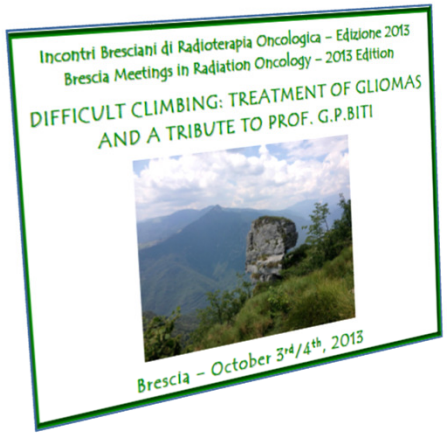

First line therapy of glioblastoma. Chemo-radiotherapy integration: for some but not for all?

Michela Buglione
Radioterapy Oncology – Brescia University

Outline

- the standard
- why should we choose the patients?
- how could we choose the patients?
- which are the choices?
- the choice of choosing: is it the right choice?

Outline

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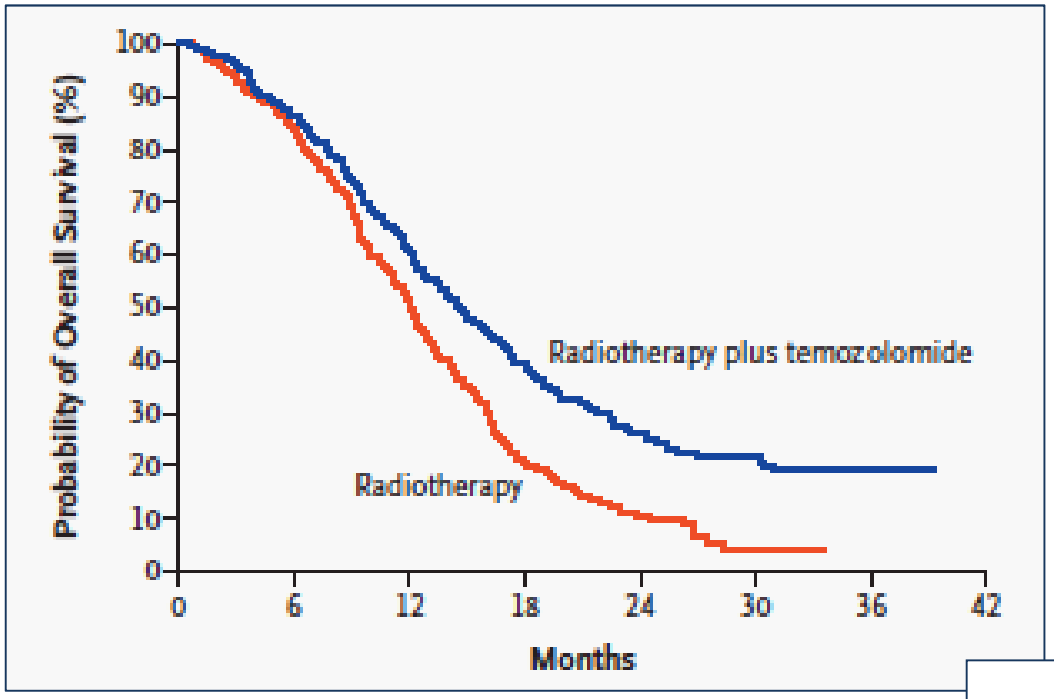
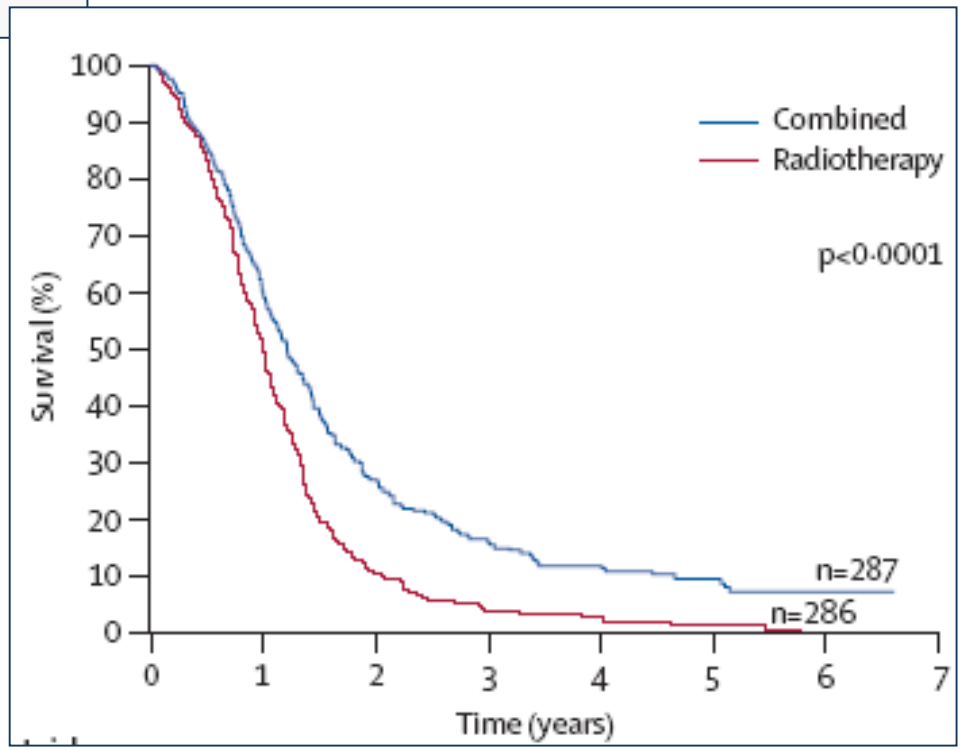


Stupp 2005 NEJM

Stupp 2009 Lancet Oncol



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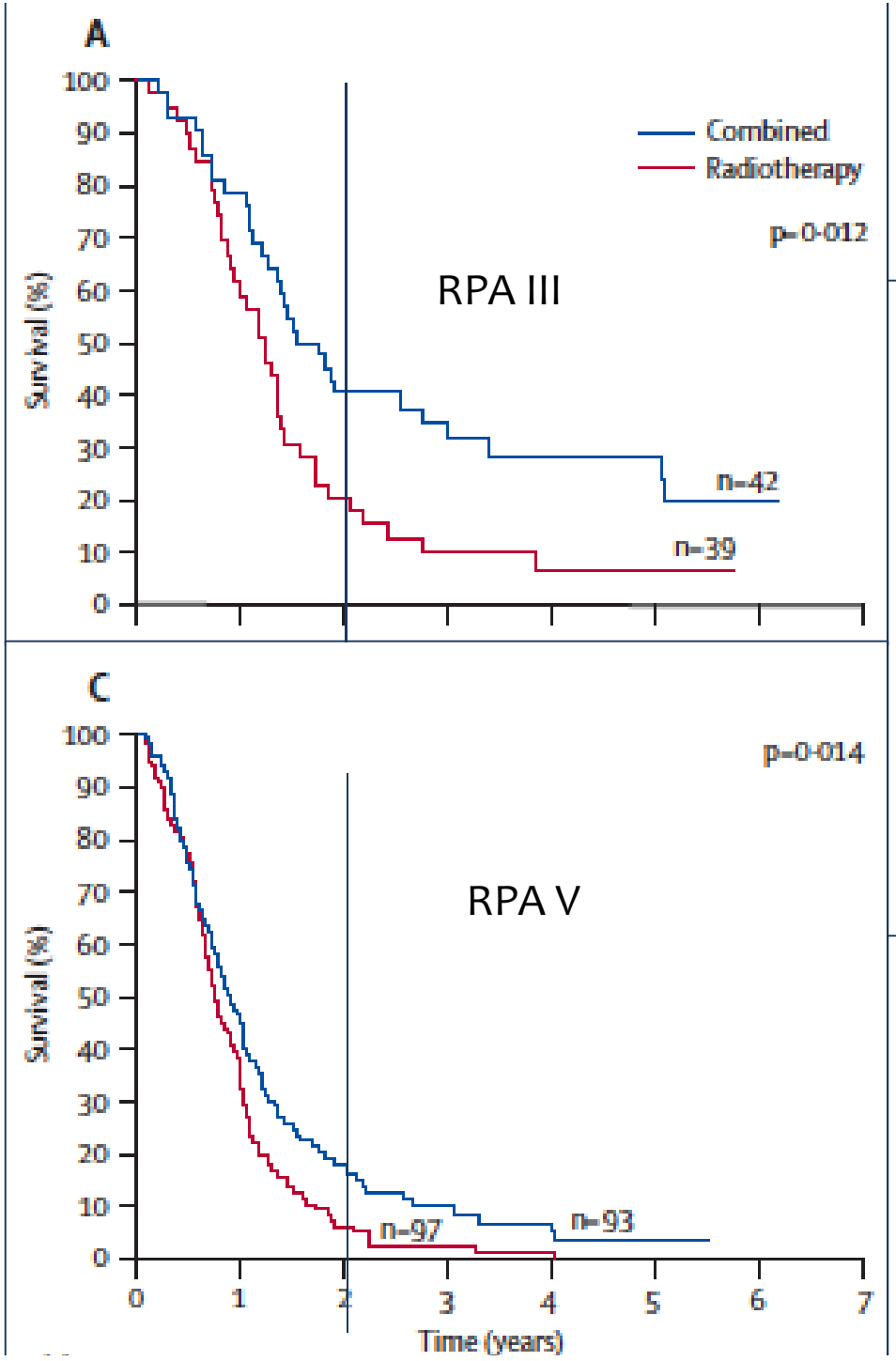
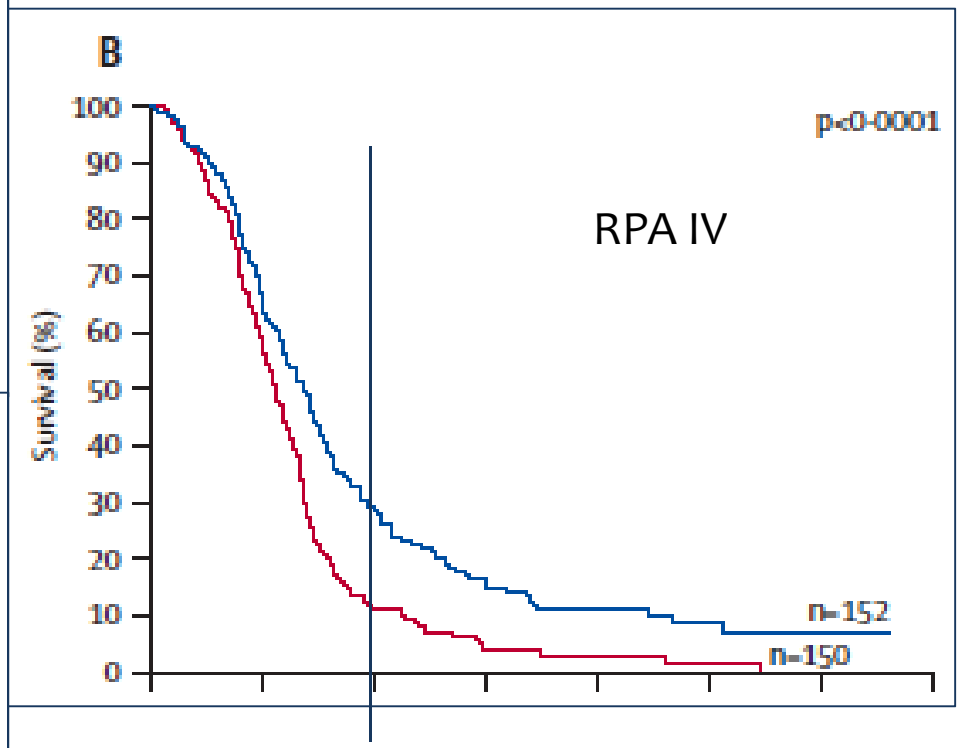
Why?

	Deaths/ patients	Hazard ratio (95% CI)	Median (months; 95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
Age <50 years							
Radiotherapy	83/88	1·0	13·6 (11·6–15·6)	14·8 (8·3–23·0)	6·5 (2·5–13·1)	4·9 (1·5–11·3)	4·9 (1·5–11·3)
Combined	79/95	0·6 (0·4–0·8)	17·4 (15·3–21·5)	34·7 (25·3–44·3)	25·4 (17·0–34·7)	20·1 (12·4–29·1)	17·0 (9·8–25·9)
Age ≥50 years							
Radiotherapy	195/198	1·0	11·9 (10·6–12·6)	9·1 (5·6–13·7)	3·4 (1·4–6·7)	2·3 (0·8–5·2)	0·7 (0·1–3·5)
Combined	175/192	0·7 (0·5–0·8)	13·6 (11·8–15·1)	23·5 (17·7–29·7)	11·4 (7·3–16·5)	8·2 (4·7–12·9)	6·4 (3·2–11·0)
Age 50–60 years							
Radiotherapy	109/111	1·0	12·0 (10·0–14·2)	11·8 (6·6–18·6)	4·2 (1·5–9·4)	2·1 (0·4–6·6)	1·1 (0·1–5·1)
Combined	101/109	0·7 (0·5–0·9)	14·6 (13·6–17·9)	24·8 (17·1–33·2)	11·0 (6·0–17·7)	8·0 (3·8–14·2)	6·4 (2·6–12·6)
Age >60 years							
Radiotherapy	86/87	1·0	11·8 (10·4–12·7)	5·7 (2·1–12·0)	2·3 (0·4–7·2)	2·3 (0·4–7·3)	0
Combined	74/83	0·7 (0·5–0·97)	10·9 (8·9–14·9)	21·8 (13·5–31·2)	12·3 (6·1–20·8)	8·8 (3·6–16·9)	6·6 (2·1–14·7)

Stupp R 2009 Lancet Oncol

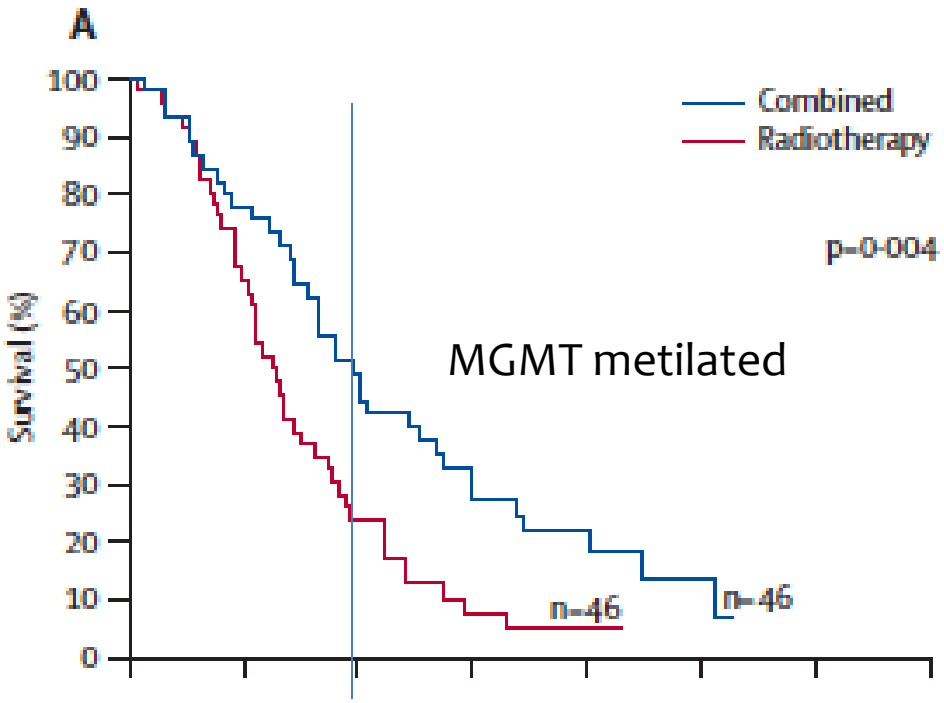
Why?

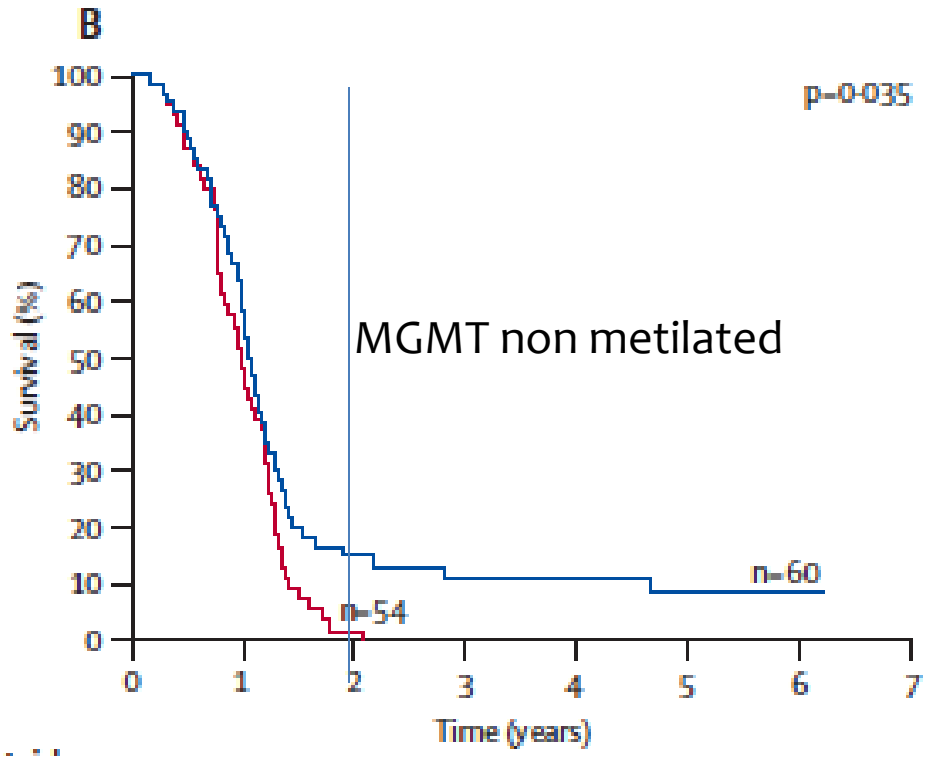




Stupp 2009 Lancet Oncol

Why?





Stupp 2009 Lancet Oncol

Outline

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How? Age

The life expectancy of elderly pts with GBL is significantly shorter than in younger pts

How? Age

Age itself?

Why the life expectancy of elderly pts with GBL is significantly shorter than younger pts ?

Holdhoff M 2013 JNCCN

How? Age

Biological factors?
-Less IDH1 mutation
-Less m-MGMT
-TP53 mutation
-EGFR amplification

Age itself?

Why the life expectancy of elderly pts with GBL is significantly shorter than younger pts ?

Holdhoff M 2013 JNCCN

How? Age

Age itself?

Biological factors?
-Less IDH1 mutation
-Less m-MGMT
-TP53 mutation
-EGFR amplification

Less therapy?
-Less resection
-Less radiotherapy
-Less cht

Iwamoto FM 2008 Ann Neurol

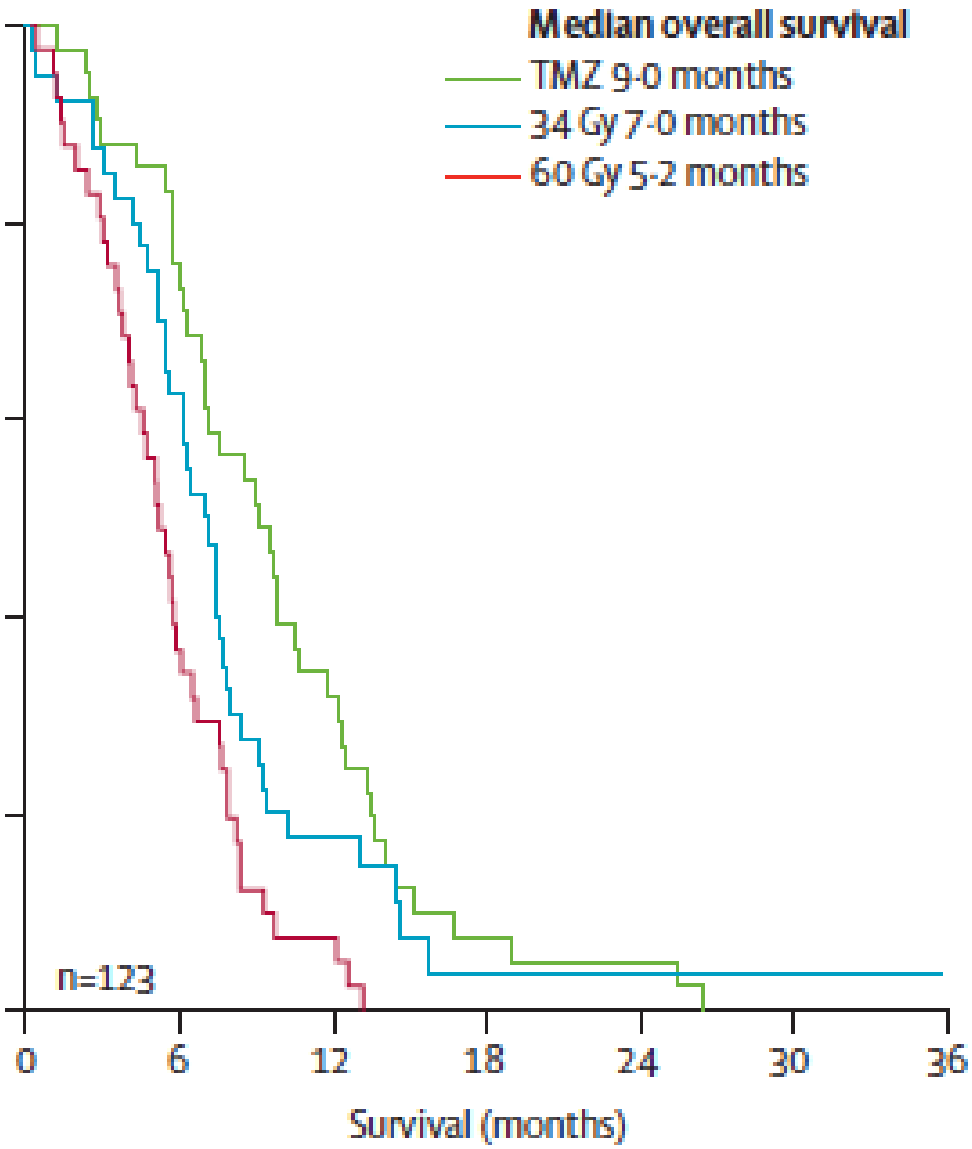
-More need of supportive care
-More frequent toxicity

Why the life expectancy of elderly pts with GBL is significantly shorter than younger pts ?

Holdhoff M 2013 JNCCN

How? Age

Nordic randomized phase III trial



> 70 yy

Malmstrom A 2012 Lancet Oncol

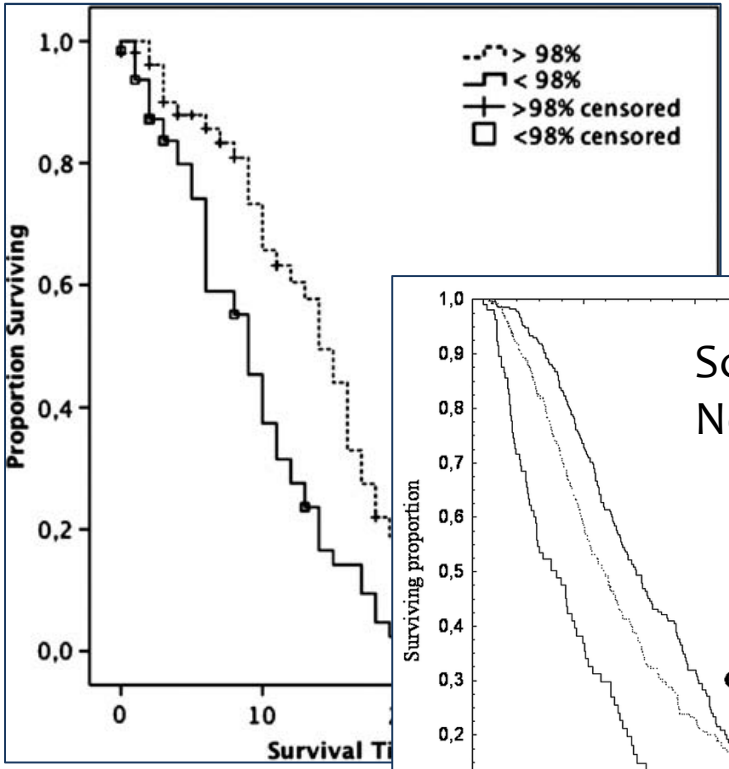
How? Extent of surgery

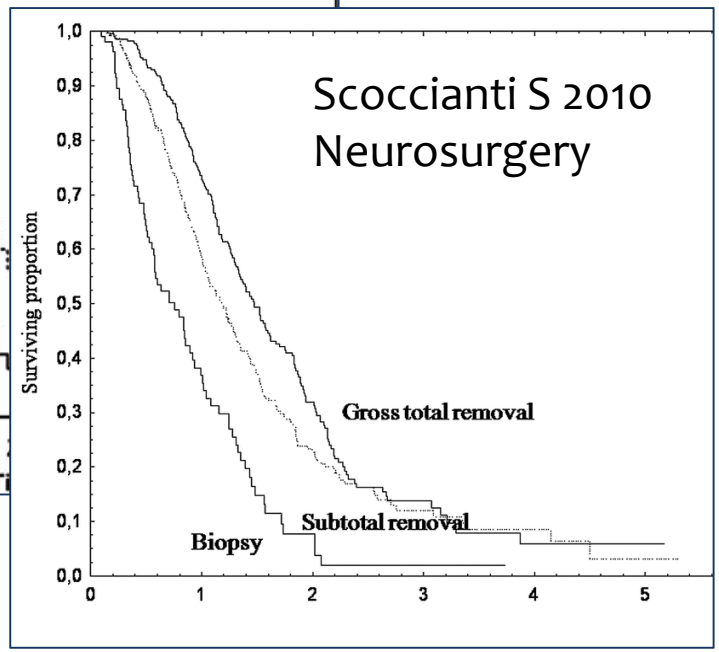
Radical surgery is better than partial surgery or biopsy

How? Extent of surgery

A complete surgical excision of HGG is impossible

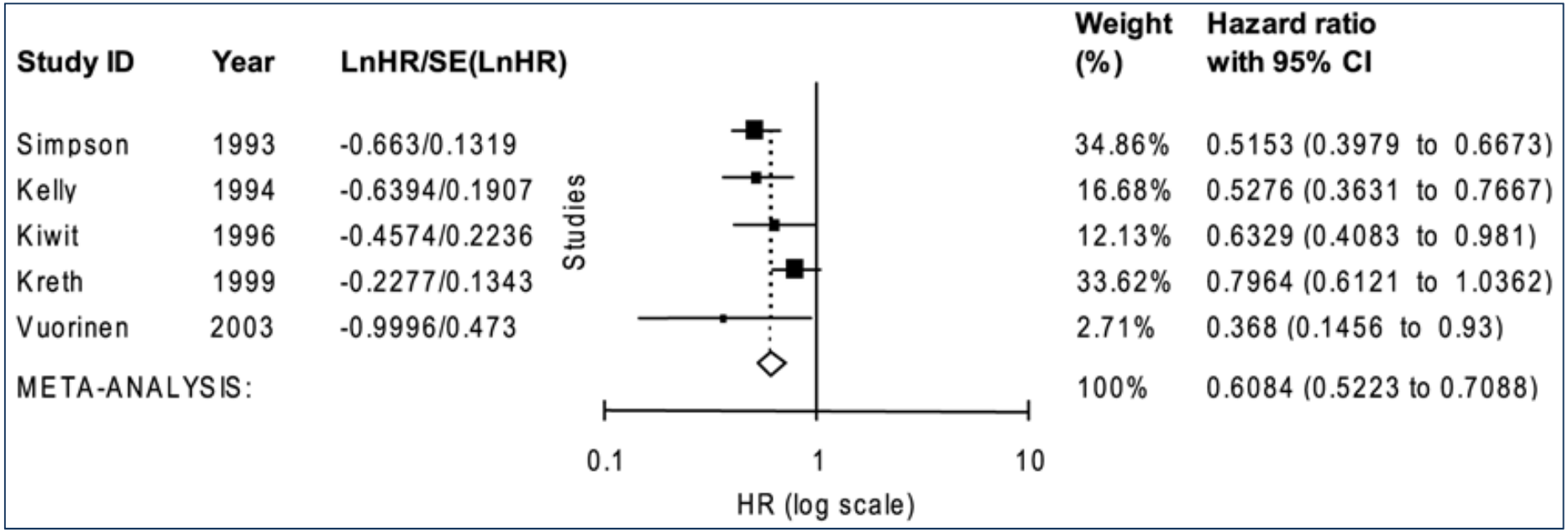
Is the extent of resection really an independent factor in predicting survival?





Radical surgery is better than partial surgery or biopsy

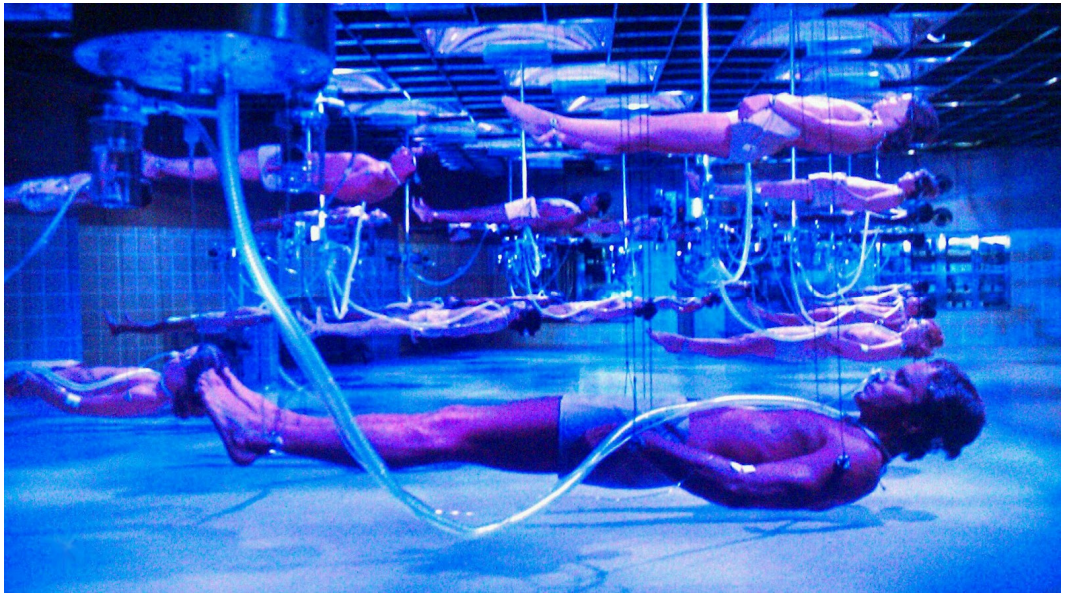
How? Extent of surgery



Radical surgery is better than partial surgery or biopsy

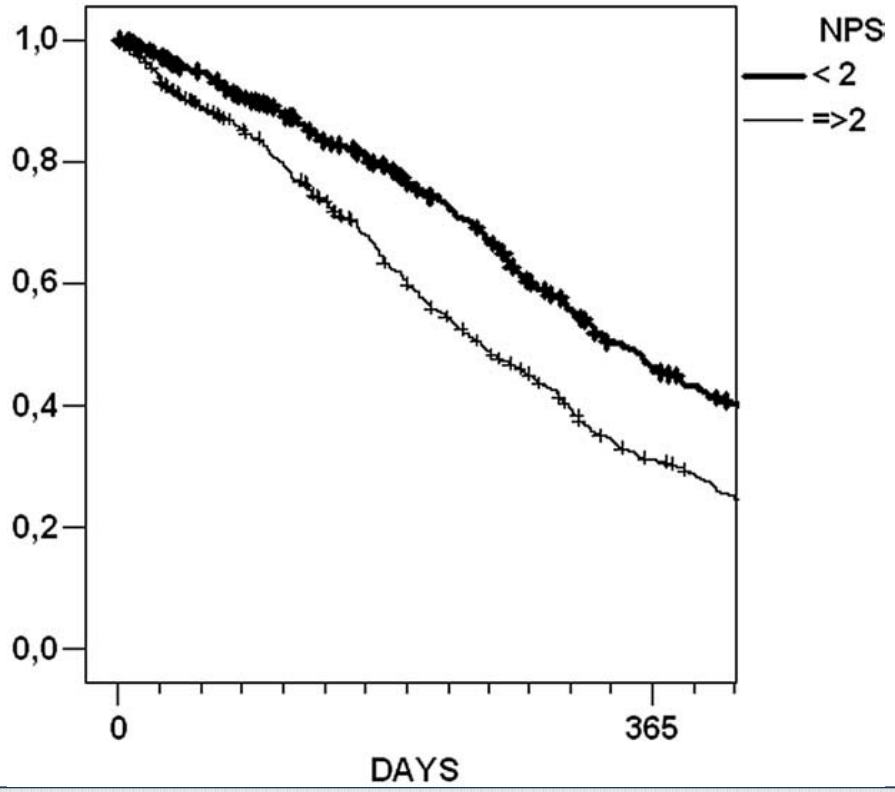
Tsitlakidis A 2010 J Neurosurg

How? General and neurological PS



Patients with poor general and neurological performance have a worse prognosis

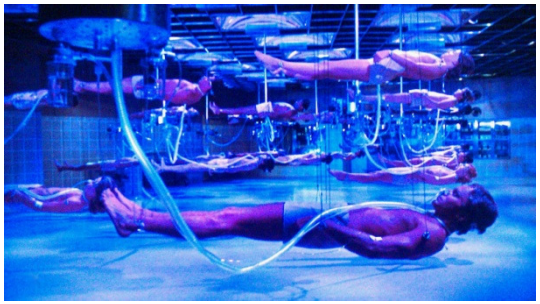
How? General and neurological PS



Patients with poor general and neurological performance have worse prognosis than the others

Magrini SM 2006 IJROBP

How? RPA "*new version*"

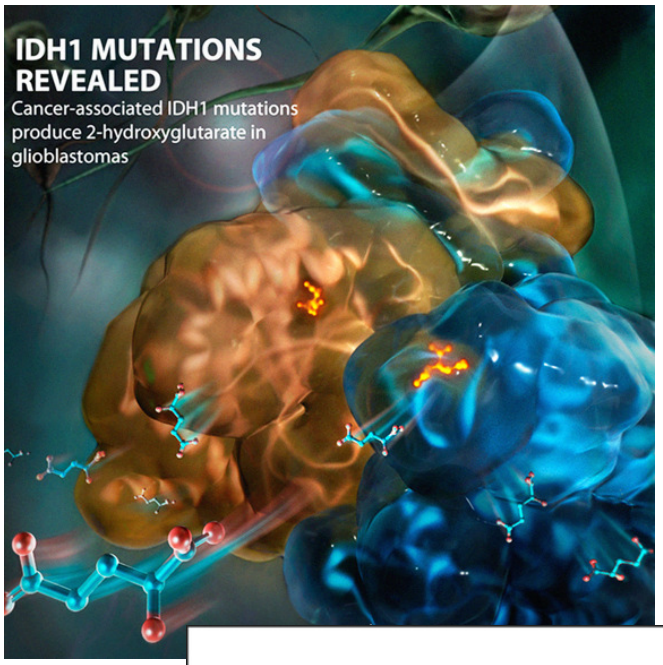


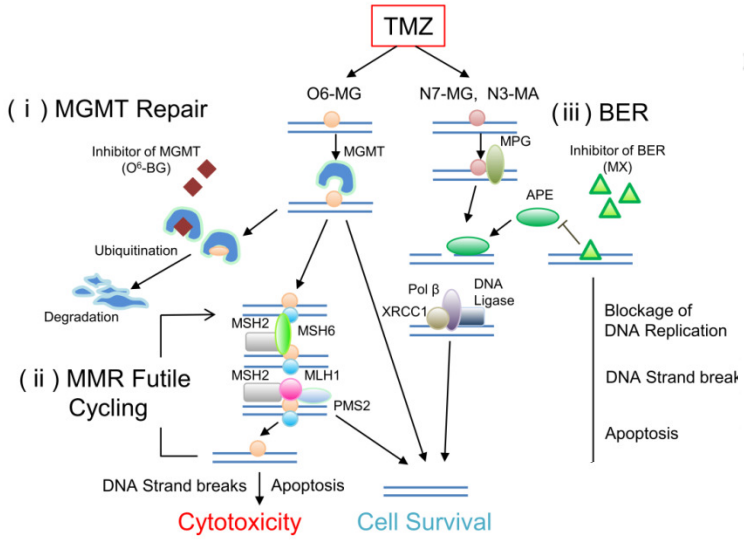
RPA class	Definition variables	Survival (mo)
III	<50 y and KPS >=90	17.1
IV	• <50 y and KPS <90 • >=50 y, KPS >=70, resection, and working	11.2
V	• >=50 y, KPS >=70, resection, and not working • >=50 y, KPS >=70, biopsy only • >=50 y, KPS< 70	7.5

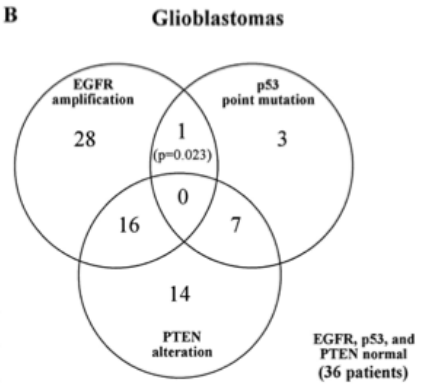
Three new simplified RPA classes

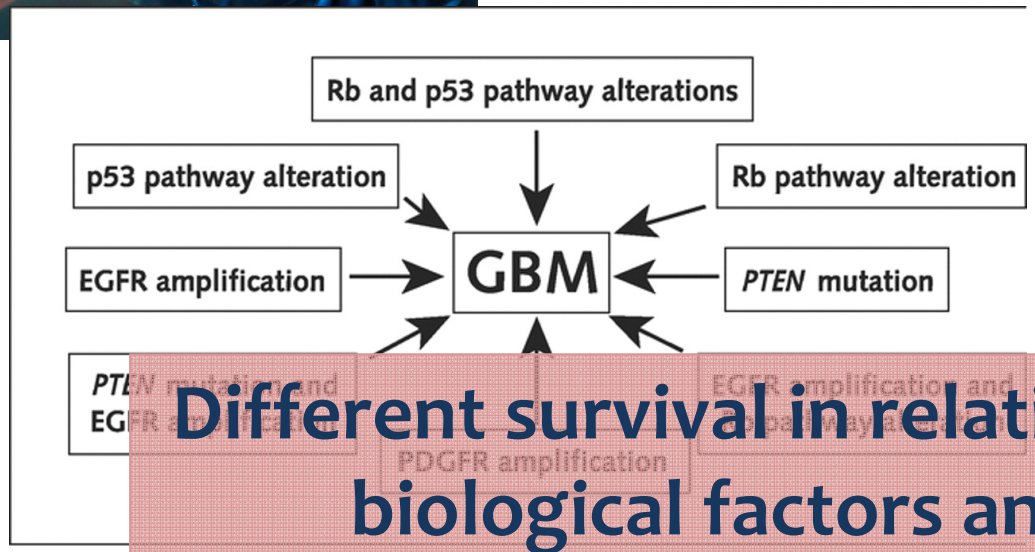
Li J 2011 IJROBP

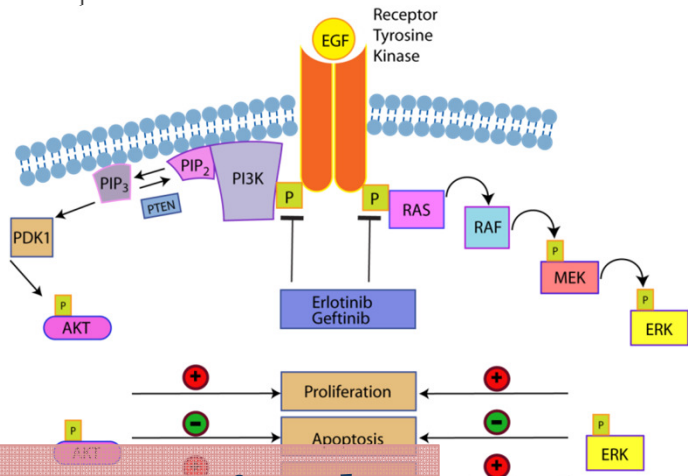
How? Biological aspects











Different survival in relation to single biological factors and their combination

How? Biological aspects *"MGMT methylation"*

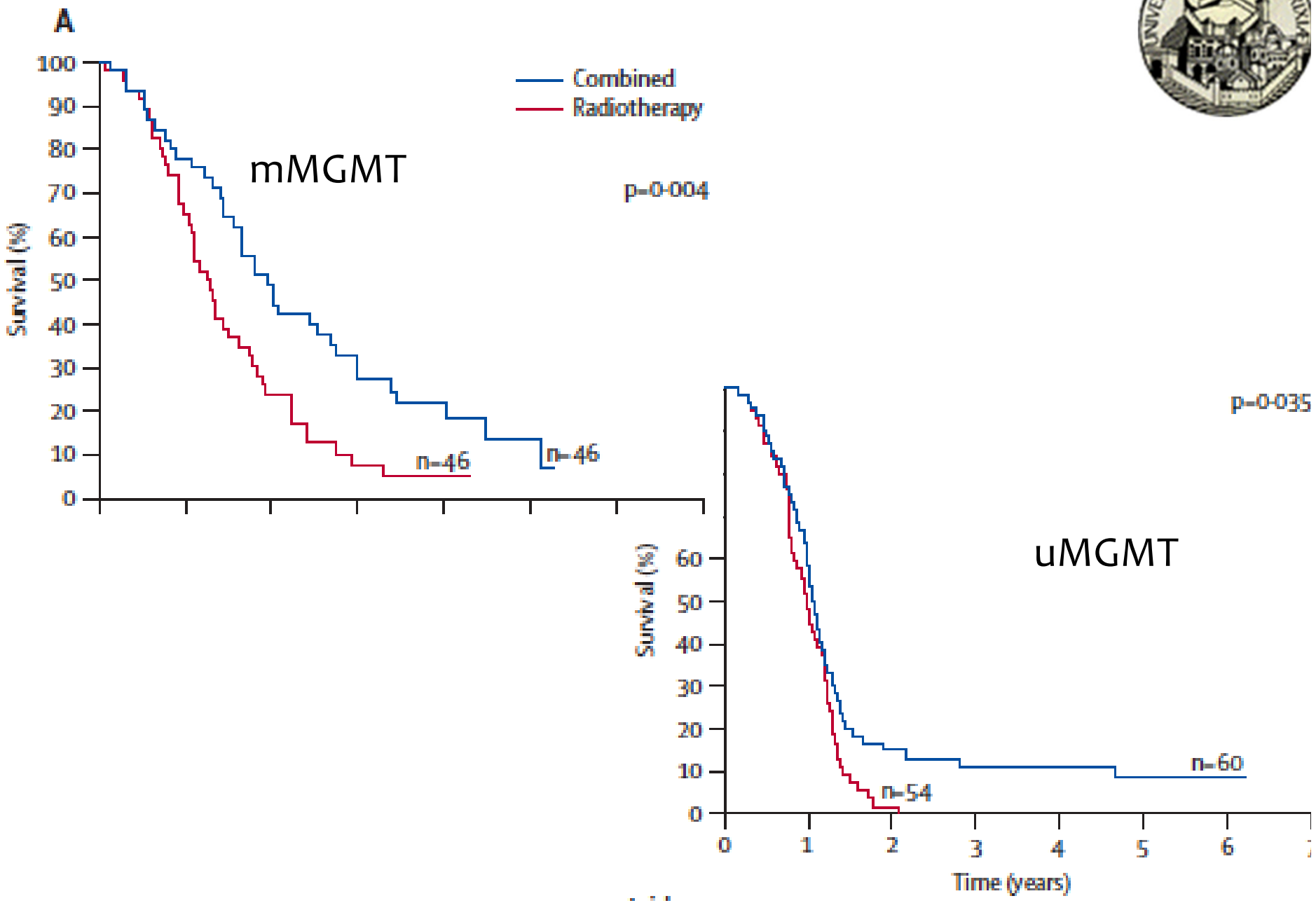
- Biological effect → reduced DNA repair, association with G-CIMP phenotype in IDH1/2 mutant tumours

- Better response to chemotherapy→ better OS and PFS

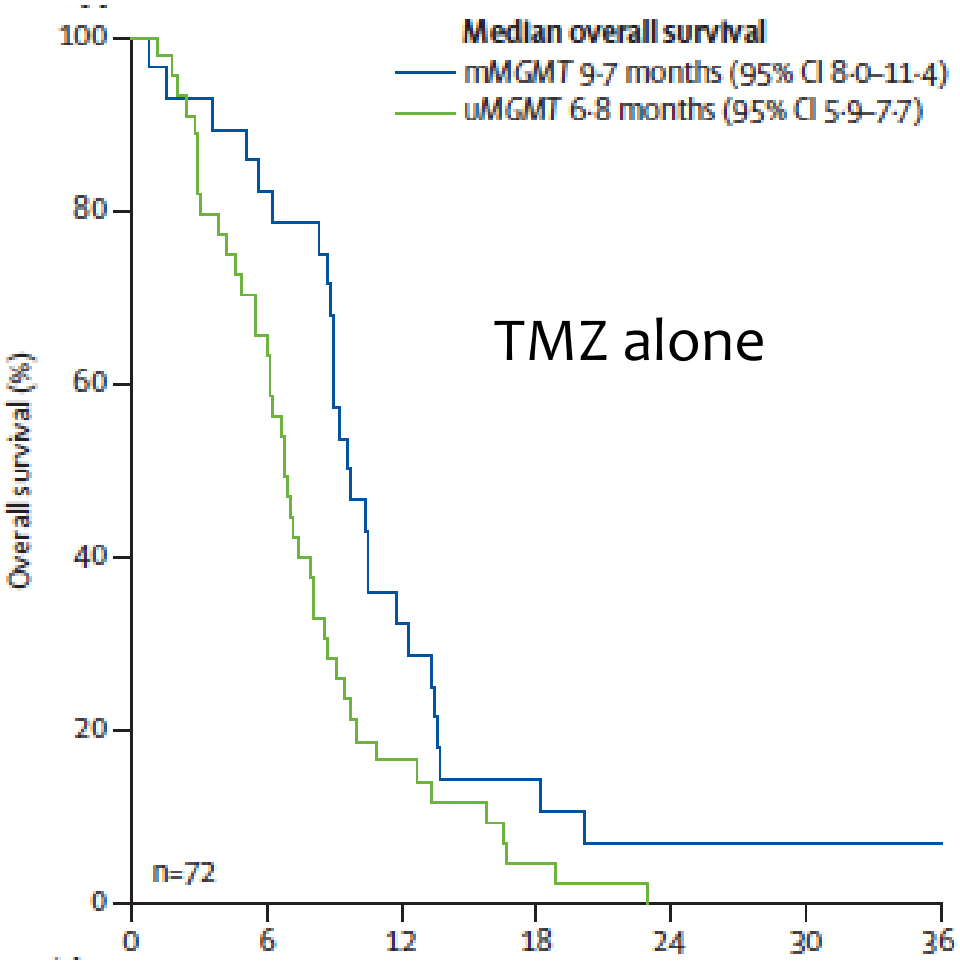
- Problems related to the identification methods have been debated

- None of the present or ongoing trials answering this question: patients with MGMT methylation should be treated with TMZ (alone or concomitant and adjuvant to RT) or not?

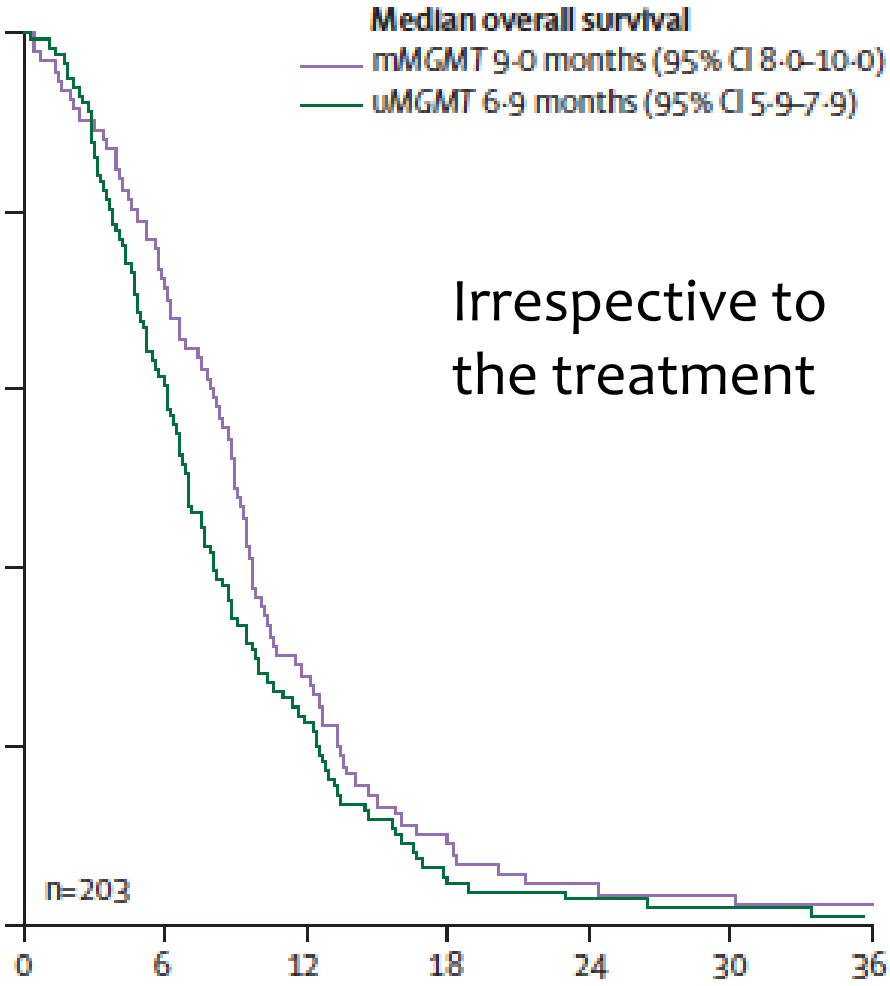
Weller M 2013 Lancet Oncol



Stupp R 2009 Lancet Oncol



TMZ alone



Irrespective to the treatment

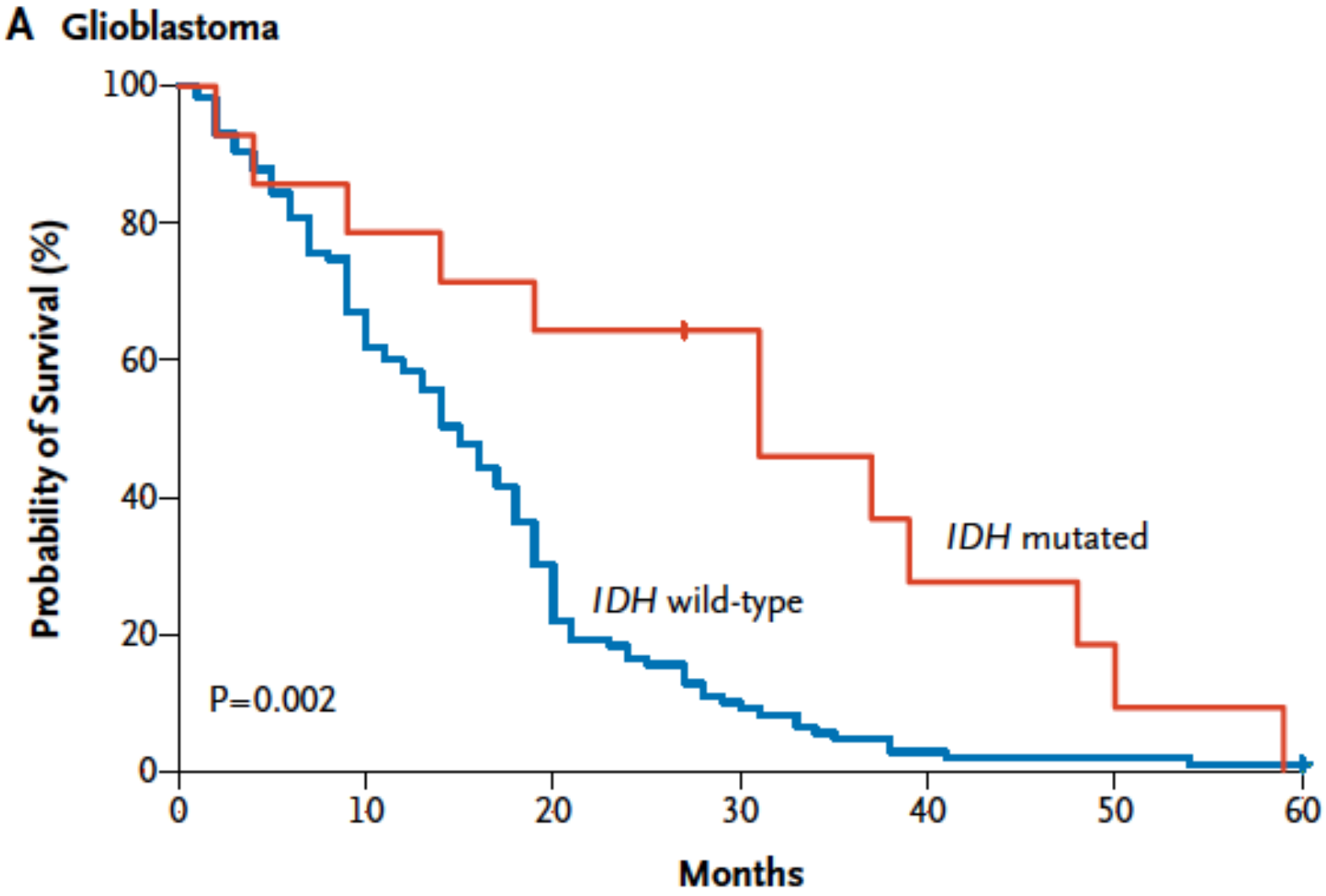
Malmstrom A 2012 Lancet Oncol

How? Biological aspects *"IDH mutation"*

- Biological effect → increased concentrations of 2-hydroxyglutarate, association with G-CIMP phenotype
- Differentiate IDH-wild type worse vs IDH mutant glioma better prognosis
- IDH status could be included in future classification
- IDH-mutant tumours are driven by specific epigenetic alterations, phenotypically characterized by a status (G-CIMP-positive) suitable for specific therapeutic interventions
- ***IT HASN'T A DEFINED ROLE IN CLINICAL DECISION MAKING***

Weller M 2013 Lancet Oncol

How? Biological aspects



Yan H 2009 NEJM

How? Biological aspects
"EGFR v III rearrangement"

- Biological effect → deletion of the gene EGFR: results in a costitutive and ligand independent oncogenic mutation

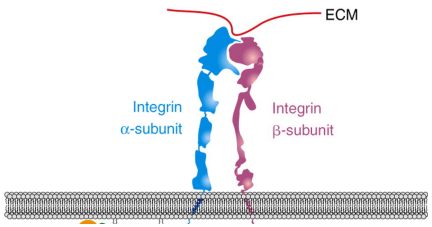
- The mutation can probably be considered a negative prognostic factor (reduces long term survival)

- Target treatments against EGFR are not effective

- EGFR v III mutation is an immunogenic factor that could possibly be used as target for "*vaccination*"

- EGFRvIII mRNA has been detected in the serum of patients with EGFR vIII positive-glioblastoma→ it could be useful to monitor response to therapy and to detect relapse

Weller M 2013 Lancet Oncol



How? Biological aspects *"integrins"*

- Integrins → cell adhesion molecules involved in glioma cell migration/invasion and angiogenesis

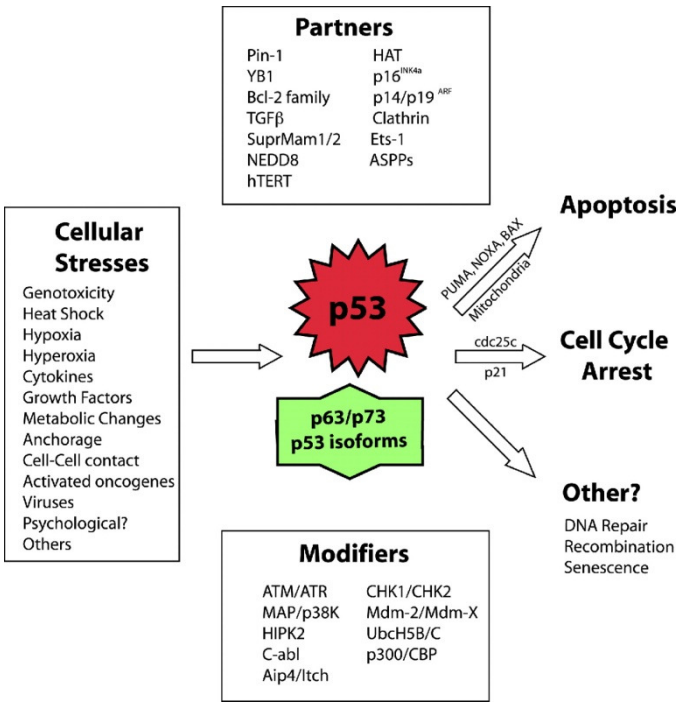
- Any integrin, if overexpressed, is involved in multi-drug resistant glioma cells and is responsible for their increased adhesive and invasive capacities.

- Others are up-regulated on the endothelium cells during tumour angiogenesis and are rapidly accessible in tumour blood vessels; they stimulate endothelium cells proliferation, migration and lumen formation

- Elevated levels of integrins were found in glioma stem cells

Martin S 2012 Frontiers in Oncol

How? Biological aspects
"p53 in glioma"



- P53 expression is related with p53 mutation;
- Problems are evident regard the prognostic value of p53 in GBL ; it is not validated as independent prognostic factor
- p53 is involved in regulation of neural stem cells→ its alteration can increase loss of cell differentiation and increase in neurospehere renewal
- conflicting results are evident about the relationship between p53 and response to TMZ

Martin S 2012 Frontiers in Oncol

How? Biological aspects
"gene profile"

- Determination of gene expression profile derived from classic tumour samples ⟷ clinical outcome
- The HOX signature and EGFR expression → independent negative prognostic factors
- The functional association of HOX gene signature with glioblastoma stem cells have been confirmed and the negative prognostic effect was confirmed

Murat A 2008 JCO
Gallo M 2013 Cancer Res

- A new classification of GBL based on supervised gene expression profiling, guided by patients outcome:

a) pro-neural
b) proliferative
c) mesenchymal

glioblastoma

Phillips HS 2006 Cancer Cell
Verhaak RGV 2010 Cancer Cell

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glioblastoma

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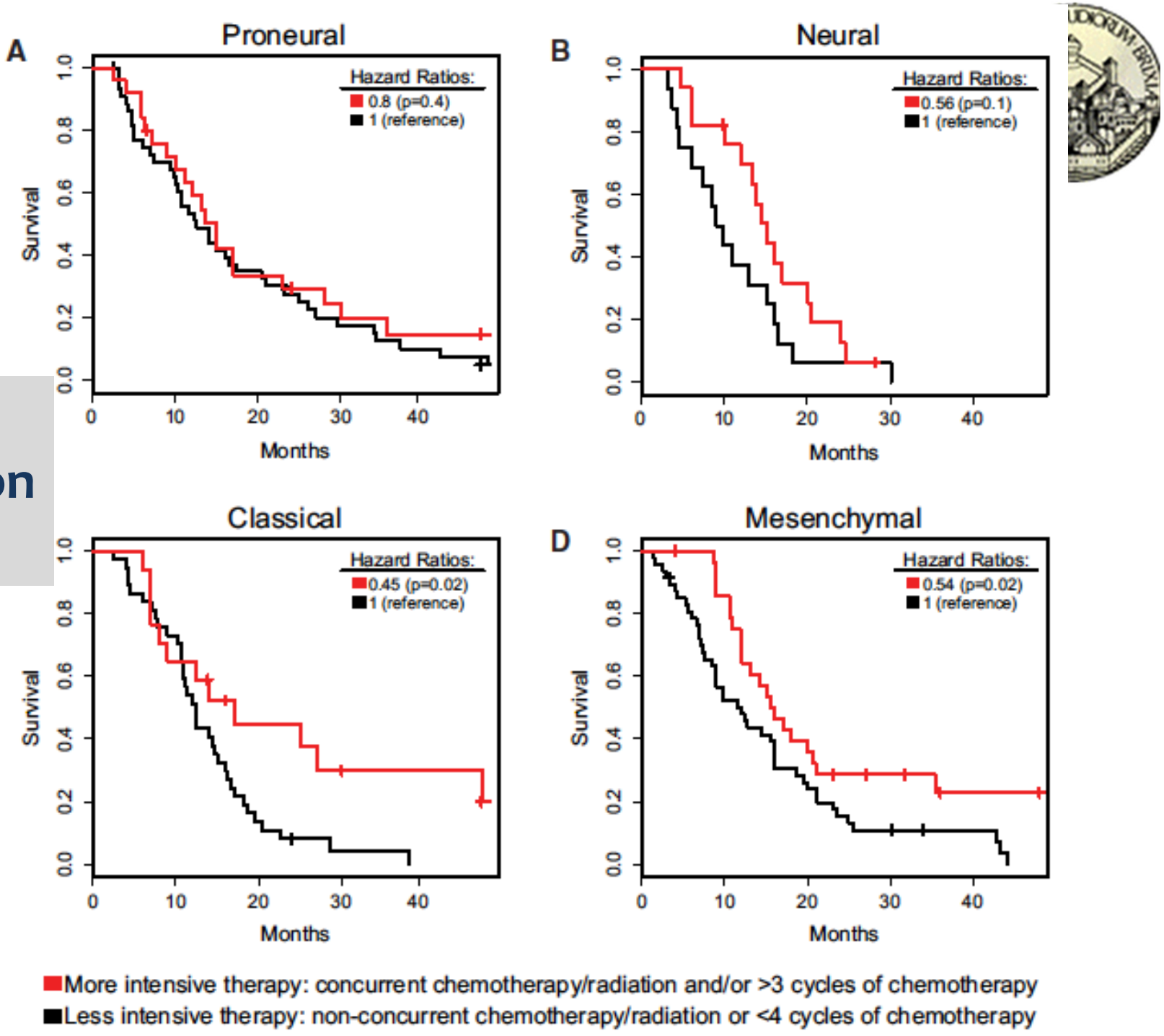
Gene expression profile



Outline

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Which choices?

- Combined treatment

- Single treatment

a. Radiotherapy alone
b. Chemotherapy alone
c. Others ?

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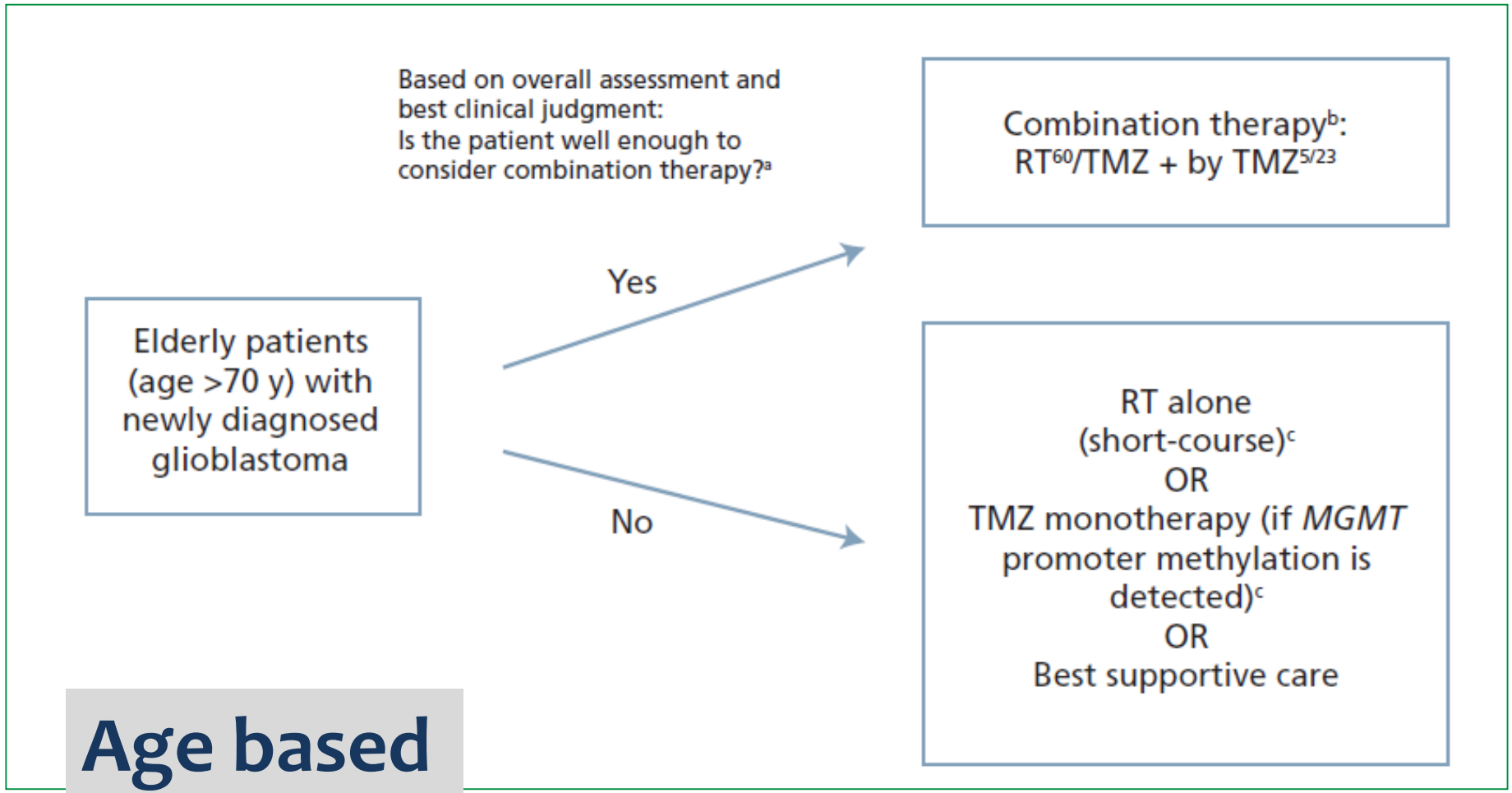
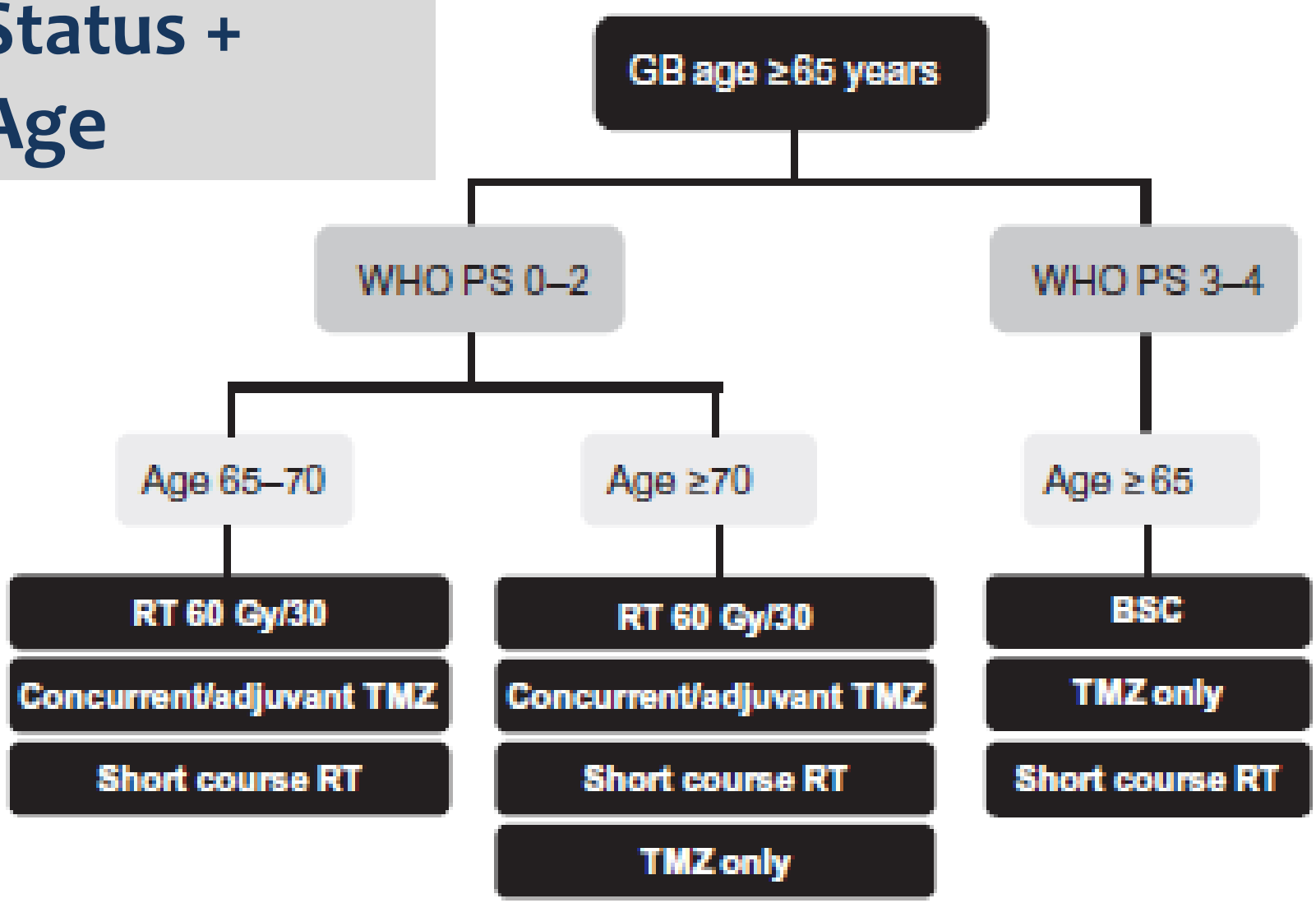
The choice of choosing



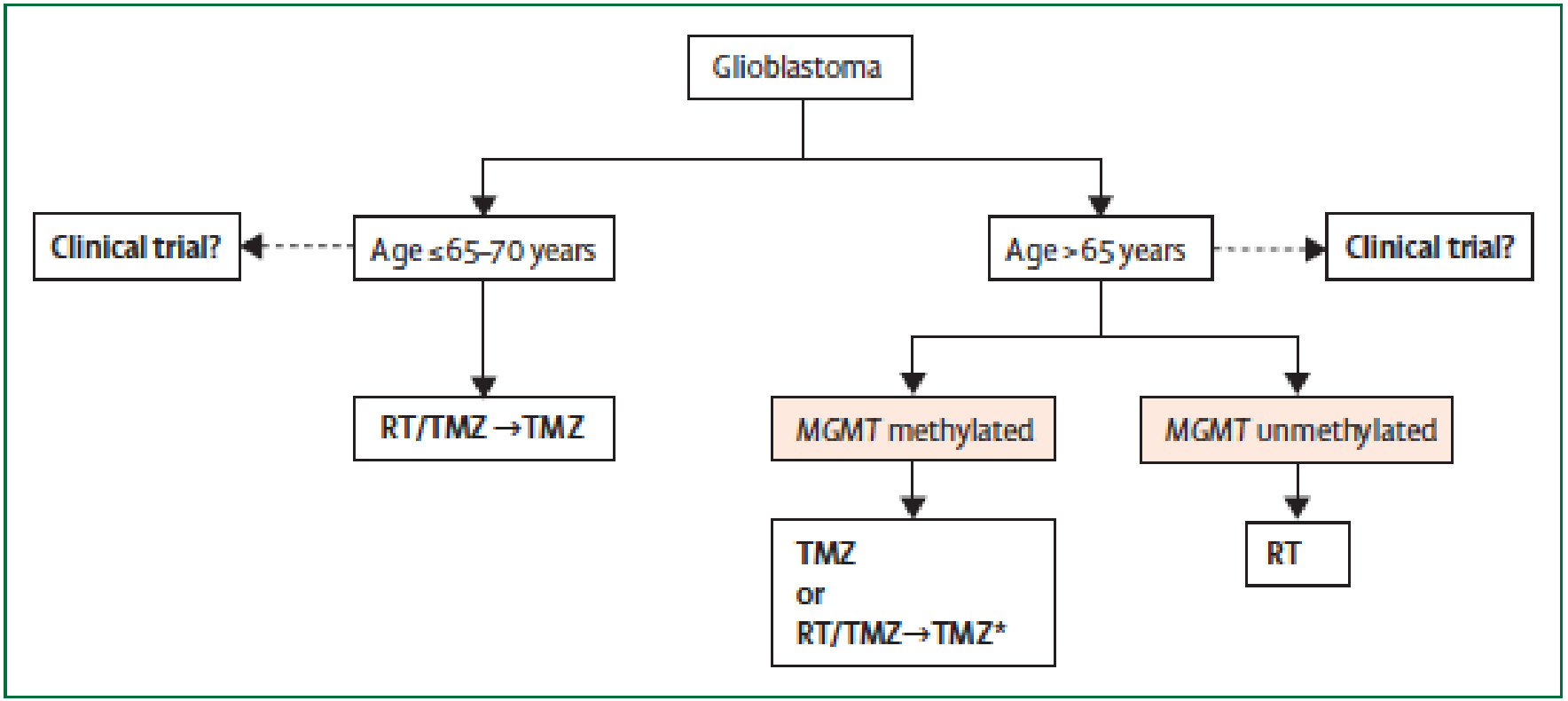
Age based approach

Holdhoff M 2013 JNCCN

Performance Status + Age

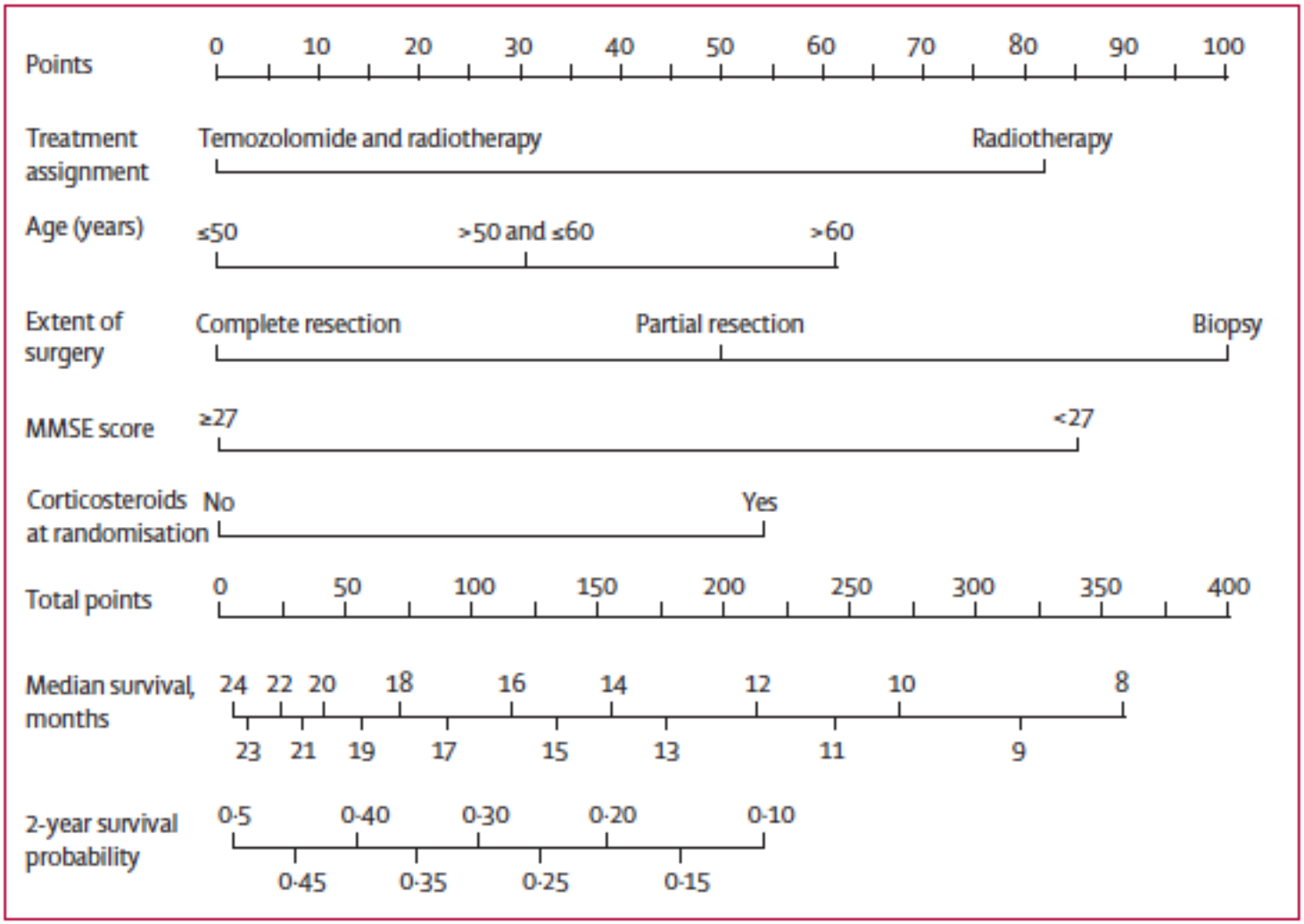


Lapierre M 2013 Cancer Treat Rev



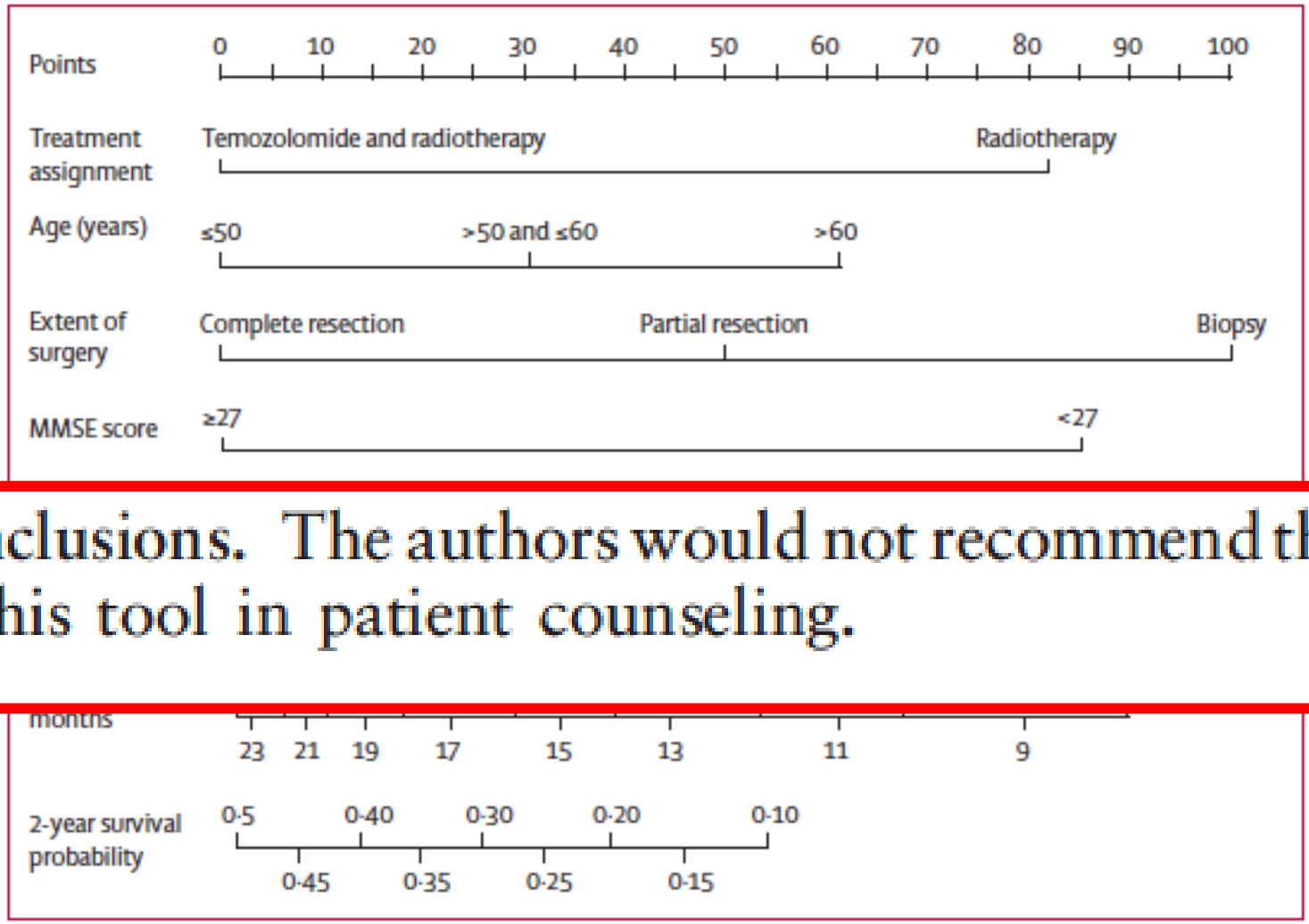
Biomarker based approach

Lapierre M 2013 Cancer Treat Rev



Nomogram based approach

Gorlia T 2008 Lancet Oncol



Conclusions. The authors would not recommend the use of this tool in patient counseling.

Nomogram based approach

Parks C 2013 Neuro-Oncology

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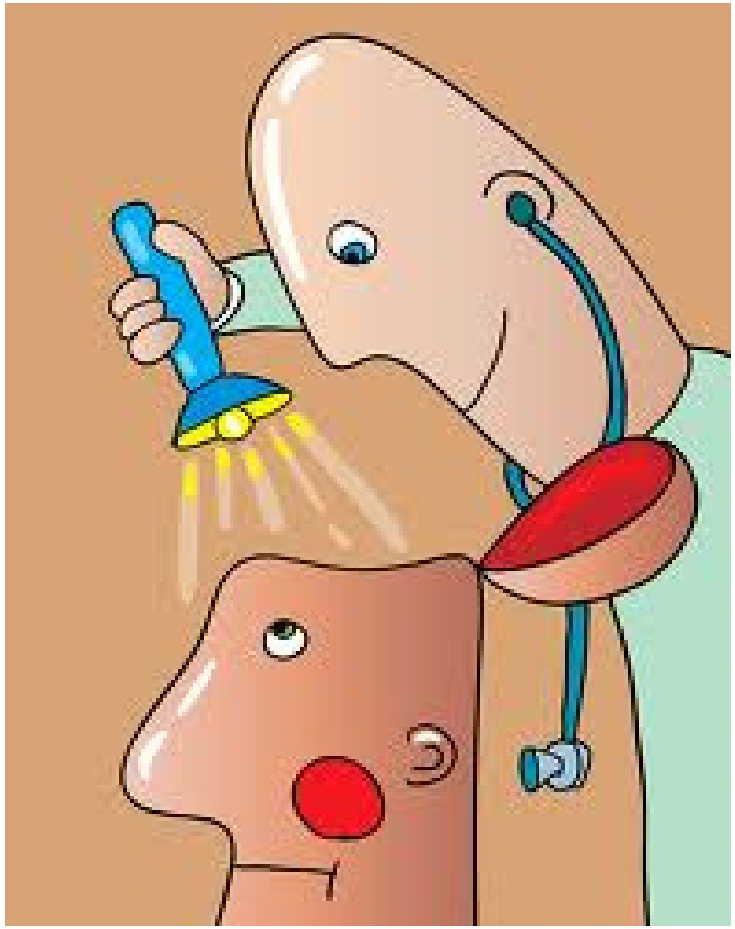
- **Chemo-radiotherapy integration: for some but not for all?**

- for the ***majority*** of our patients
- mostly dependent on ***performance status***
- for different reasons for the different patients
- of course, this is only a temporary choice…



Continuing to study the problem:

- New biological target
- New target/non target therapies
- New integrations

Thank you for your attention