Childhood LGG: therapeutic managment.

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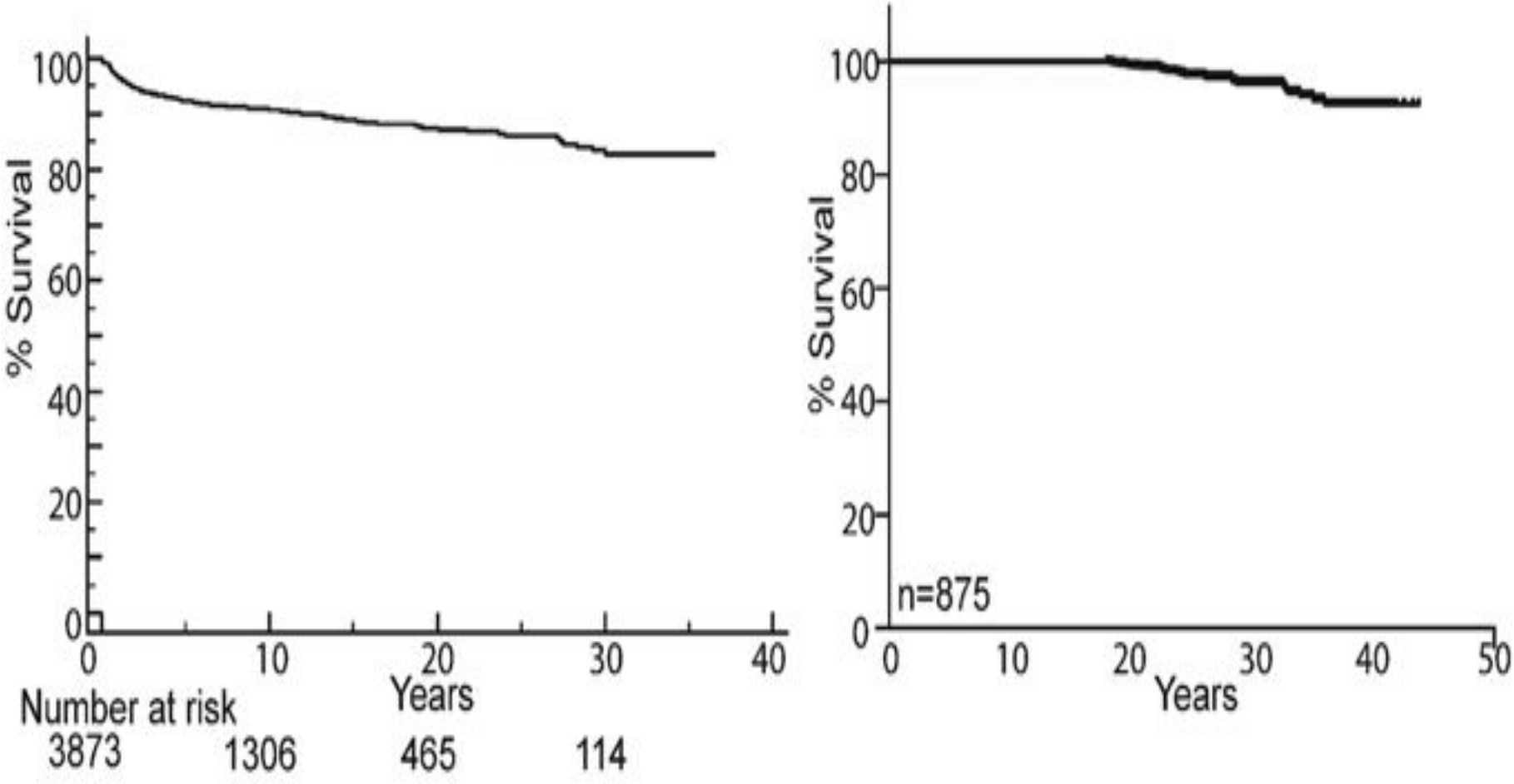
UOA di Radioterapia

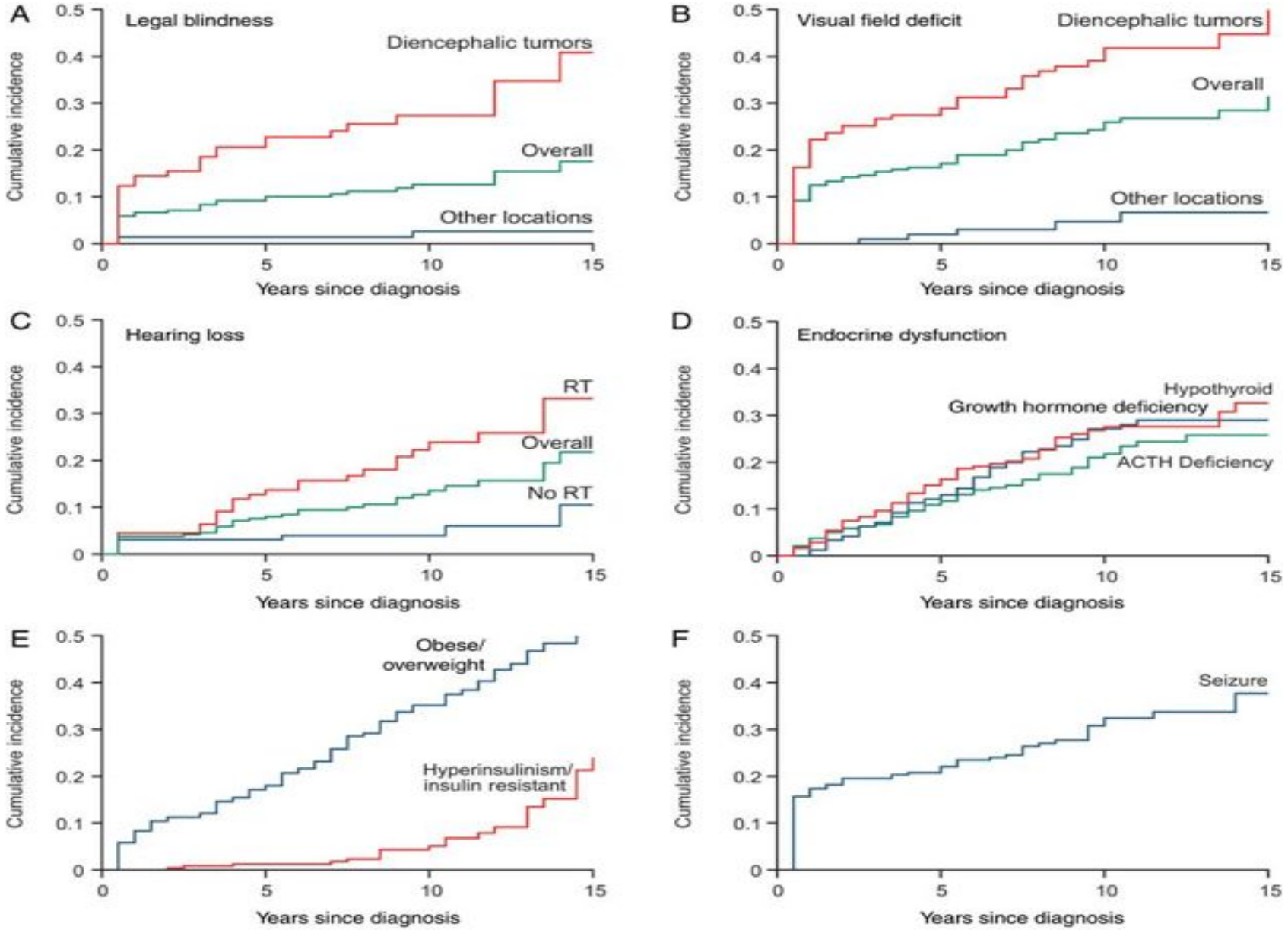
Low grade Glioma

- 40% of pediatric brain tumors
- Pathologically, anatomically, clinically and biologically heterogeneous
- Leptomeningeal metastases in 5%
- Frequently protracted clinical course

Long-Term Outcome of 4,040 Children Diagnosed With Pediatric Low-Grade Gliomas: An Analysis of the Surveillance Epidemiology and End Results (SEER) Database

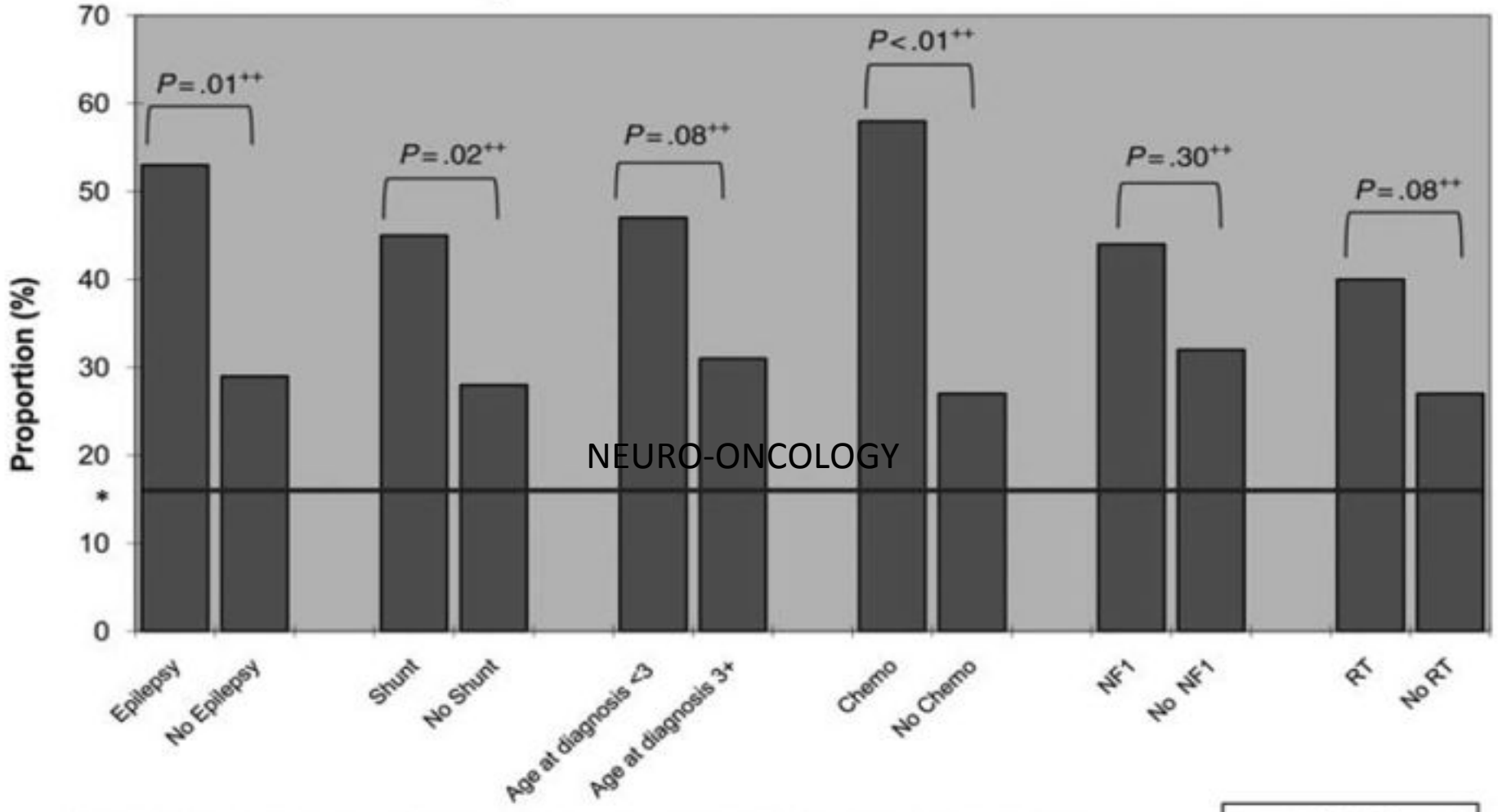


Pediatr Blood Cancer 2014



Armstrong et al.: Neuro-Oncology 2010

Proportions of IQ score lower than 85



* Proportions of IQ scores <85 in all clinical groups are significantly different ($P<.001$) than proportions in the normal population (16%)

++ *P*-values for comparison (*t*-test) between two groups

Armstrong et al.: Neuro-Oncology 2010

Balance between anti-tumor effect and long-term morbidity of therapy

IC-LLG 1 1996-2004

- **International Consortium Germany, Italy, UK**
- **New paradigm in LGG management**
- **Standardized schema:**
  - ✓ **initial period of observation at diagnosis**
  - ✓ **protocols for RT and CT**

IC-LLG 1 Protocol

Clinical diagnosis
or
Complete/partial resection
in absence of
Signs/symptoms of progressive disease
Significant symtoms
Severe neurologic conditions

INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

If at
Diagnosis
or during
Observation
Signs/symptoms of progressive disease
Significant symtoms
Severe neurologic conditions

OBSERVATION ONLY

A.I.E.O.P.
Associazione Italiana Ematologia Oncologia Pediatrica

Age < 5 years

CT

RT

Age > 5 years

RT

CT

Progression

IC-LLG 1 Radiation Therapy

- **Gad enhanced T1-T2 MRI**
- **1cm margin for CTV (2 if only CT scan used)**

- **Intracranial primaries: 54 Gy/30F**
- **Spinal primaries: 50.4 Gy/28F**
- **Children aged less than 5 years: 50.1 Gy/30F**

IC-LLG 2 2004-2012

- **Built upon achievements of LGG1**
- **Initial observation policy**
- **Non surgical treatment for progression:**

  Randomization Carbo +/- VP16

  Age threshold for initial RT: 8 years

IC-LLG 2 Radiation Therapy

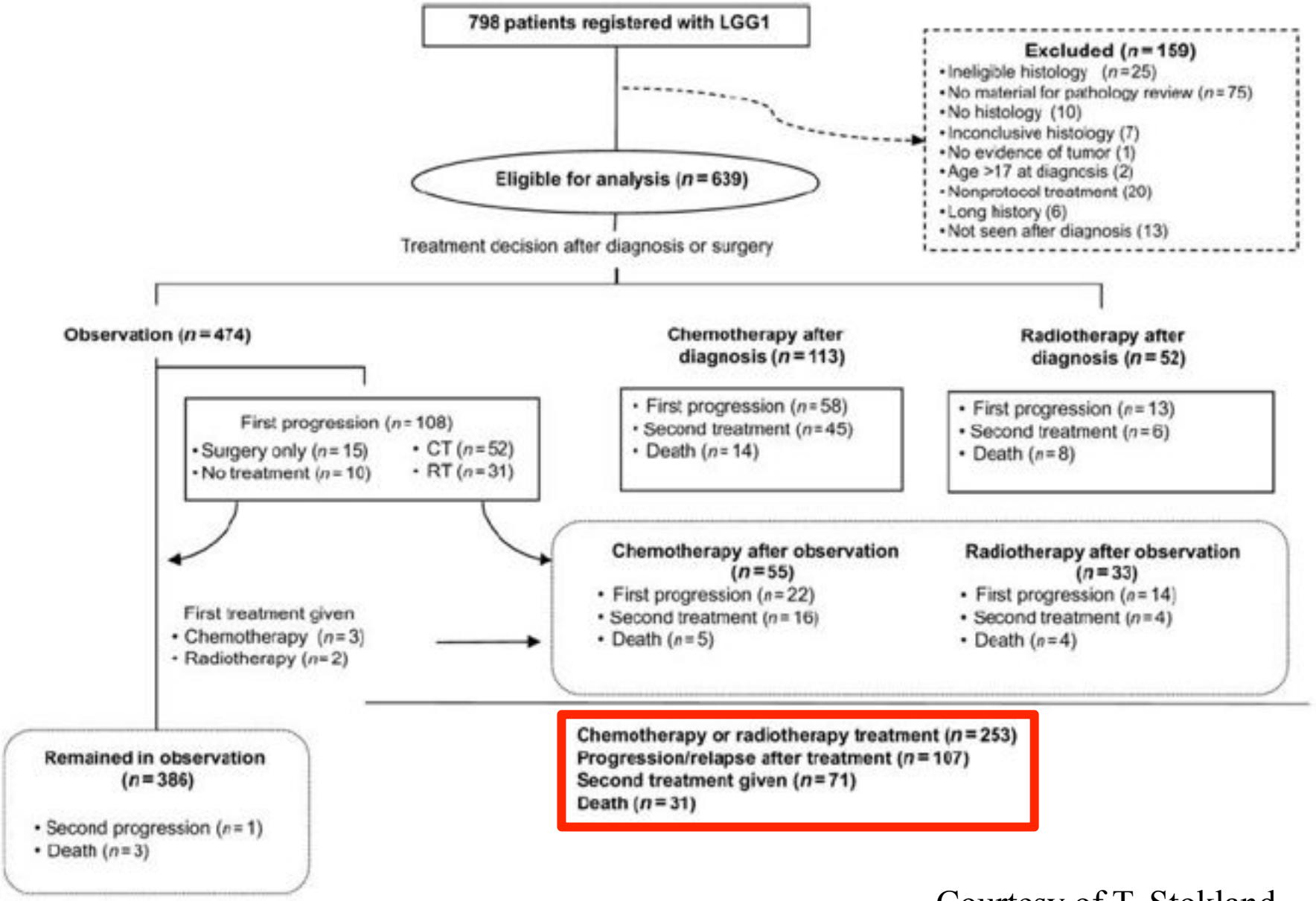
- **Intracranial primaries: 54 Gy/30F**
- **Spinal primaries: 50.4 Gy/28F**
- **Children aged less than 5 years: 50.1 Gy/30F**

To record integral dose to target and normal tissue as basis for future assessment of QoL of long term survivors

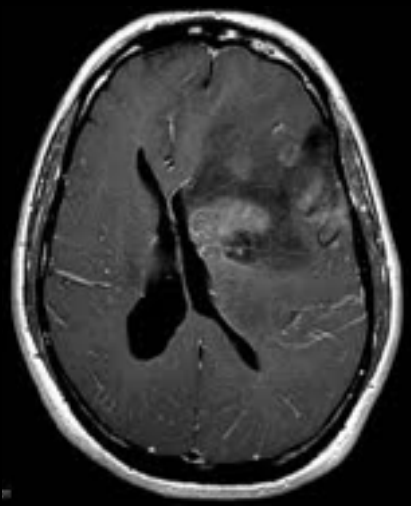
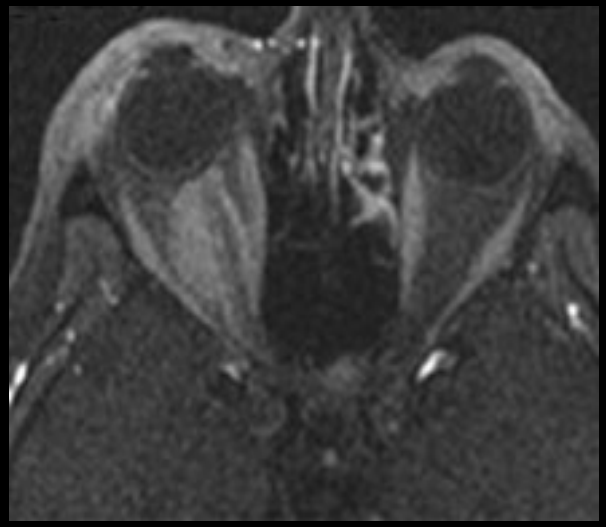
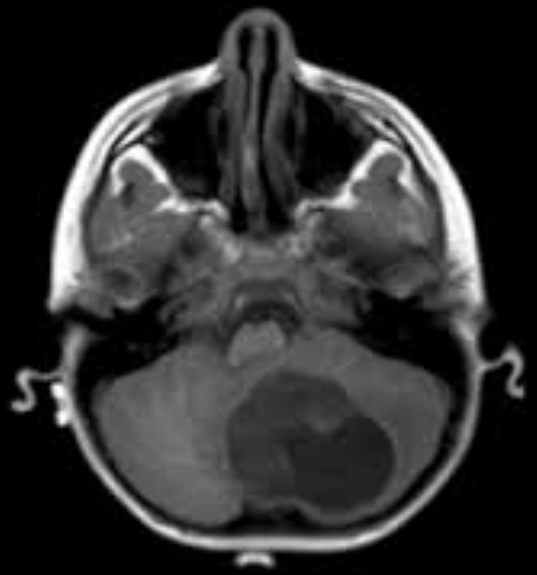
To assess response of tumor and symptoms to RT with respect to primary treatment or after CT failure

To assess the pattern of relapse when using novel treatment techniques

To assess the efficacy of cranio-spinal RT for metastatic disease



Courtesy of T. Stokland

Age, histology, anatomical site and extent of resection were independent risk factors for progression

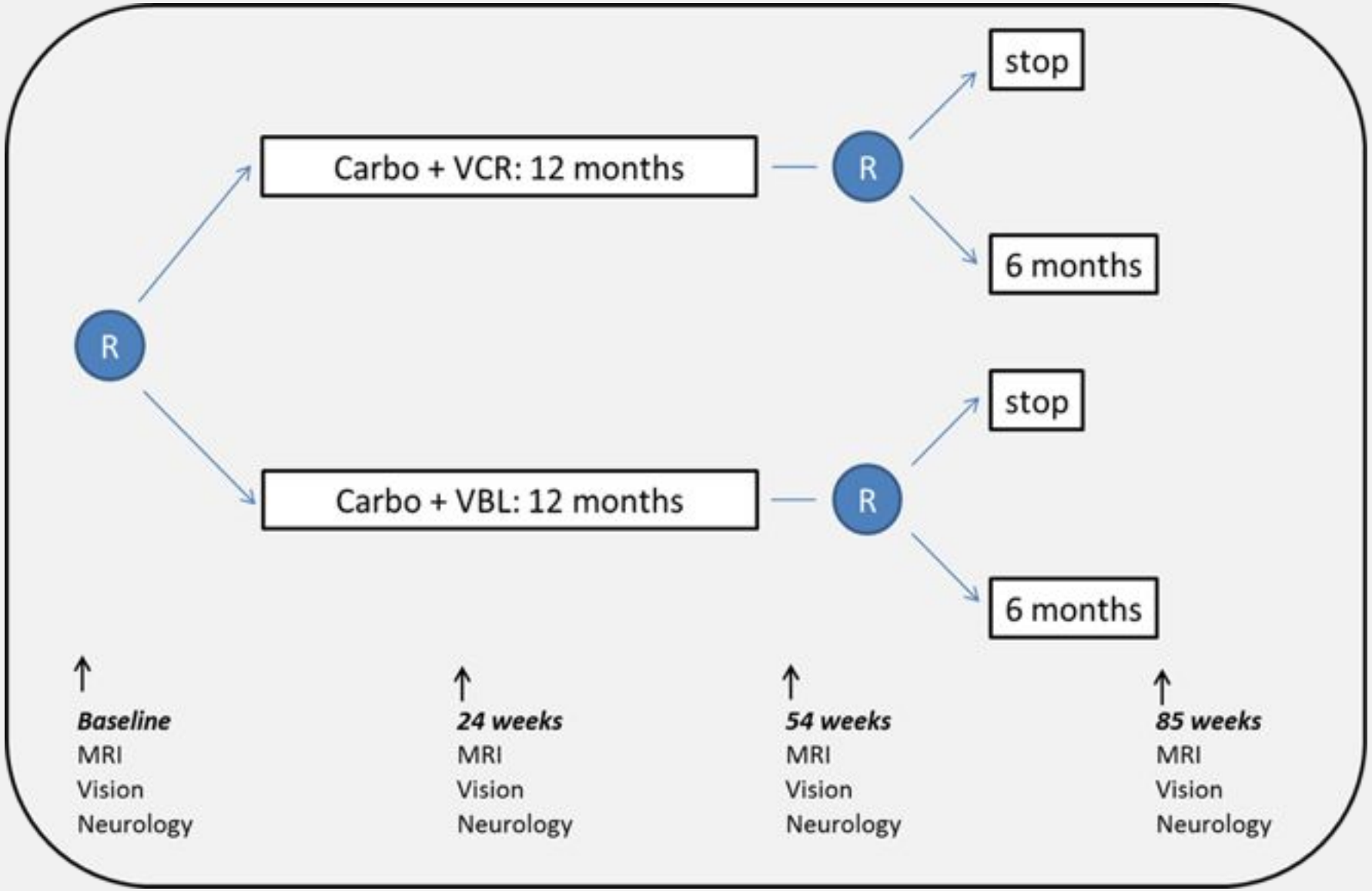
Strategic subgroups for a new trial as based upon literature and own data

Strategy group	1	2	3	4
Age	≤ 18	<1	1-18	1-18
Dienceph. Syndrome	No	No/yes	No	No
Dissemination	No	No/yes	No (except at age >1 to <11 years?)	No
Extent of resection	incomplete / no resection	incomplete / no resection	incomplete / no resection	incomplete / no resection
Localisation	Any	Chiasm-hypothal.	Any	Any
Histology	???	Any (PA I°)	Pilocytic A. I° (no histology?)	A/O/OA II°
Molecular genetics	NF 1	BRAF-Mutations		

IC-LLG 3 2014 Strategy

- **Midline Supratentorial Pilocytic Astrocytoma**
  - ✓ **Randomized Vinblastine vs Vincristine: evaluation of neurotoxicity and control of neurological symptoms**
  - ✓ **Randomized trial of duration of CT**
- **High Risk Groups**
  - ✓ **Age less than 1 year**
  - ✓ **Grade 2 Astrocytoma**
- **Strategy for NF1 patients**
- **Visual assessment**
- **Quality of survival studies**

The SIOP LGG-201X study:



IC-LLG 3 Radiation Therapy

- **Planning on Gad enhanced T1-T2-Flair MRI**
- **Dose: 50.4 Gy/28F**
- **Pilocytic: CTV margin 0.5 cm**
- **Grade 2: CTV margin 1-1.5 cm**

The OARs will be outlined as separate ROI:

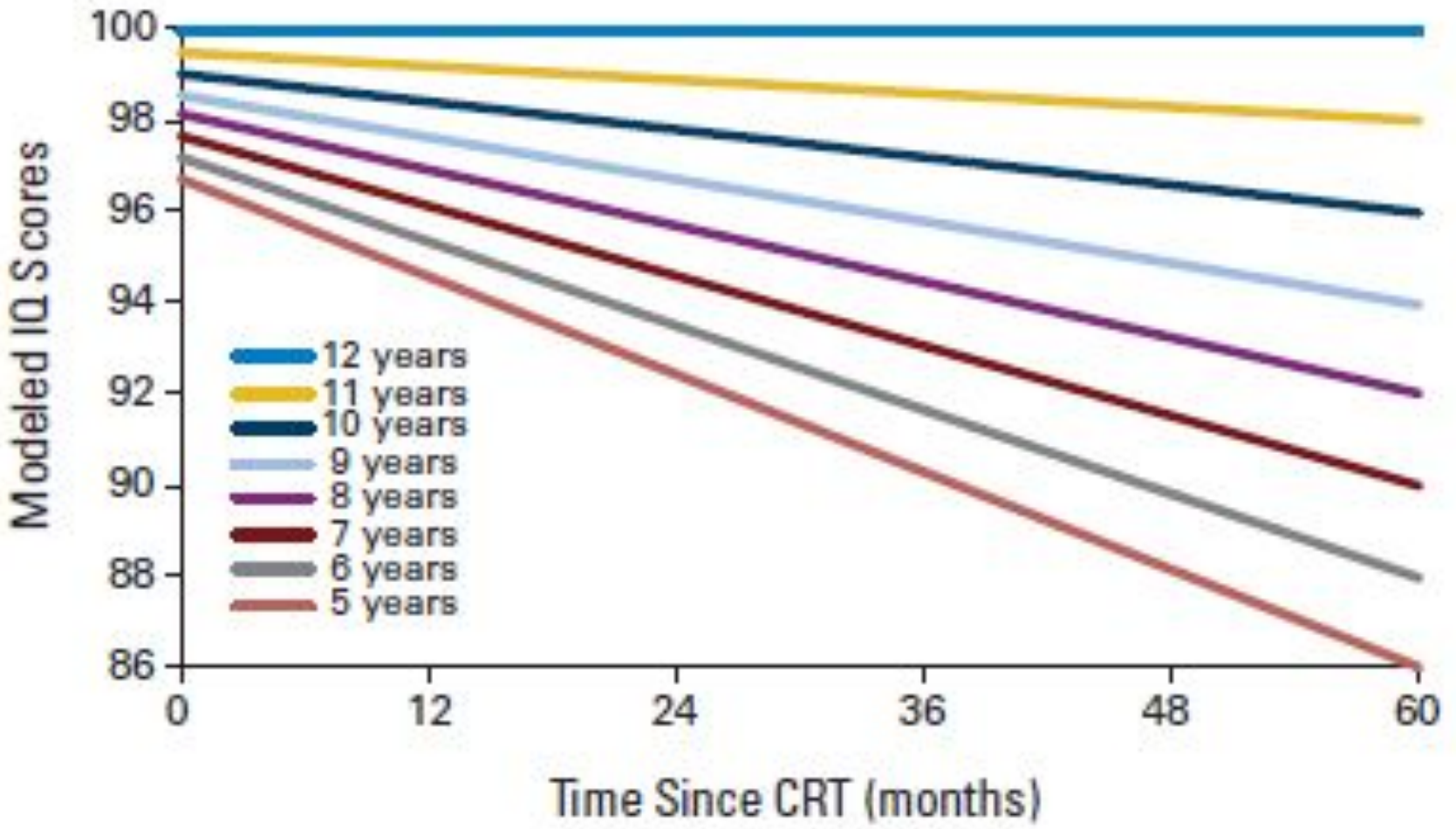
- Eyes (left / right)
- Pituitary
- Inner ear (left / right)
- Hypothalamus (left / right)
- Thalamus (left / right)
- Temporal lobe (left / right)
- Hippocampus (left / right)
- Supratentorial brain
- Brain stem
- Optic nerves (left / right)
- Optic chiasm

IC-LLG 3 Dose constraints

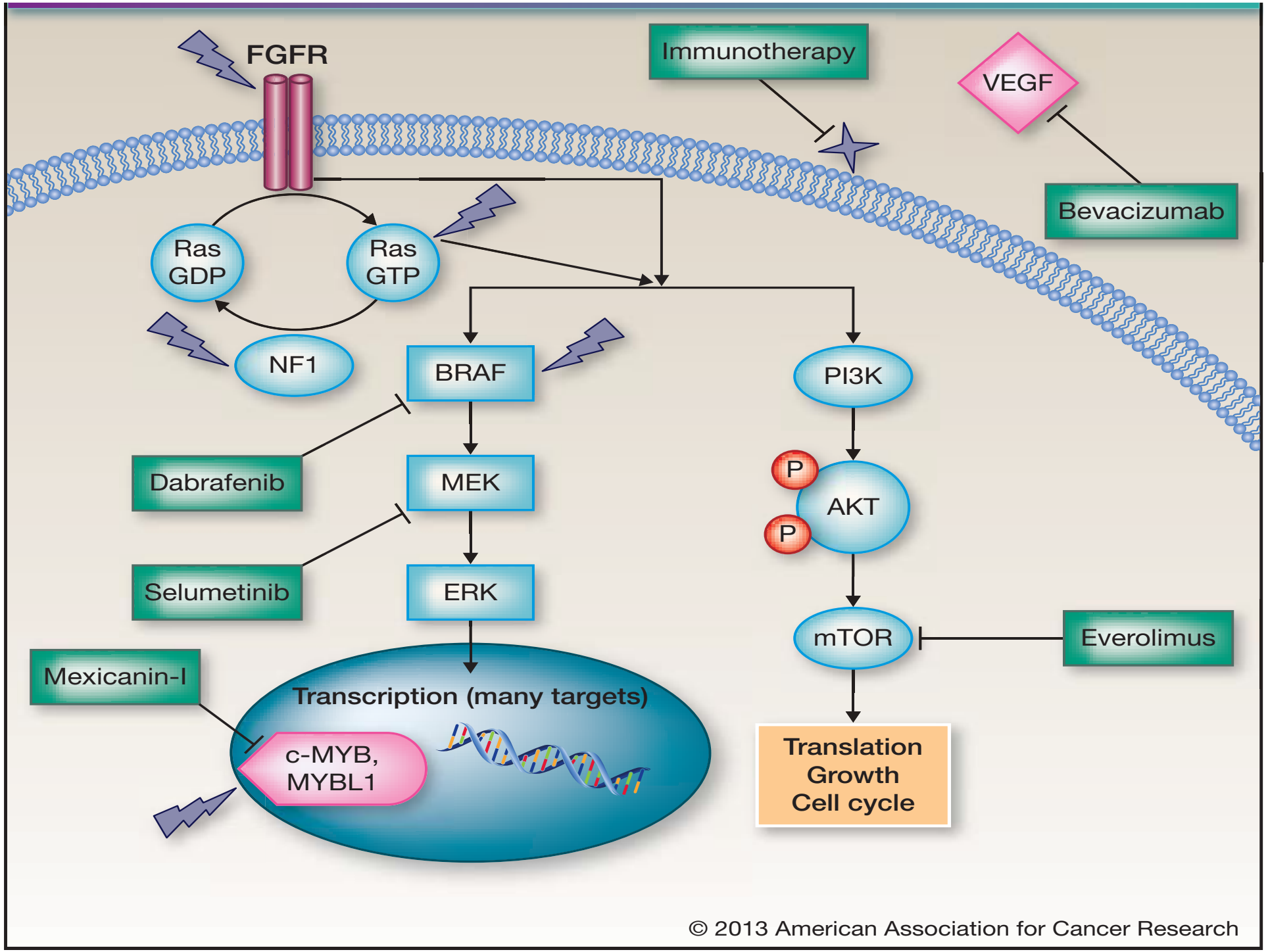
- **Supratentorial brain excluding PTV:**
  92%<25; 70%<30; 65%<35; 53%<40; 34%<45; 24%<50; 16%<55 Gy
- **Temporal lobe left and right separately**
  30%<25; 60<20 Gy
- **Hippocampus left and right separately**
  30%<30; 60%<25 Gy
- **Mean dose to cochlea**
  <30 Gy

RT Open Questions

- Tumour control/pattern of relapse/safety margins
- Reduction of side effects
- Differences between modern technologies
- Response of tumour to treatment
- RT effect on tumour progression and OS when CT has failed
- Dose reduction
- Reduction of safety margins for CTV in pilocytic astrocytoma
- Craniospinal irradiation in metastatic disease
- Molecular genetic profiles



Merchant et al J Clin Oncol 2009


FGFR
Immunotherapy
VEGF
Bevacizumab
Ras GDP
Ras GTP
NF1
BRAF
PI3K
Dabrafenib
MEK
P
AKT
P
Selumetinib
ERK
mTOR
Everolimus
Mexicanin-I
Transcription (many targets)
c-MYB, MYBL1
Translation
Growth
Cell cycle
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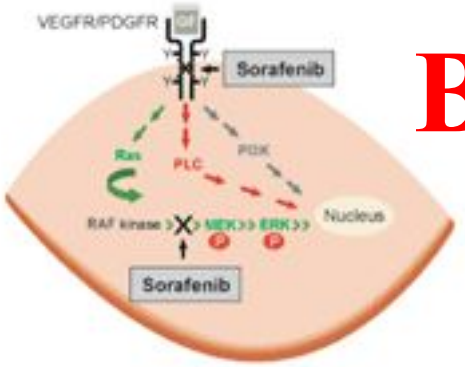


BRAF inhibitor (Sorafenib)
an "amazing failure"

- **Nine patients (82%) came off trial due to radiological tumor progression after 2 or 3 cycles, including 3 patients with confirmed BRAF duplication**
- **Sorafenib produced unexpected and unprecedented acceleration of tumor growth in children with PLGA, irrespective of NF1 or tumor BRAF status**
- **In vitro studies with sorafenib indicate that this effect is likely related to paradoxical ERK activation**

Conclusions

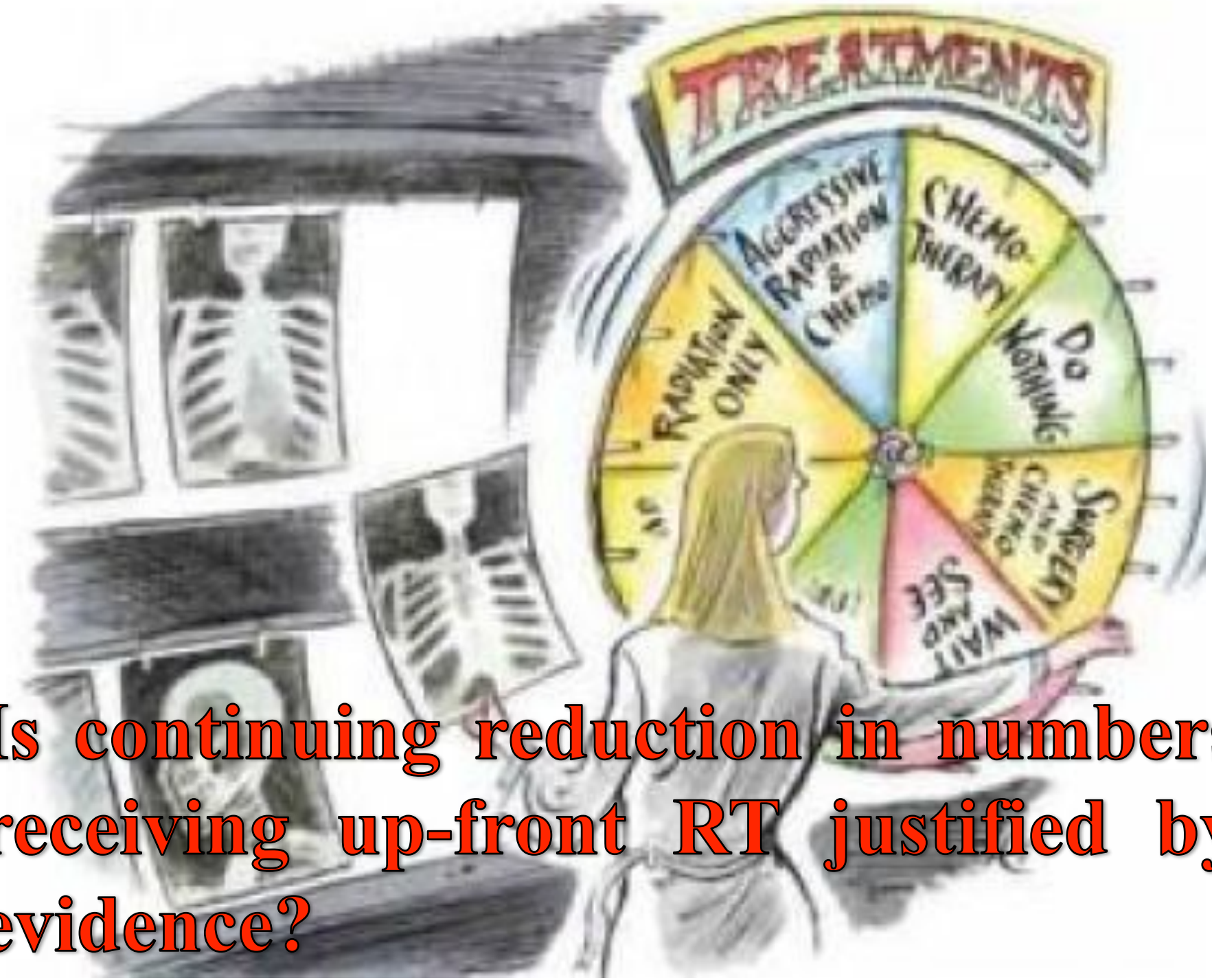
LGG comprise a heterogeneus mix of tumors

Evolving strategies aimed at balancing tumor control with long term effects

RT remains an important modality for long term local control

Better understanding of late effects, including impact of RT parameters

Modern technology employed with the aim of sparing late effects where possible



Is continuing reduction in numbers receiving up-front RT justified by evidence?