisk testning

Potentiell komplikation efter kirurgi i bakre skallgropen

Cerebellär mutism syndrom

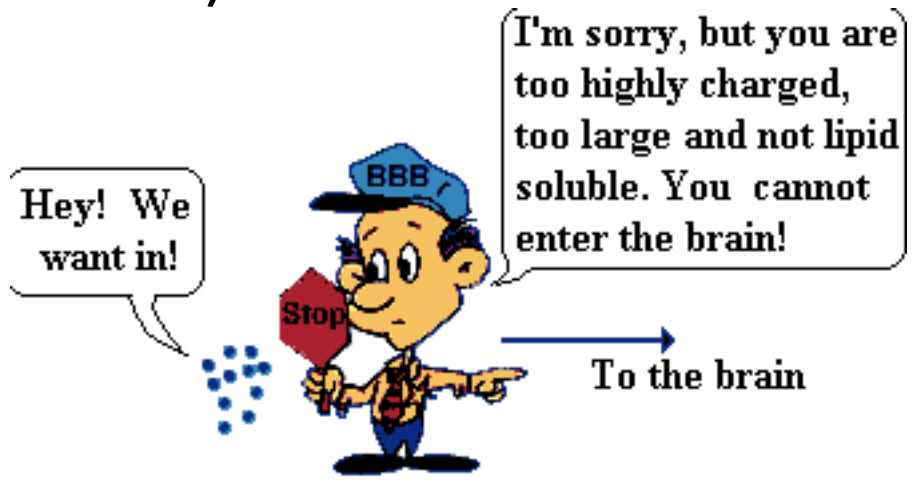
- 10% till 20% ef posterior fossa kirurgi
- 1 till 15 dagar efter op
- Minskat tal eller mutism
- Personlighetsförändring, affektlabilitet
- Hypotoni, ataxi, dysfagi
- Duration 1d - 4 mån
- Finns ingen behandling
- Ofta persisterande dysartri och ataxi

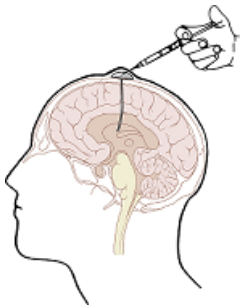
Pågående nordisk studie

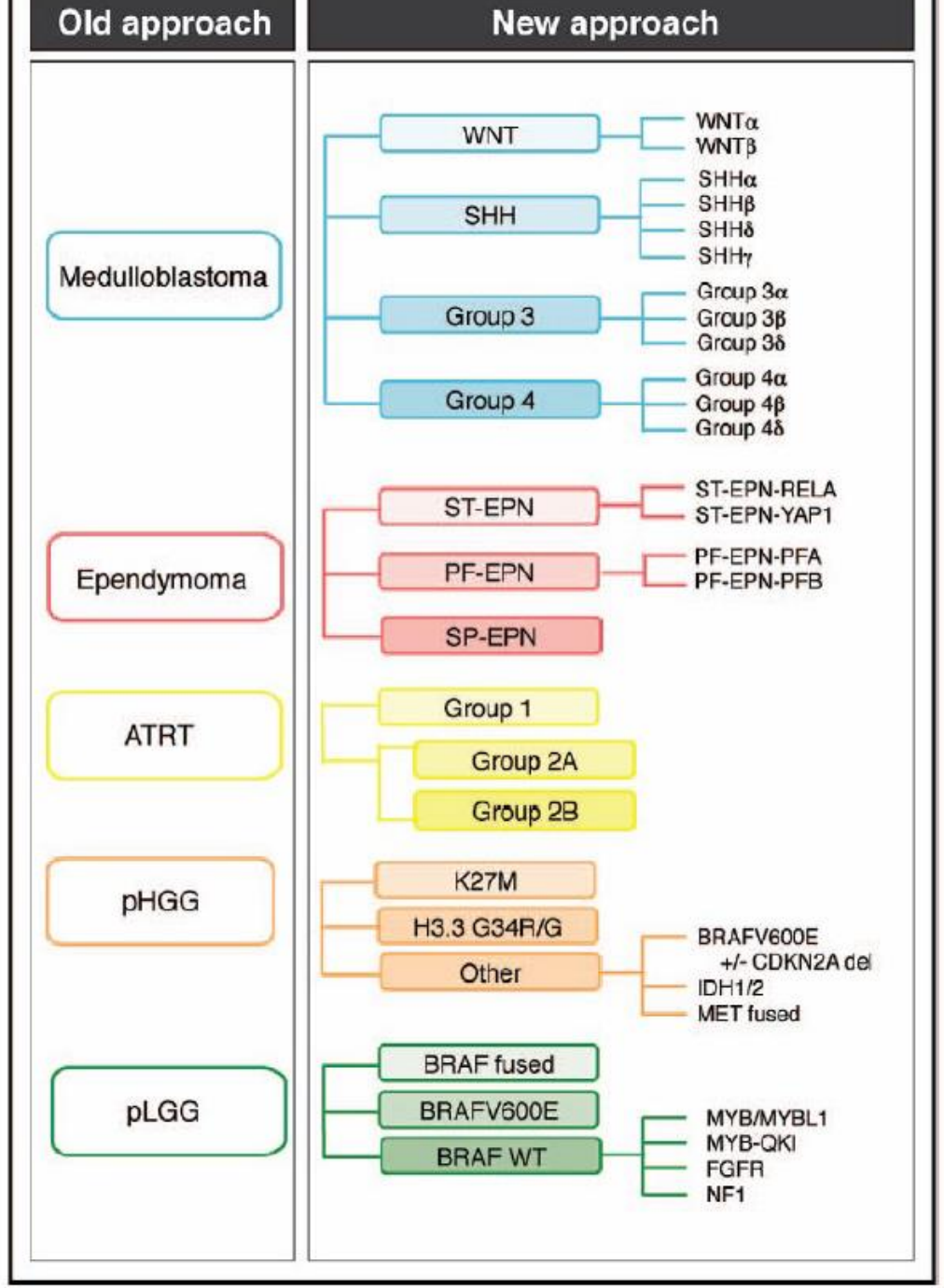
Behandling av tumör

Utifrån PAD svar:

- Strålbehandling (fotoner/protoner)?
- Cytostatika?
- Även ith behandling via rickham?







Integrerad diagnos

Histopatologi

Molekylärbiologi/genetik

Epigenetik

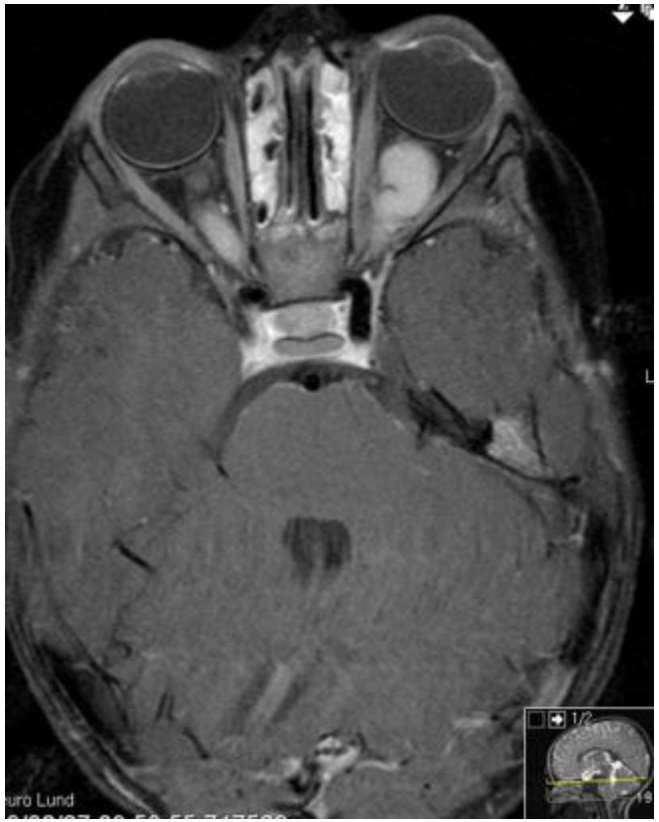
Guerreiro Stucklin et al. 2018

Låggradiga gliom (LGG, WHO grad I-II)

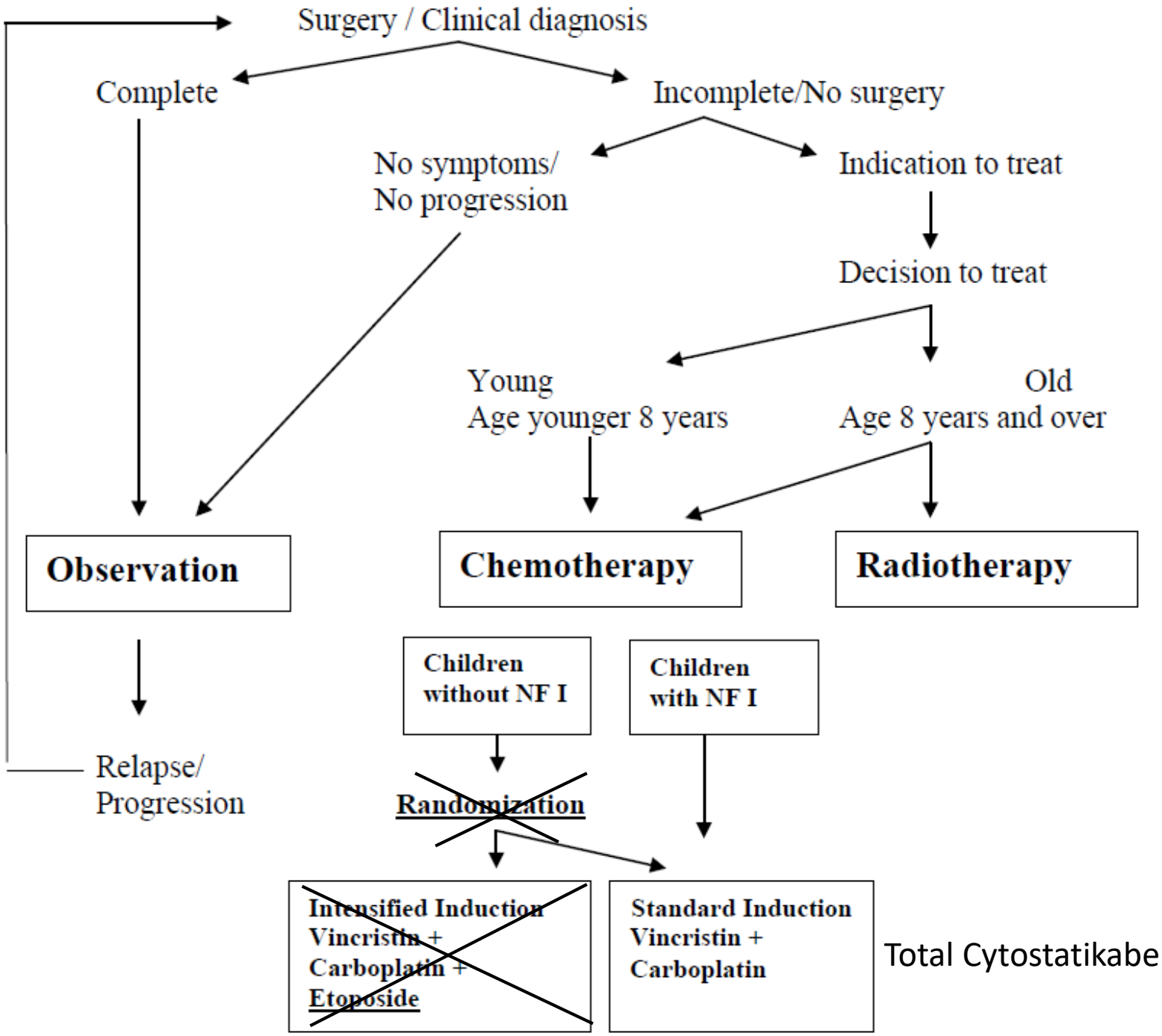
30-40%

Pilocytärt astrocytom I, Gangliogliom I,
Pleomorft Xantoastrocytom II,
Oligodendrogliom II, Astrocytom II, mfl

40% botade med endast radikal kirurgi



LGG
SIOP 2004



Total Cytostatikabeh i 81v

Radikal kirurgi/inte radikal kirurgi/Ingen kirurgi:

- Observation

Klinisk försämring/radiologisk progress:

- Cytostatika (vincristin+ carboplatin i 18 mån alternativt Vinblastin veckovis)

BRAF V600E mutation?

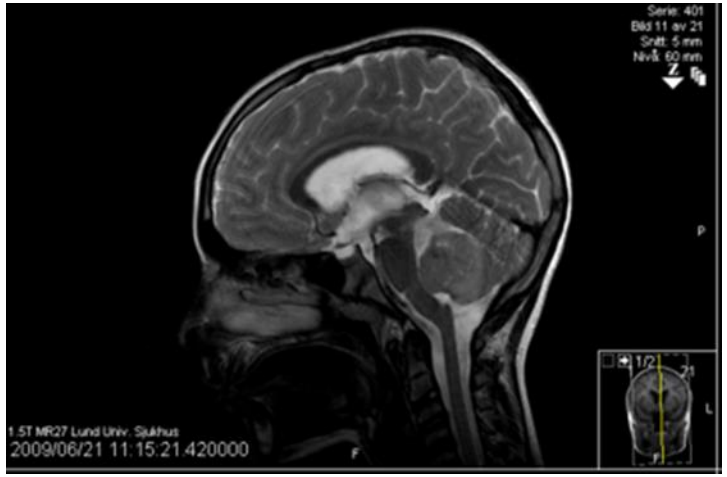
Overall survival = 90%

Många patienter överlever med kvarvarande tumör

Nytt protokoll **LOGGIC** (NF1 neg):

Medulloblastom

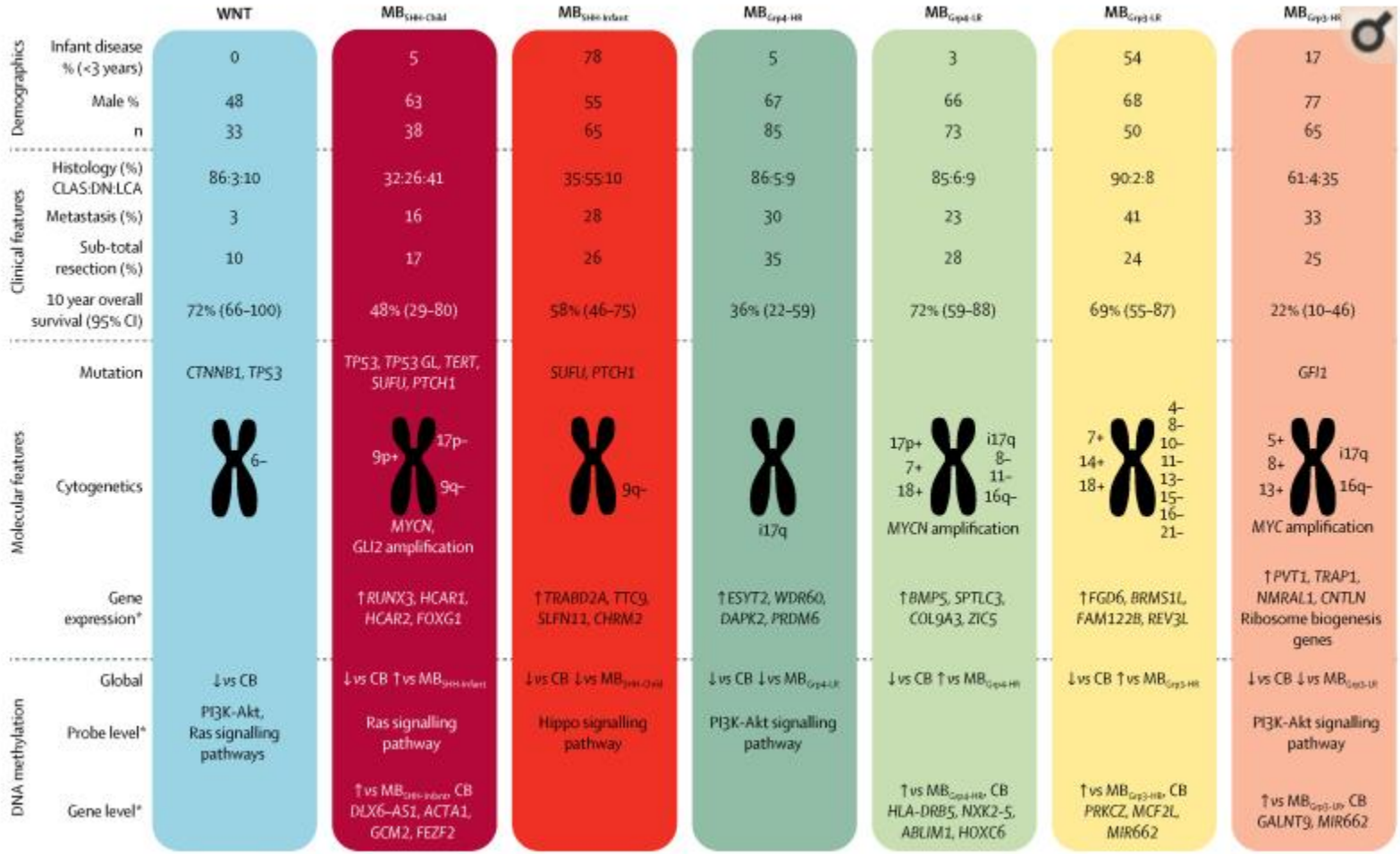
15-20%



Molecular Subgroups of Medulloblastoma

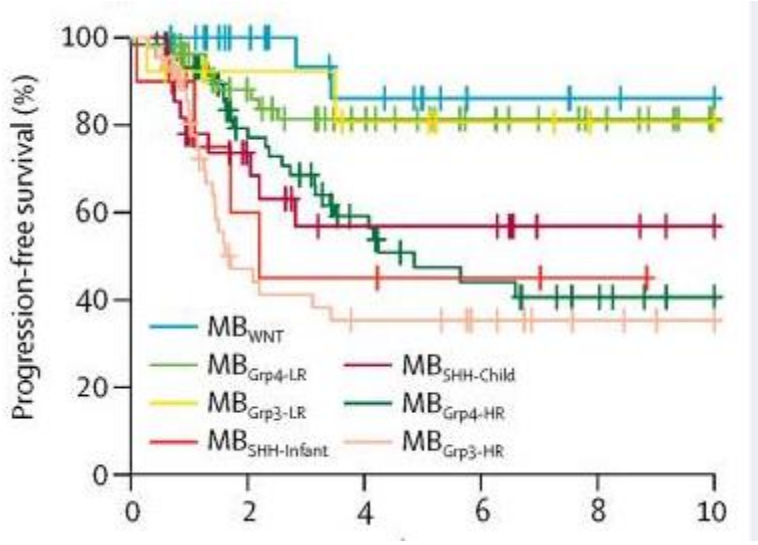
CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C

	WNT	SHH	Group 3	Group 4
DEMOGRAPHICS				
Age Group: (infant, child, adult)				
Gender:	♂♂:♀♀	♂♂:♀♀	♂♂:♀	♂♂:♀
CLINICAL FEATURES				
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate
GENETICS	6-	3q+, 9q-, 10q-	7+, 1q+, 17q+, 18q+, 11p-, 8-, 5q-, 10q-, 16q-	7+, 17q+, 18q+, 11p-, X-, 8-
	CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification
GENE EXPRESSION	WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
	MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*



Schwalbe et al Lancet Oncology 2017

Progressionsfri överlevnad för Medulloblastom – olika subgrupper

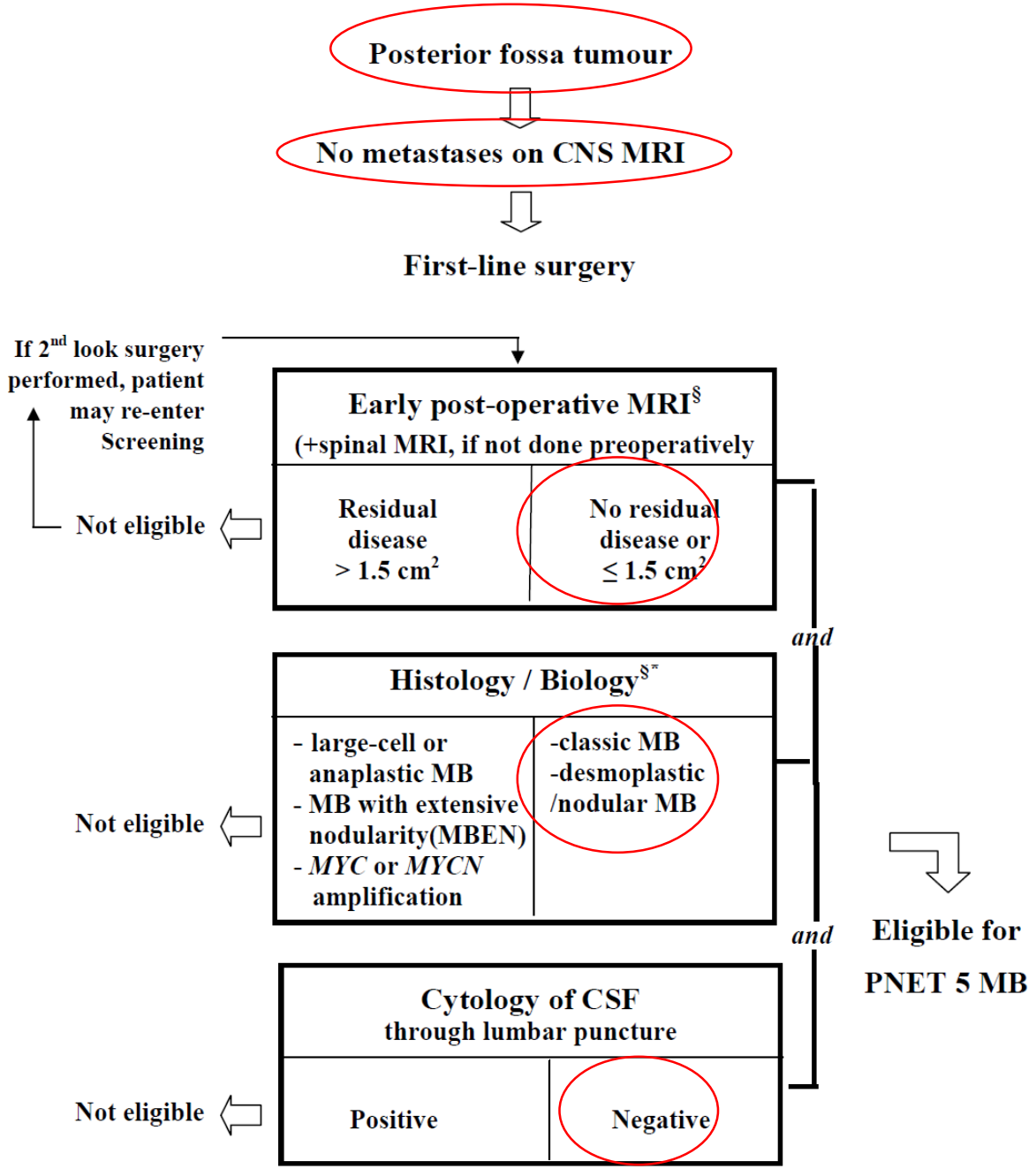


Years since diagnosis

Schwalbe et al Lancet oncology 2017

SIOP PNET 5 MB

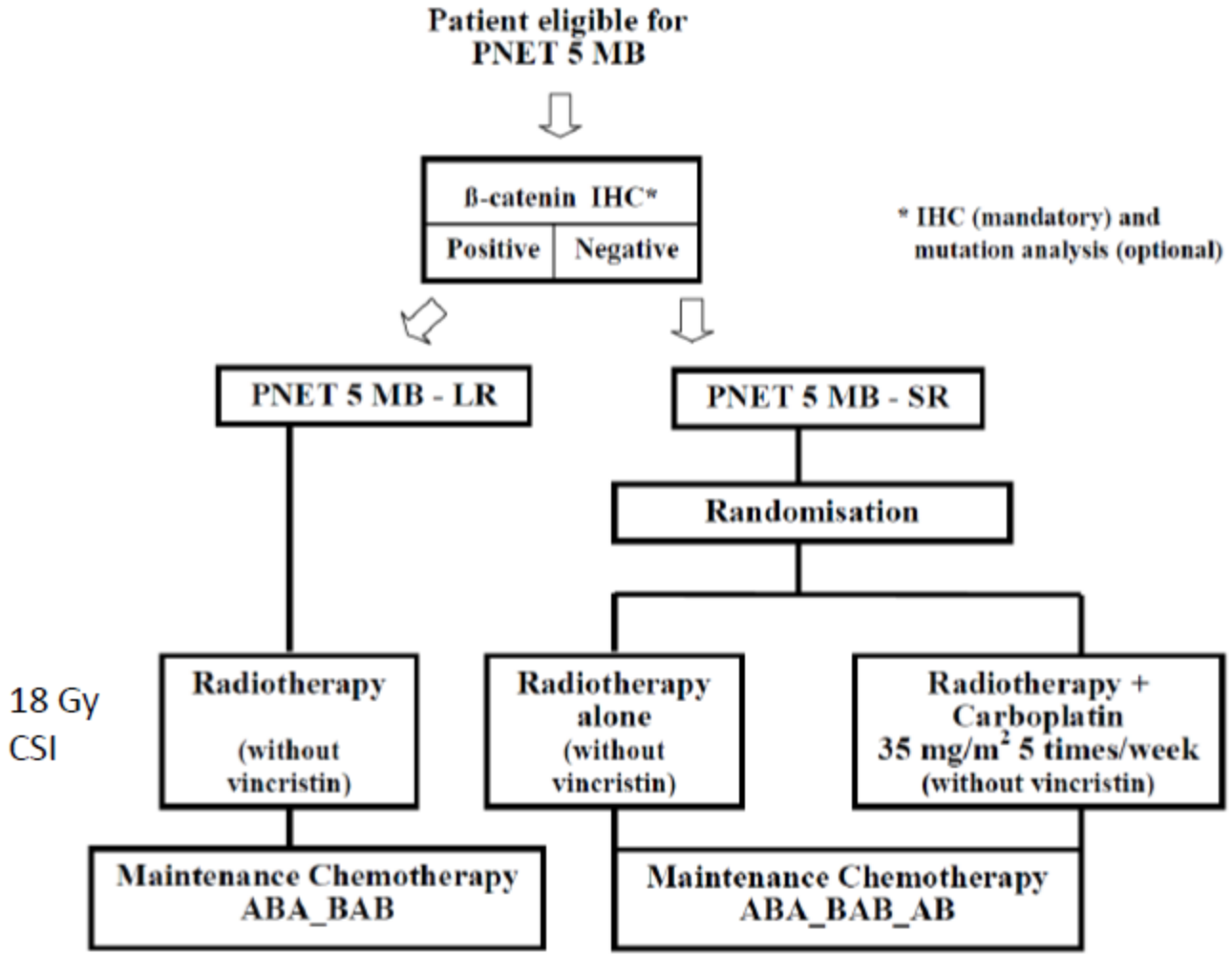
before amendment



Second surgery

Referenspatolog

Remiss för strålning


Patient eligible for
PNET 5 MB
ß-catenin IHC*
Positive
Negative
* IHC (mandatory) and
mutation analysis (optional)
PNET 5 MB - LR
PNET 5 MB - SR
Randomisation
18 Gy
CSI
Radiotherapy
(without
vincristin)
Radiotherapy
alone
(without
vincristin)
Radiotherapy +
Carboplatin
35 mg/m2 5 times/week
(without vincristin)
Maintenance Chemotherapy
ABA_BAB
Maintenance Chemotherapy
ABA_BAB_AB

SIOP PNET 5 MB after amendment, version 12

	PNET 5 MB – LR	PNET 5 MB – SR	PNET 5 MB – WNT-HR	PNET 5 MB – SHH TP53	PNET 5 MB Registry
Mandatory asessments	• Histology by central reference assessment • Early post-operative cranial MRI by central reference assessment • Pre- or postoperative craniospinal MRI by central reference assessment • *MYC*/*MYCN* amplification • β-catenin mutation and β-catenin by IHC (Monosomy 6 optional) • Cytology of CSF through lumbar puncture • For all SHH-activated MB: mandatory somatic (blood control) preinclusion sequencing of *PTCH*, *SUFU* & *TP53* genes • Please see further recommended genetic counselling and assessments on pages 11 and 181				
Inclusion criteria	• CMB or DMB • and CTNNB1 mutation • and < 16 years • and M0 • and R < 1.5 cm^2 • and *MYC*/*MYCN* negative	• CMB or DMB • and Group 3 or 4 MB or SHH *TP53* wt • and M0 • and R < 1.5 cm^2 • and *MYC* negative • and *MYCN* negative (and *MYCN* positive in group 4 MB)	• CMB, DMB or LCA MB • WNT ≥ 16 years or WNT without *CTNNB1* mutation or WNT < 16 years and M+ or R+ • M0 or M+ • R0 or R+ • *MYC*/*MYCN* negative or positive	• All stages • All subtypes • > 3-5 years • SHH MB • *TP53* somatic or germline (including mosaicism) mutation	• All stages • All subtypes • All ages • Pathogenic germline alteration (except *TP53* for SHH)

SIOP PNET5 MB upcoming amendment, version 12

Ependymom

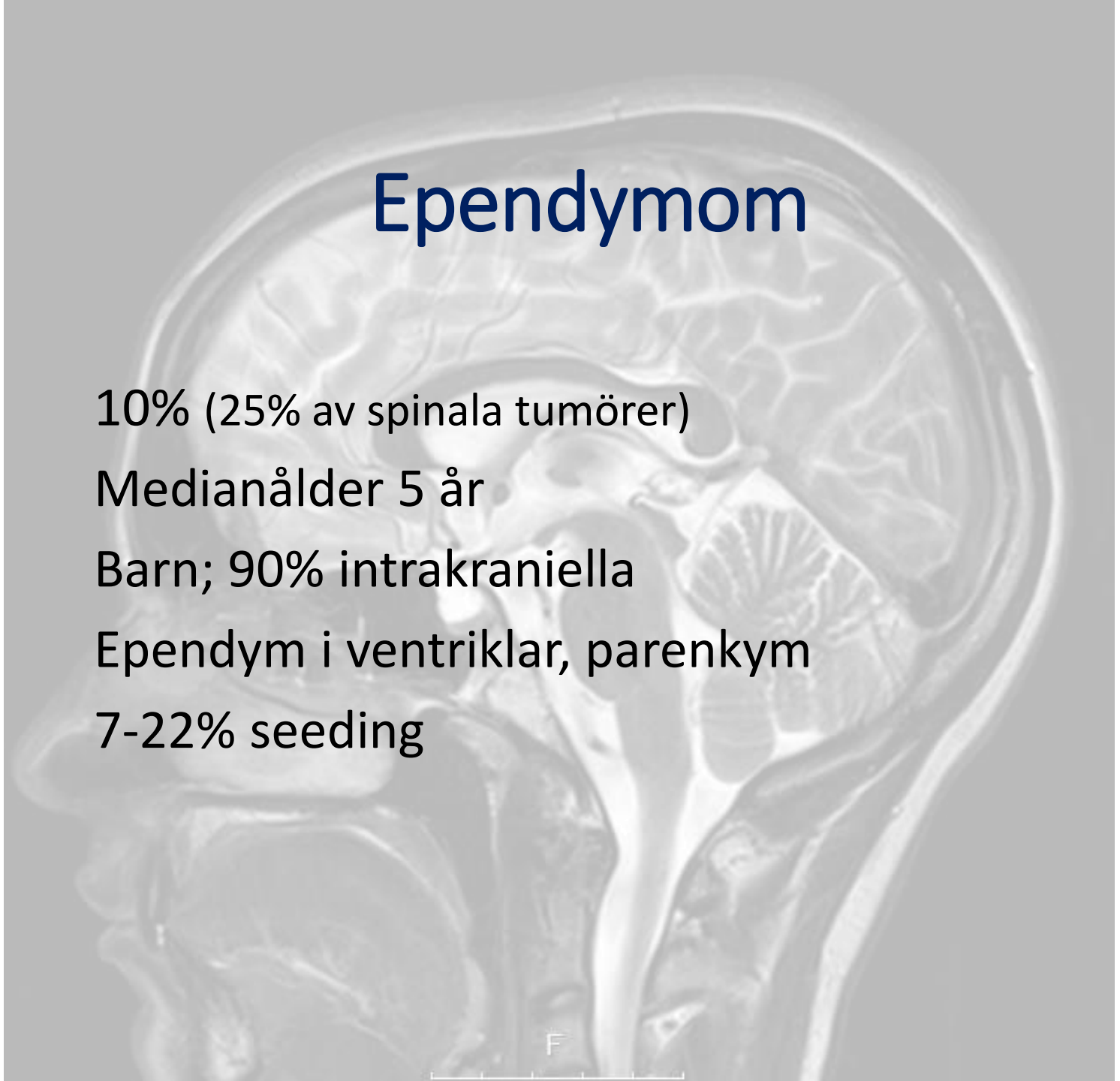
10% (25% av spinala tumörer)

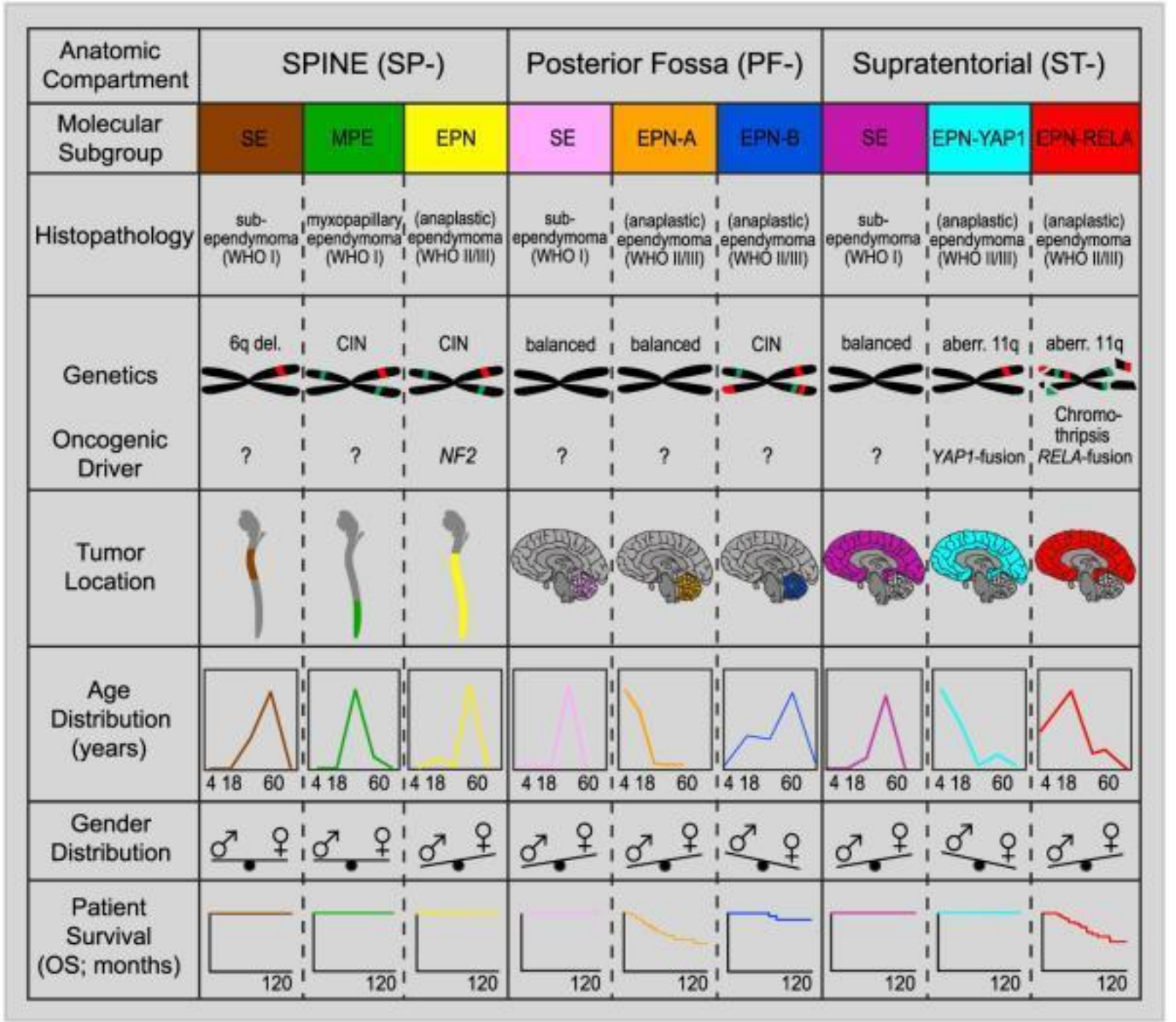
Medianålder 5 år

Barn; 90% intrakraniella

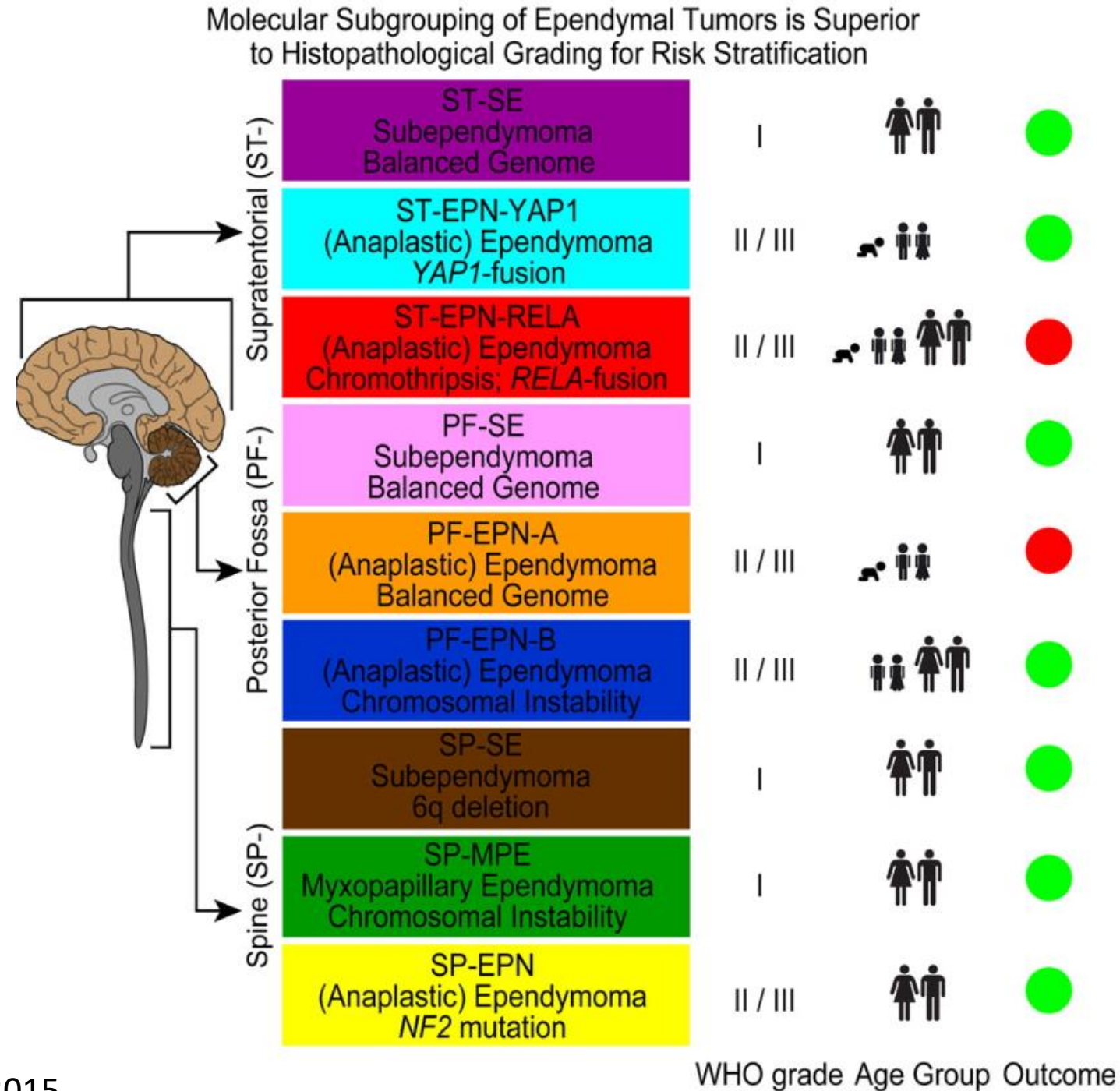
Ependym i ventriklar, parenkym

7-22% seeding



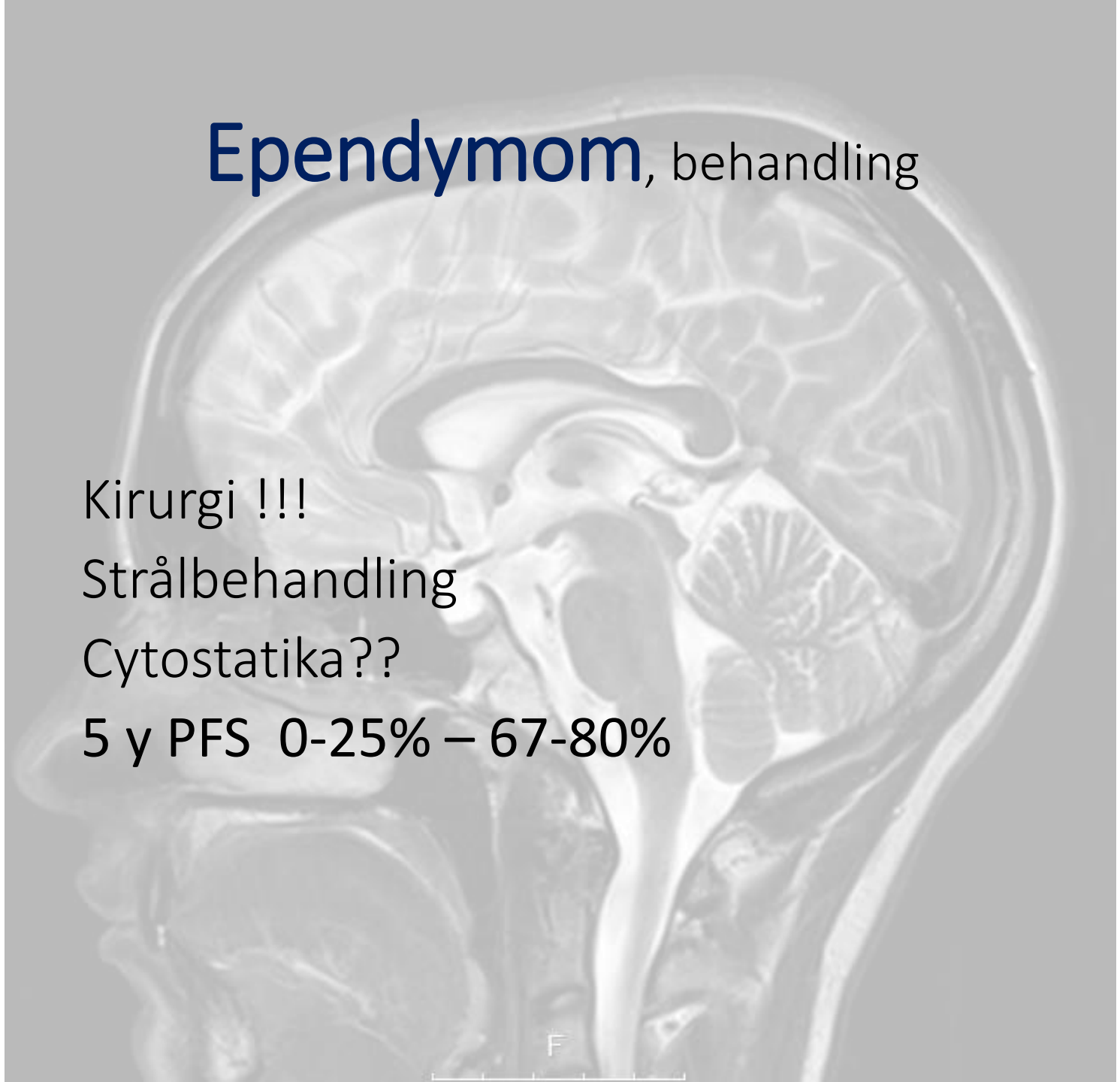


Pajtler et al



Pajtler et al Cancer Cell 2015

Ependymom, behandling



Kirurgi !!!

Strålbehandling

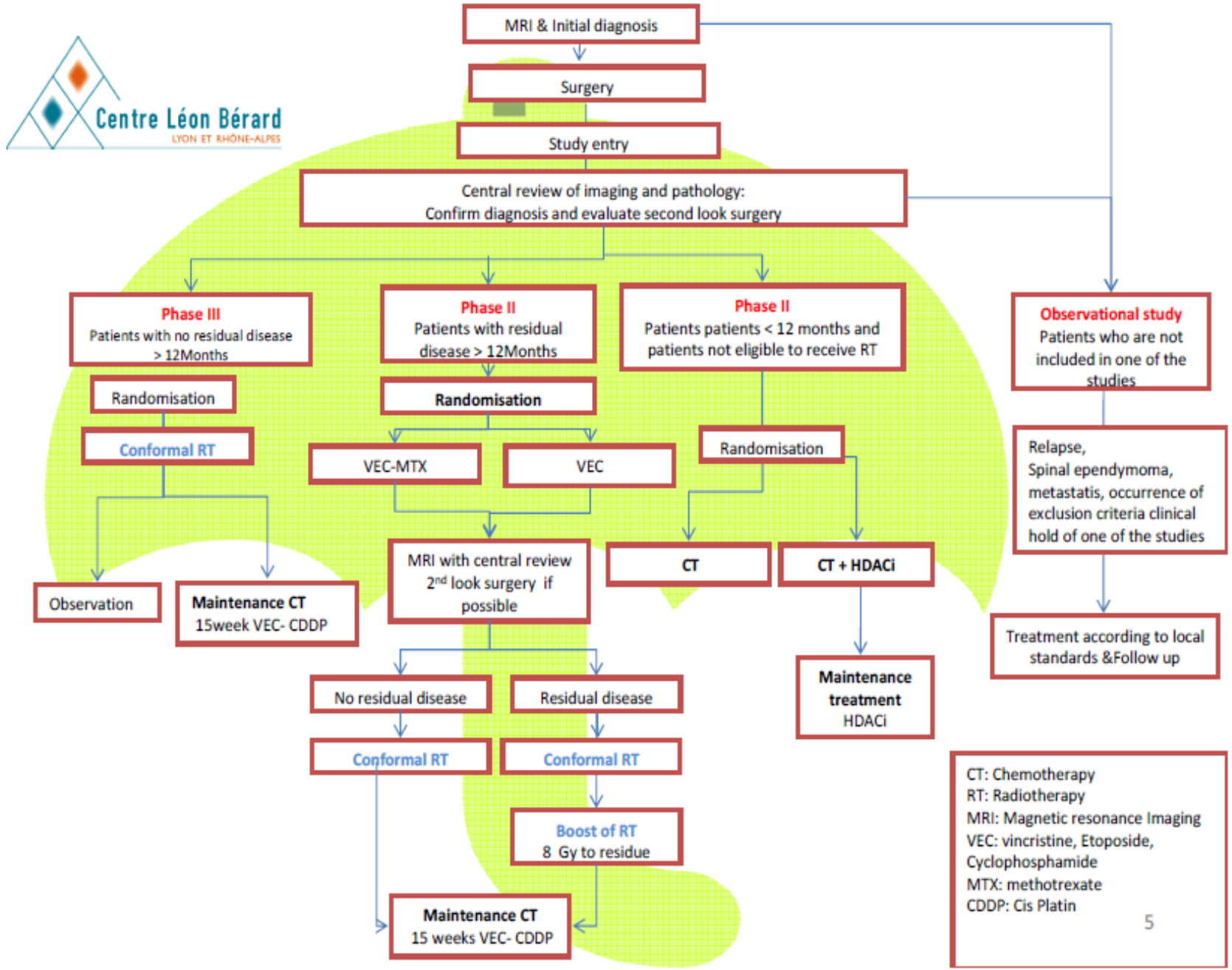
Cytostatika??

5 y PFS 0-25% – 67-80%

SIOP EPENDYMOMA II

An international clinical program for the diagnosis and treatment of children, adolescents and young adults with ependymoma

Final Version 3.0_ January 17th, 2017


Centre Léon Bérard
LYON ET RHÔNE-ALPES
MRI & Initial diagnosis
Surgery
Study entry
Central review of imaging and pathology:
Confirm diagnosis and evaluate second look surgery
Phase III
Patients with no residual disease > 12Months
Phase II
Patients with residual disease > 12Months
Phase II
Patients patients < 12 months and patients not eligible to receive RT
Observational study
Patients who are not included in one of the studies
Randomisation
Conformal RT
Randomisation
VEC-MTX
VEC
Randomisation
Relapse,
Spinal ependymoma, metastatis, occurrence of exclusion criteria clinical hold of one of the studies
Observation
Maintenance CT
15week VEC- CDDP
MRI with central review
2nd look surgery if possible
CT
CT + HDACi
Treatment according to local standards &Follow up
Maintenance treatment
HDACi
No residual disease
Residual disease
Conformal RT
Conformal RT
Boost of RT
8 Gy to residue
Maintenance CT
15 weeks VEC- CDDP
CT: Chemotherapy
RT: Radiotherapy
MRI: Magnetic resonance Imaging
VEC: vincristine, Etoposide, Cyclophosphamide
MTX: methotrexate
CDDP: Cis Platin

Germ cell tumörer

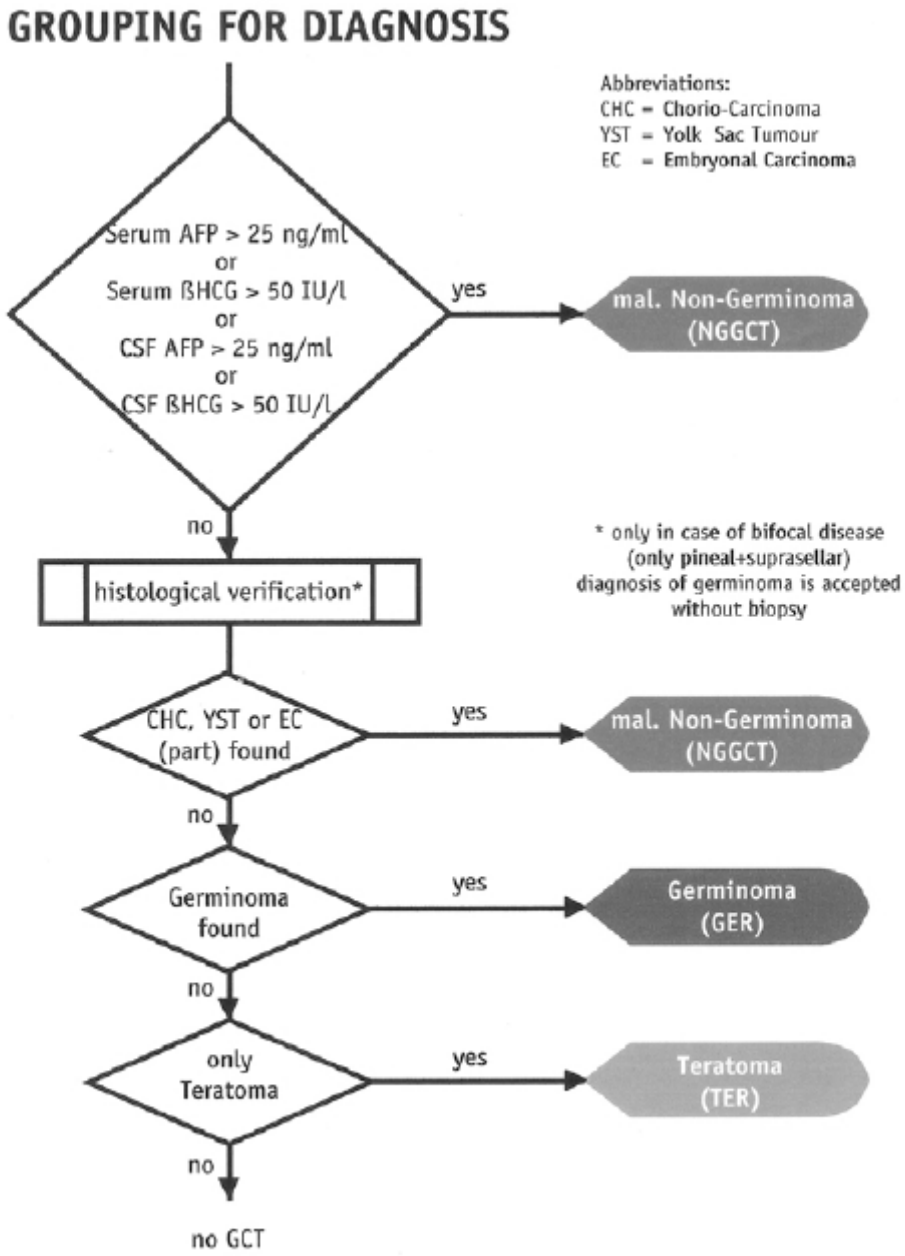
3,7% av CNS tumörer < 14 åå

Medellinjen
51% Germinom
25% mixed GCT
5% Teratom

AFP + **HCG** i plasma och likvor

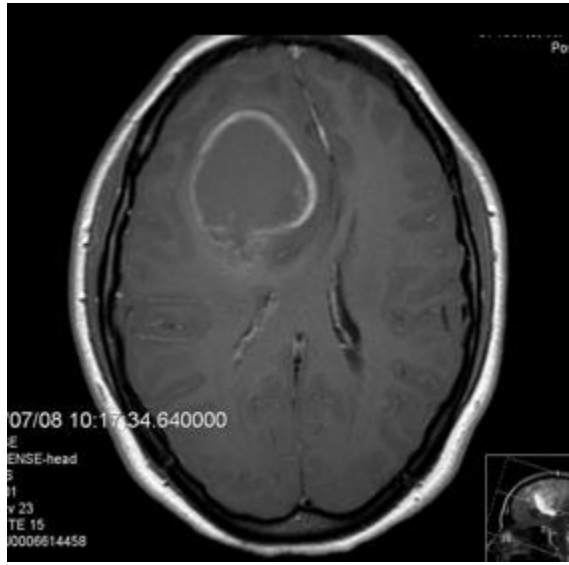
Prognos:

- Germinom 90-95% 10 års överlevnad
- Malignt non-germinom 65%



Höggradiga gliom (HGG) **WHO grad III-IV**

7-10 %



Anaplastiskt astrocytom III
Anaplastiskt oligodendrogliom III
Glioblastoma multiforme IV

} 65% supratentoriella

Behandling:

- Kirurgi
- Strålning + Temozolamid + 6-12 mån Temozolamid + ev Lomustin

Prognos: WHO grad inte av betydelse för pHGG?

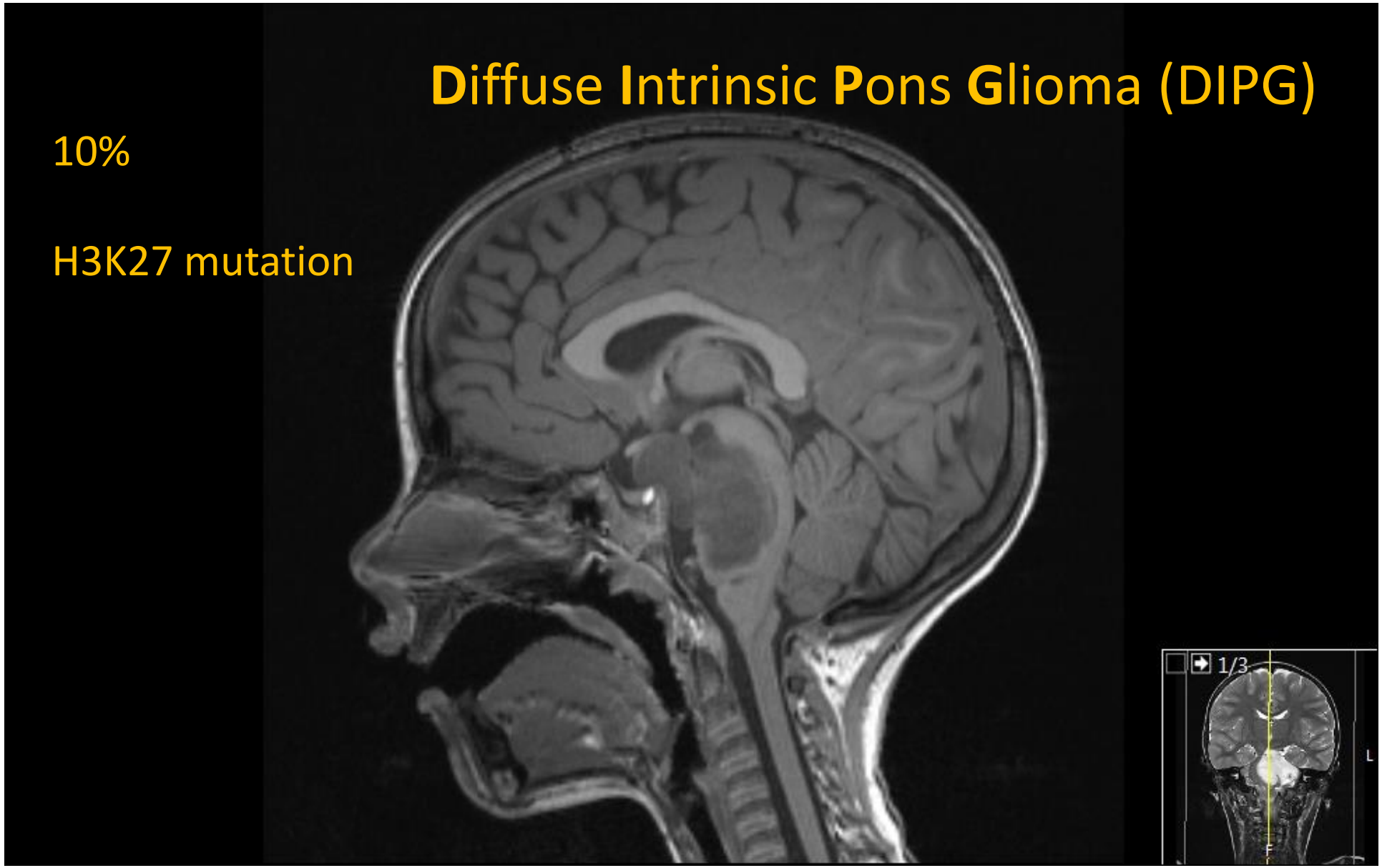
Medellinjelokalisation och högt Ki67 index sämre prognos

Bättre för spädbarn!

Diffuse **I**ntrinsic **P**ons **G**lioma (DIPG)

10%

H3K27 mutation

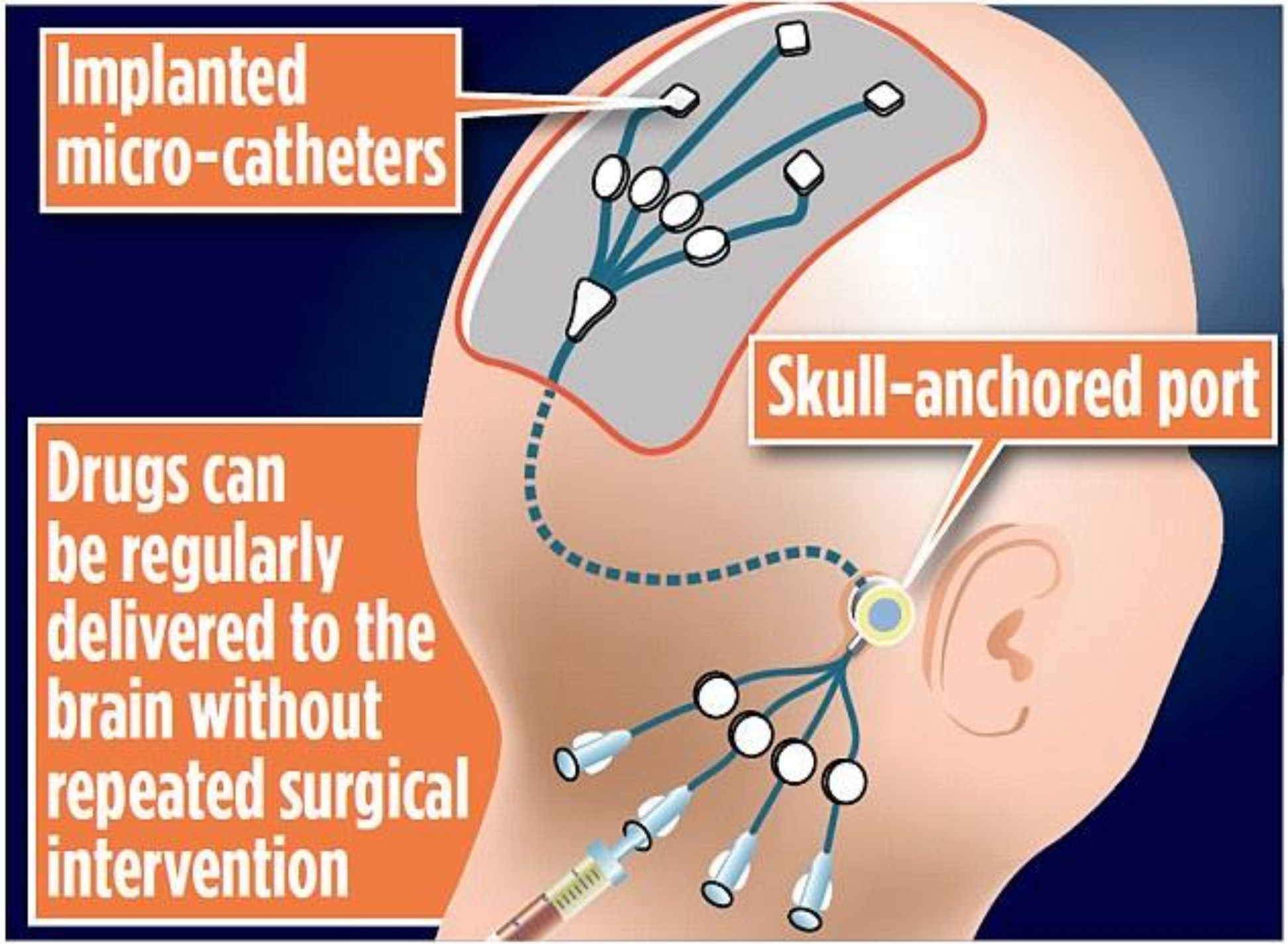


DIPG behandling

Steroider
Stereotaktisk biopsi**!?**
Strålbehandling 54-59 Gy
Cytostatika?
Prognos: Median överlevnad 9 mån
2 år OS ca 5%

- **BIOMEDE** (**Bio**logical **Me**dicine for **D**IPG **E**radication)

- Convection enhanced delivery?
- Intraarteriell infusion??


Implanted micro-catheters
Skull-anchored port
Drugs can be regularly delivered to the brain without repeated surgical intervention

Rebestrålning

- Recidiv
- > 6 mån efter tidigare strålbehandling

Riktlinjer; Svensk barnradioterapigrupp

75% överlevnad

Sena komplikationer

Hormonell rubbning

GH > LH/FSH > ACTH > TSH

- **GH**: > 30 Gy - 50-100% GH brist inom 5 år
  18-24 Gy - GH brist kan visa sig efter 10 år
- Ca 8% behöver pubertetsinduktion
- Spinal strålbeh kan påverka fertilitet
- **ACTH** brist ca 30% efter >50 Gy – cortisol o ACTH!
- Primär **hypothyroidism** 30% av MB 5 år efter diagnos

Neurokognitiva sena komplikationer
Cerebrovaskulär sjd
Hörselnedsättning
Katarakt
Sekundär malignitet

Viktigt med långtidsuppföljning!!

SALUB - Svensk **A**rbetsgrupp för **L**ångtids**U**ppföljning efter **B**arncancer

Kapitel 8. Neurologiska och neurokognitiva biverkningar – centrala nervsystemet (CNS)

Bilaga 1 Riktlinjer för utredning och rehabilitering av barn med tumör i centrala nervsystemet
Källa**:** Svenska Arbetsgruppen för Rehabilitering efter Barncancer (**SAREB**)

http://www.cancercentrum.se/samverkan/cancerdiagnoser/barn/vardprogram/

¨Seneffekt¨ mottagning

Lund
Göteborg

Uppsala
Stockholm
Umeå
Men inte Linköping…


TACK

INFORM

(**In**dividualized therapy **Fo**r **R**elapsed **M**alignancies in childhood)

80% överlevnad för barn med CNS tumör som grupp.
De återstående 20% nås inte med mer behandling av samma slag.

WGS
Exome seq
RNA seq
Gene expression
850k meth array

21 dgr
Telefonkonferens varje fredag

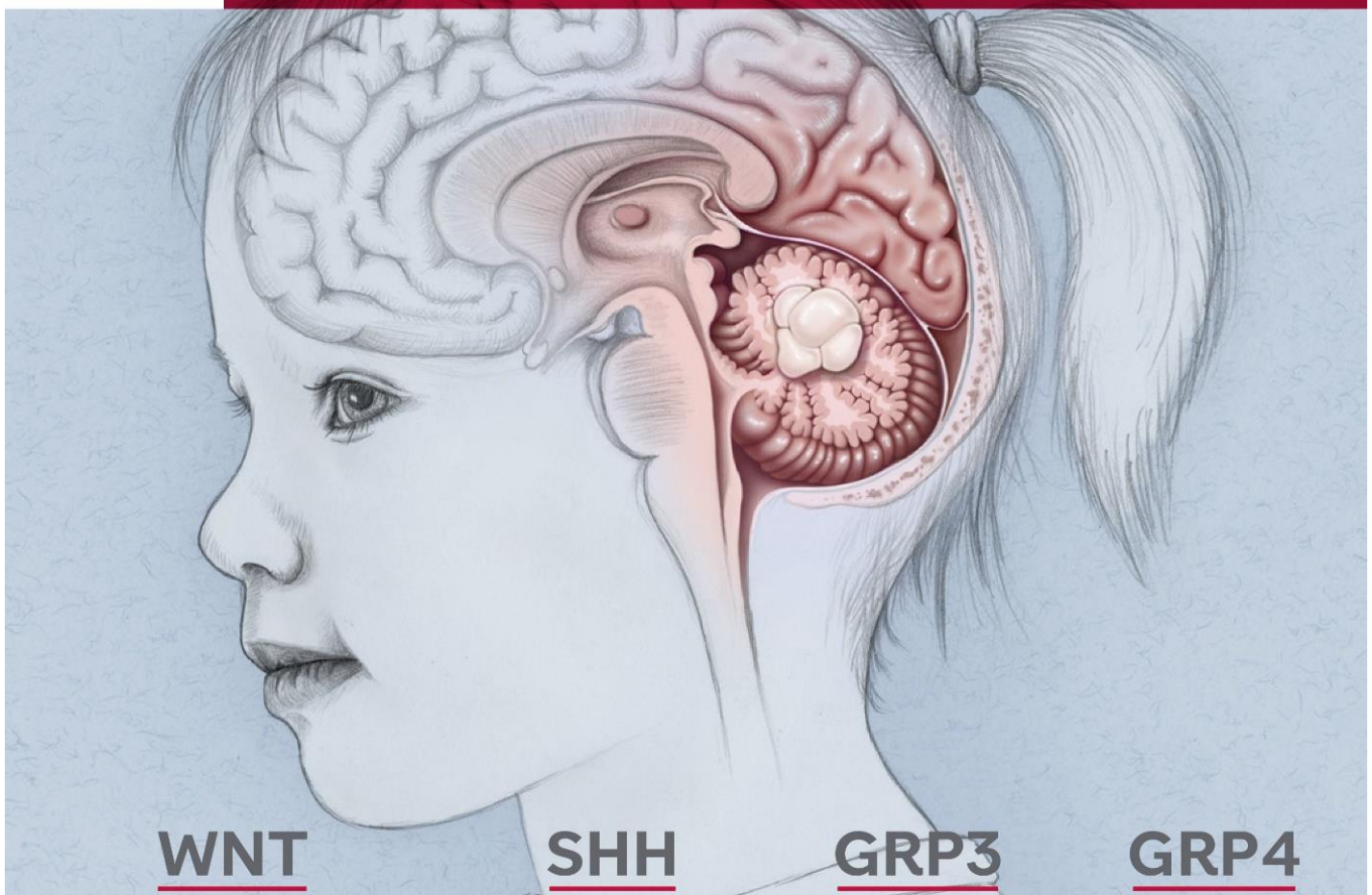
Target prio (7-1): very high  very low


TACK!

Behandling:

- Germinom, icke metastaserat: 2 kurer cytostatika följt av fokal strålning
- Germinom, metastaserat: Kraniospinal strålning
- Malignt non-germinom: 4 kurer med ¨tyngre¨ cytostatika följt av fokal strålning
- Malignt non-germinom: 4 kurer + kraniospinal strålning

PROPOSED GUIDELINES
for medulloblastoma genetic counseling and testing



WNT	SHH	GRP3	GRP4
Absence of somatic *CTNNB1* mutation Test for: *APC*	Test for: *PTCH1*, *SUFU*, *TP53*, *BRCA2*, and *PALB2*	Family history of *BRCA*-associated cancers Test for: *BRCA2* and *PALB2*	

www.stjude.org