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What's New in Neuro-Oncology: Updates from Recent ASCO Meetings

Sponsored by the University of Chicago Brain Tumor Center & the Heinrich Kluver Memorial Lectureship Endowment

Welcome and Introduction

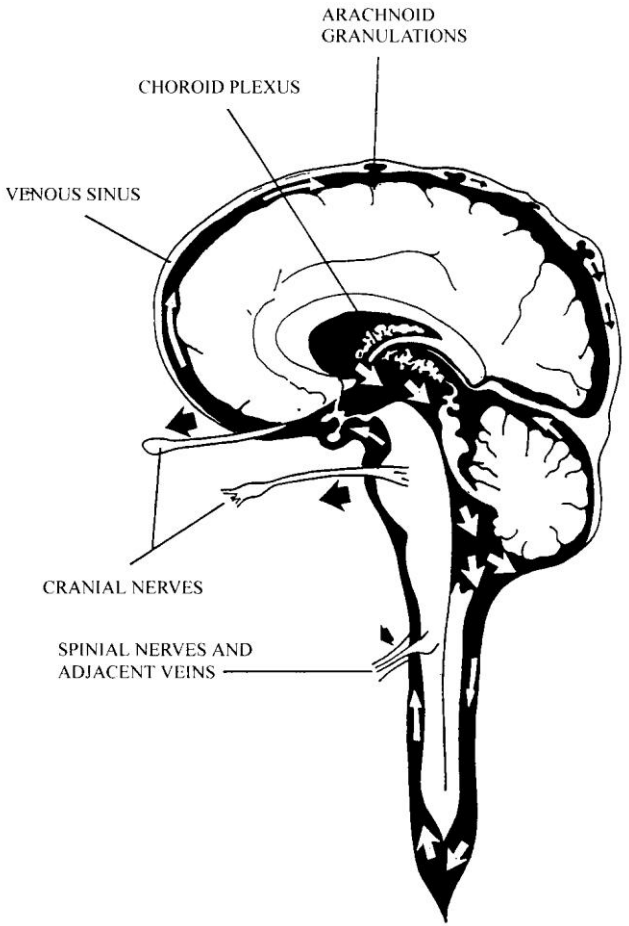
Infiltrating gliomas remain the most common and, therefore, vexing, clinical problem in neuro-oncology.

Significant advances in patient outcomes have been slow, despite substantial investments of creative thinking, time, energy, and financial resources.

Our goals are: 1) to review recent clinical trial results and 2) to discuss their impact on future directions and challenges in providing optimal care.

PROBLEMS UNIQUE TO NEURO-ONCOLOGY

- Small changes in tumor size and location can have significant impact on functional status.
- Brain anatomy and physiology limit therapeutic options.
  - Surgery
  - Radiotherapy
  - chemotherapy



PROGRAM

- Bevacizumab in Glioblastoma
  - M. Kelly Nicholas, MD, PhD
- Anaplastic Gliomas
  - Rimas Lukas, MD
- Combining Chemotherapy and Radiotherapy in Low Grade Gliomas
  - Steve Chmura, MD, PhD

DISCUSSION

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Updates in the Radiotherapeutic Management of Low-grade Gliomas

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October 15, 2013

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Introduction to Low-grade Gliomas

- Low-grade gliomas (LGG) = 20-30% of gliomas
- 70-80% of patients present with new-onset seizures
- Umbrella term for various histologies
  - Astrocytomas (67%)
  - Oligodendroglioma (13%)
  - Oligoastrocytoma (19%)
- Maximal safe surgical resection continues to be the diagnostic and therapeutic intervention of choice

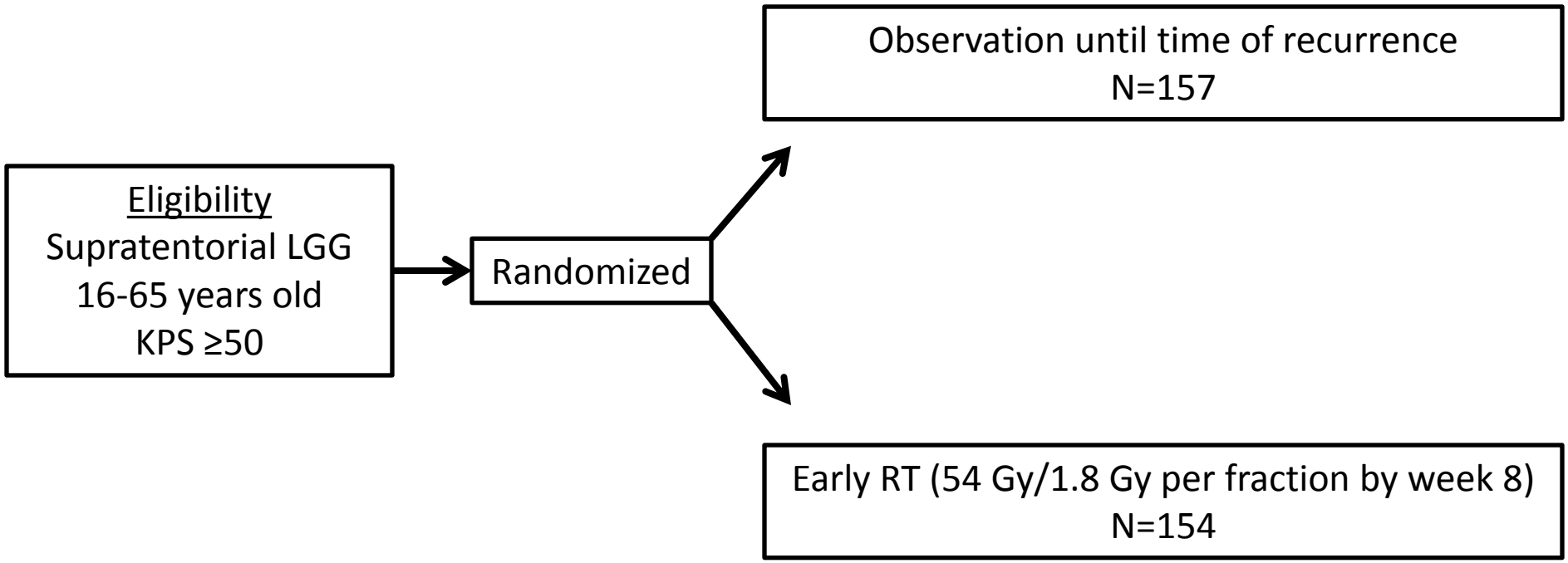
Radiotherapy in LGG: Key Questions

- Do all patients benefit from immediate RT or can some patients be observed?
  - Timing of RT
  - EORTC 22845 ("Non-believers trial")

- Predominant Pattern of failure is in RT field
  - Is there a role of dose escalation?
  - EORTC 22844 ("Believers trial")
  - Intergroup/NCCTG/RTOG/ECOG

EORTC 22845 – “Non-believers Trial”

- **Goal:** To assess the efficacy of immediate radiation therapy compared to deferring until progression



Van Den Bent, Lancet, 2005

EORTC 22845: Results

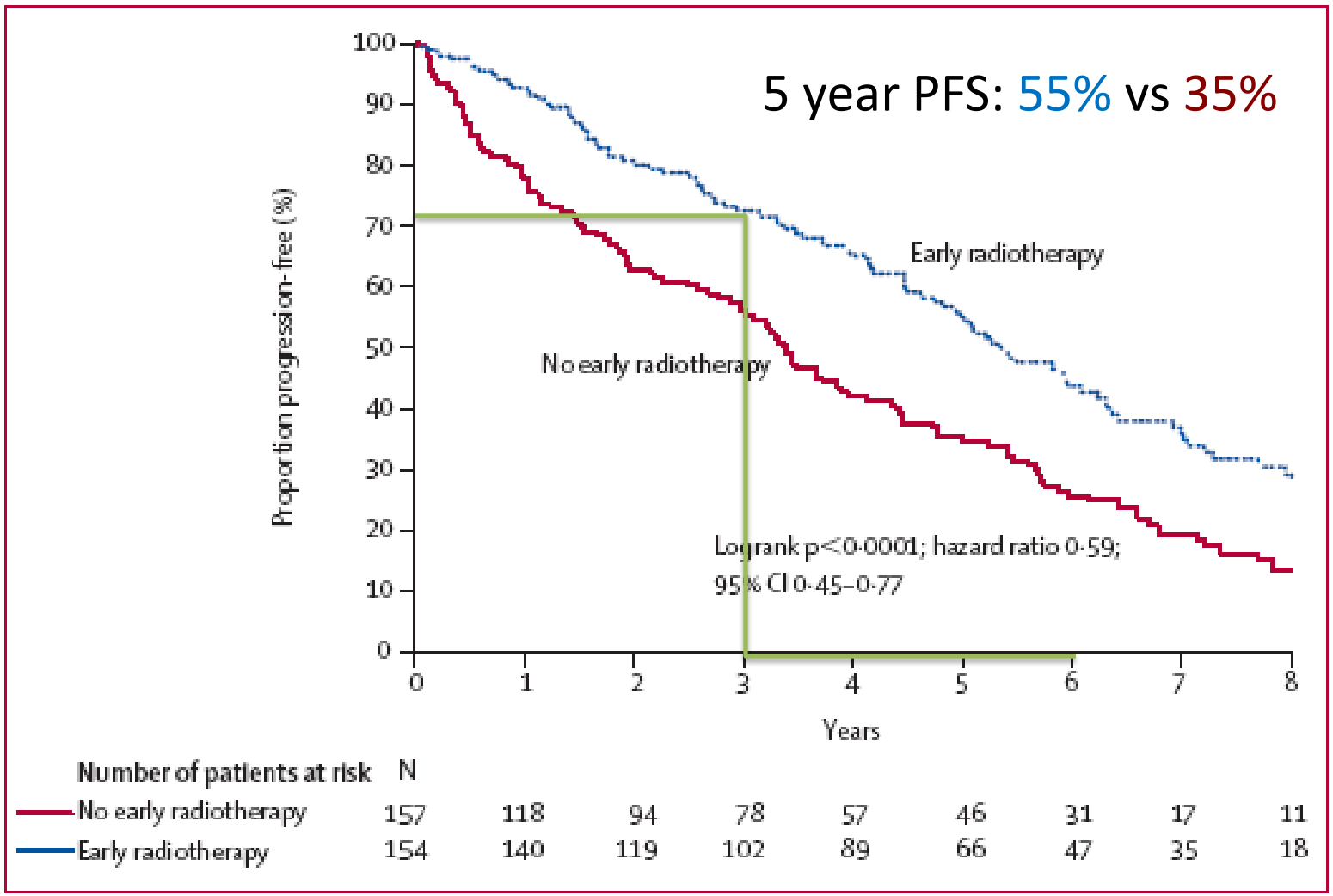


Figure 3: Progression-free survival by intention-to-treat analysis
Number of events: O=121 for control group; O=96 for early radiotherapy group.

Van Den Bent, Lancet, 2005

EORTC 22845: Results

	Early RT	Delayed RT
Median PFS	5.3 years	3.4 years ($p<0.01$)
Median survival	7.4 years	7.2 years
5-year overall survival	≈68%	≈66%
1 year seizures	25%	41% ($p=0.03$)

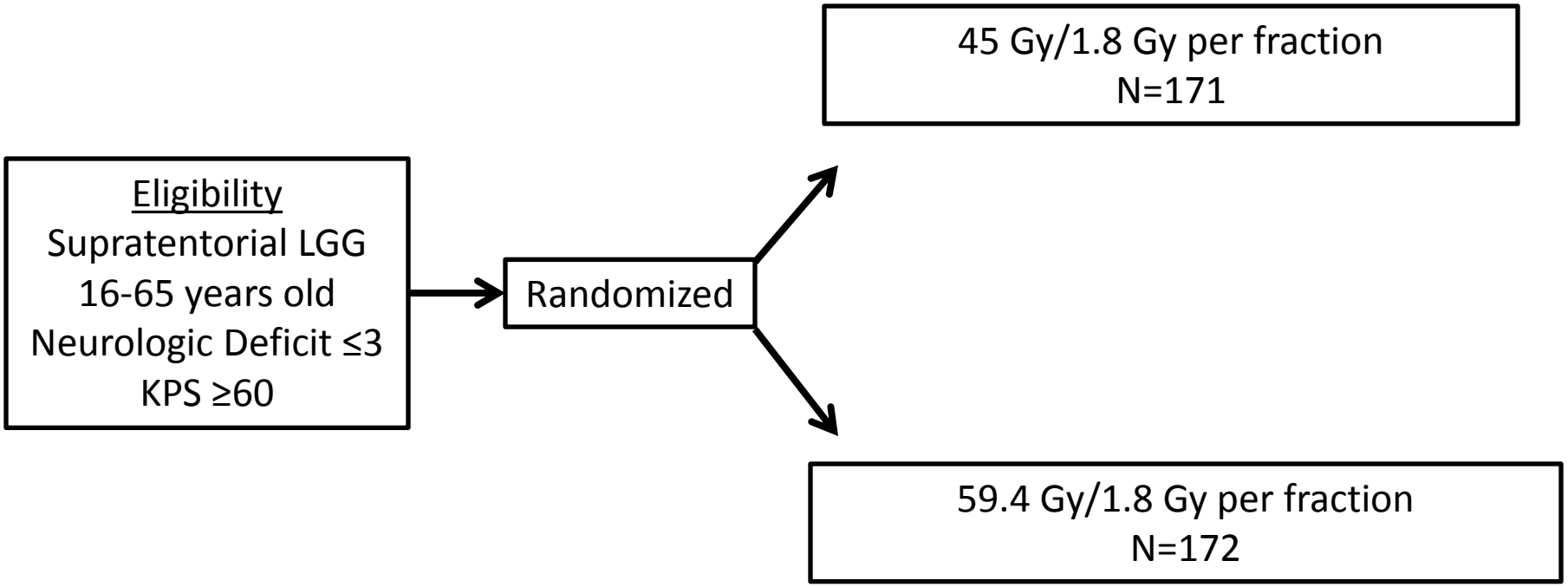
Conclusions:

- Early RT is associated with improved PFS but not OS
- Early RT results in better seizure control

Van Den Bent, Lancet, 2005

EORTC 22844 – "Believers trial"

- Goal: To identify the role of dose escalation in LGG



Karim, IJROBP, 1996

EORTC 22844: Results

	45 Gy	59.4 Gy
5-year OS	<60%	<60%
5-year CSS	48%	44%
5-year PFS	47%	50%

Conclusions:

- No benefit to dose escalation

Karim, IJROBP, 1996

EORTC Prognostic Factors

- Pooled analysis of EORTC 22844 and 22845

Poor Prognostic Factors

- ***Age ≥40***
- ***Astrocytoma histologic subtype***
- ***Largest diameter ≥6 cm***
- ***Tumor crossing midline***
- ***Neurologic deficits before surgery***

Pignatti, J Clin Oncol, 2002

Prognostic Factors for Survival in Adult Patients With Cerebral Low-Grade Glioma

By Francesco Pignatti, Martin van den Bent, Desmond Curran, Channa Debruyne, Richard Sylvester, Patrick Therasse, Denes Áfra, Philippe Cornu, Michel Bolla, Charles Vecht, and Abul B.M.F. Karim for the European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group and Radiotherapy Cooperative Group

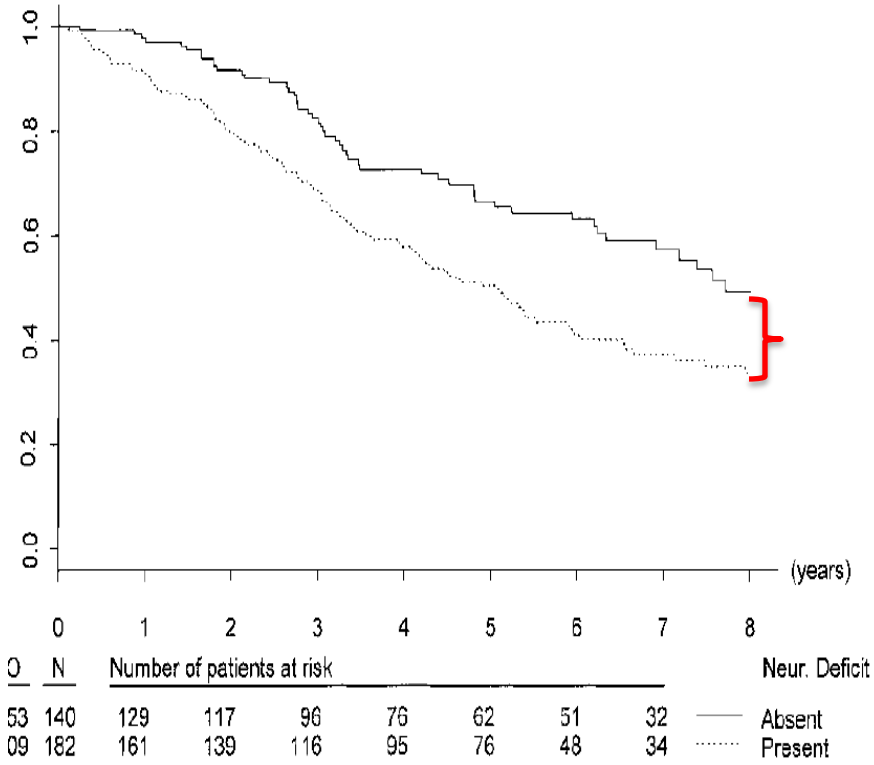


Fig 3. Neurologic deficit (construction set).

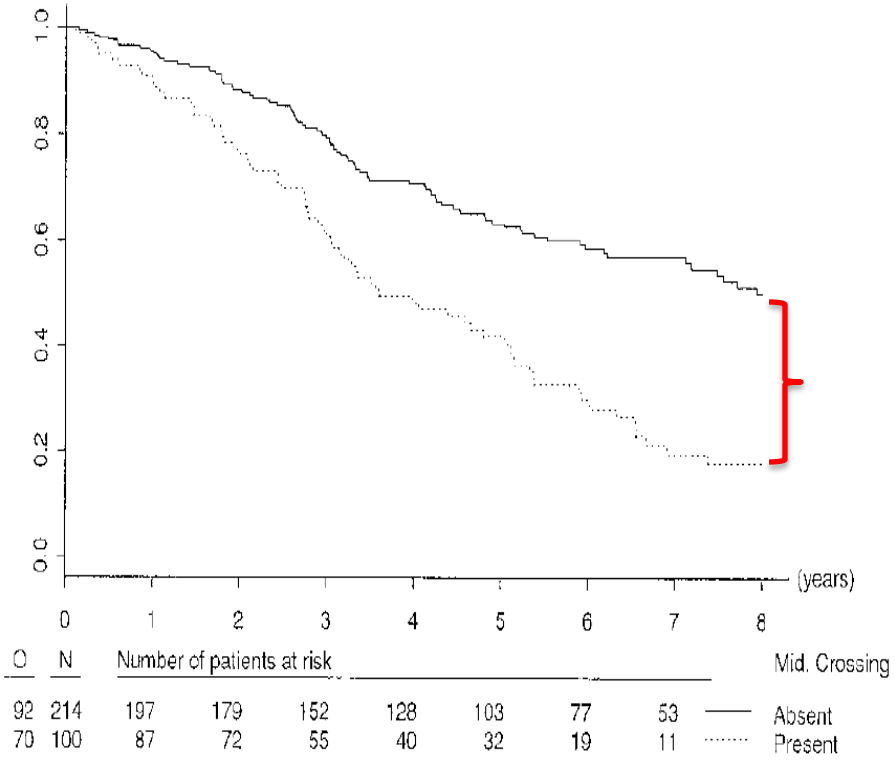


Fig 5. Tumor crossing the midline (construction set).

A Phase II Study of a Temozolomide-Based Chemoradiotherapy Regimen for High Risk Low-Grade Gliomas: Preliminary Results of RTOG 0424

- *Barbara Jean Fisher, Jeff Lui, David R. Macdonald, Glenn Jay Lesser, Stephen Coons, David Brachman, Samuel Ryu, Maria Werner-Wasik, Jean-Paul Bahary, Chen Hu, Minesh P. Mehta*

ASCO 2013

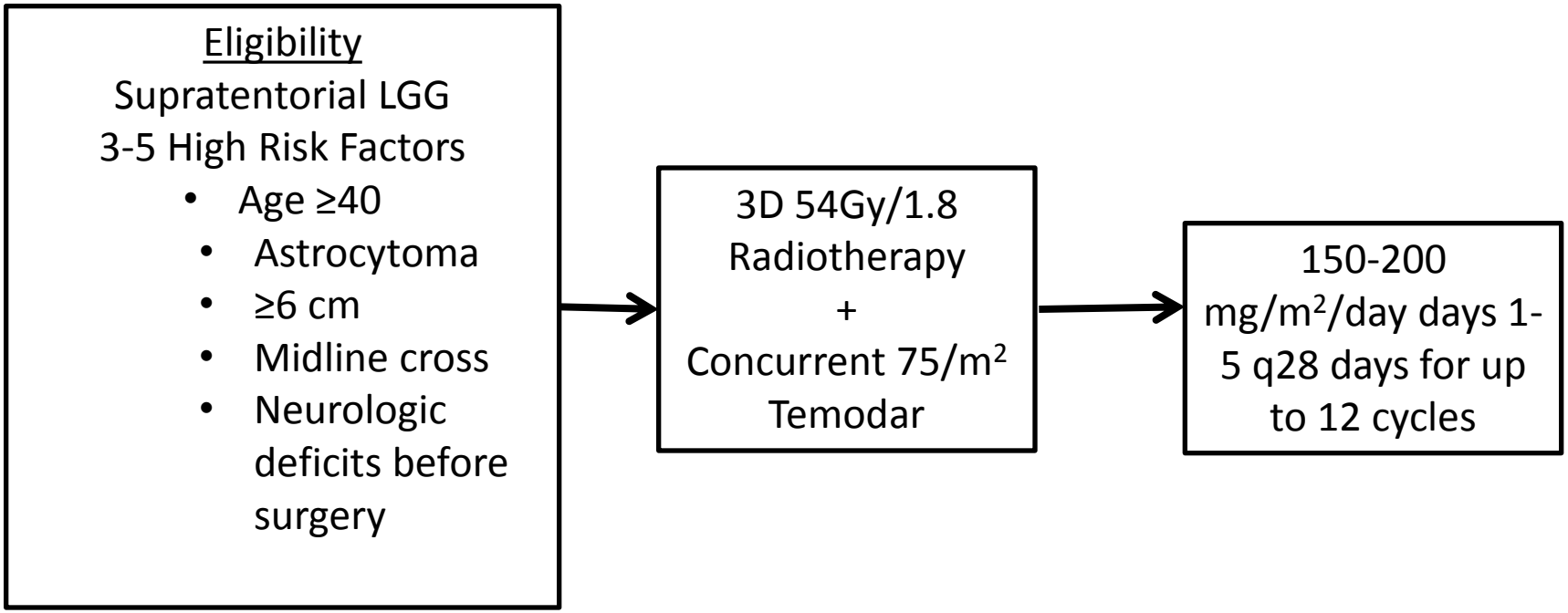
J Clin Oncol 31, 2013 (suppl; abstr 2008)

Design

- Single Arm Phase II (first developed RND)
- Compare to 3y PFS/OS historical controls from EORTC pooled analysis
- ***3-5 risk factors = high risk***
- Statistics
  - One Sided Design
  - Detect 43% increase mOS 40.5 to 57.9 months
  - Detect 20% increase 3 yr OS 54% to 65%

RTOG 0424: HRG2 Temodar+XRT

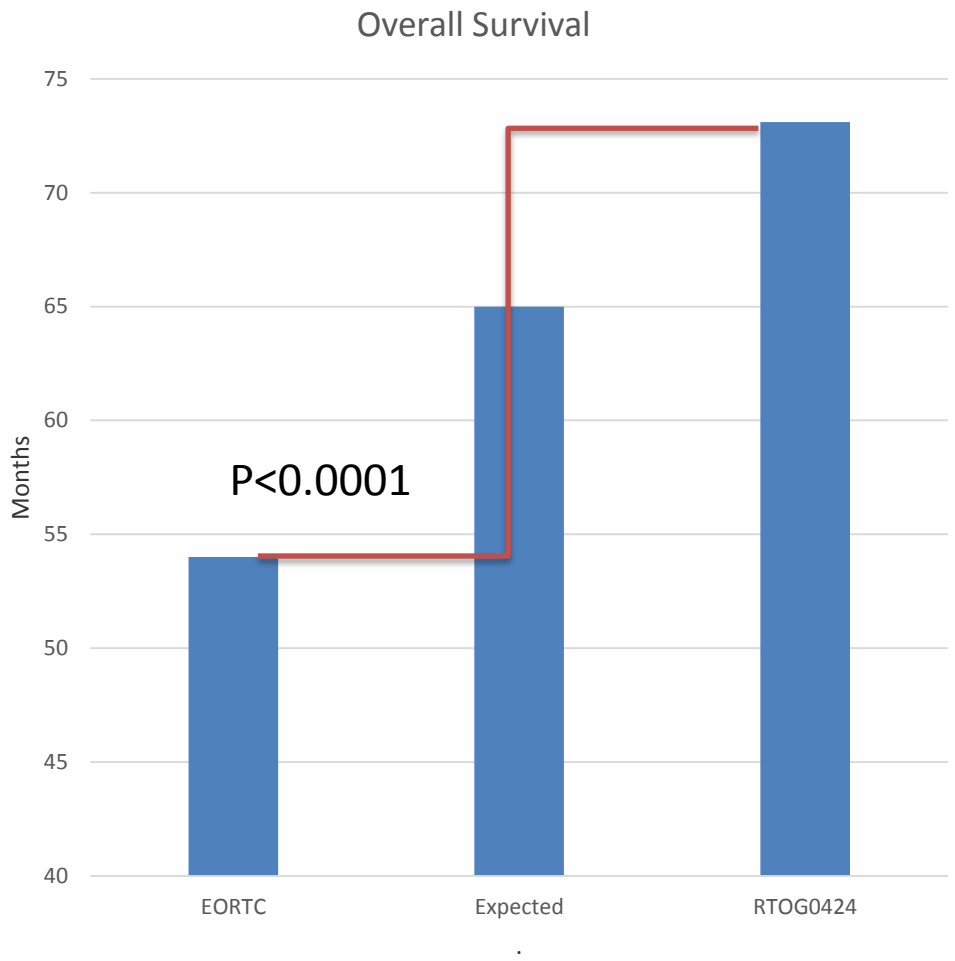
- 136 Patients



ASCO 2013

Results

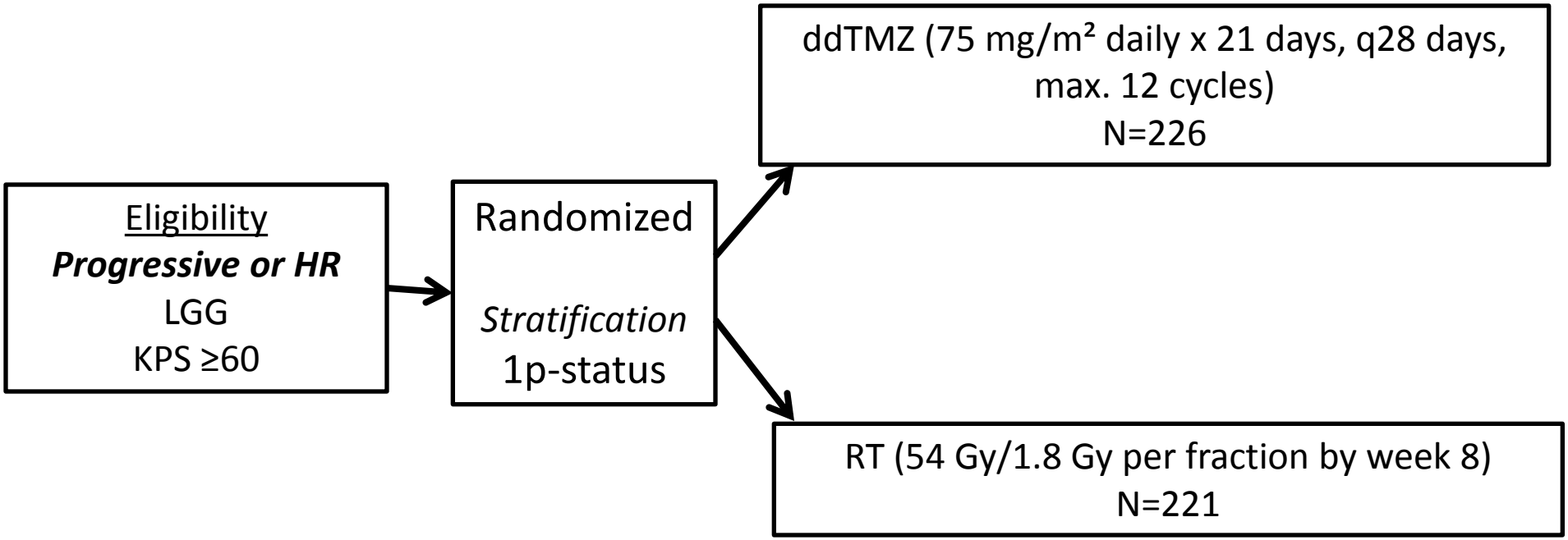
- Median FU 4.1y (3y minimum)
- Median OS not reached
- Median PFS
  - 4.5 years



NS:3 vs. 5 risk factors

Temozolomide chemotherapy versus radiotherapy in molecularly characterized (1p loss) low-grade Gliomas: A randomized phase III intergroup study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033)

- **Goal:** To assess primary chemotherapy in HR LGG vs. conventional RT for PFS and OS



J Clin Oncol 31, 2013 (suppl; abstr 2007)

	RT (n=240)	TMZ (n=237)	TMZ vs RT HR (CI), p value
Age (median, range)	44 yrs (18-72)	45 yrs (19-75)	
WHO PS 0-1	95%	97%	
Histology Astrocytoma/Oligoastro. Oligodendroglioma 1p Deleted Undetermined	36 / 24% 39% 41% 15%	33 / 25% 41% 41% 14%	
Surgery Debulking / complete Biopsy	60% 40%	61% 39%	
PFS	(median, CI)	(median, CI)	***246 events***
All patients	47 mo (40, 56)	40 mo (35, 44)	**1.16 (0.9, 1.5) p=0.23**
1p intact	41 mo (32, 55)	30 mo (24, 40)	**1.41 (0.9, 2.0) p=0.06**
1p deleted	58 mo (41, 67)	55 mo (38, N)	1.01 (0.7, 1.5) p= 0.95
	Interaction test: n.s		
OS	Not reached	74 (69, N)	108 events
All patients			0.9 (0.6, 1.3) p=0.55
1p intact			1.03 (0.6, 1.7) p= 0.9
1p deleted			**0.47 (0.2, 1.0) p=0.05**
	Interaction test: n.s		

What have we learned…

- HR LGG have poor prognosis should be treated as a separate entity
- RTOG 0424: First Phase II data to suggest TMZ+RT superior treatment in HR-LGG
- EORTC RND Phase III: Suggests similar outcome of TMZ alone vs RT alone
- Need more mature data to compare OS
- Sufficient data exists for RND trials