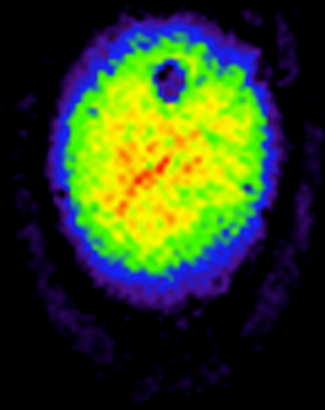
MATHEMATICAL ONCOLOGY LABORATORY

UCLM
UNIVERSIDAD DE CASTILLA-LA MANCHA

Biomarcadores avanzados **de imagen en tumores cerebrales**

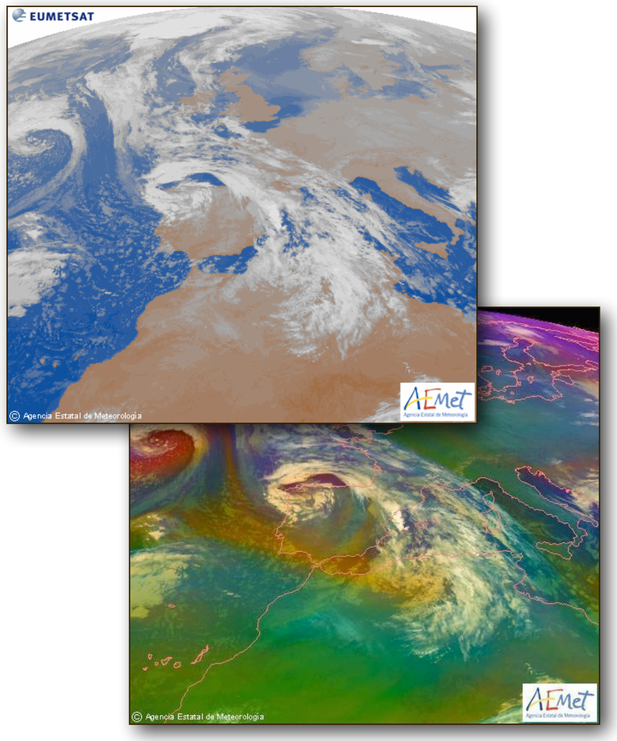


Víctor M. Pérez-García

¿Cómo encontrar biomarcadores con matemáticas?

Modelos matemáticos
‘mecanísticos’

Radiómica
Inteligencia artificial



?

sáb. 26/10	22º / 12º	Mucho sol y agradable	Precip. 0 %
dom. 27/10	20º / 15º	Intervalos de nubes y sol	Precip. 2 %
lun. 28/10	21º / 14º	Parcialmente soleado	Precip. 14 %
mar. 29/10	20º / 14º	Nubosidad variable	Precip. 40 %
mié. 30/10	17º / 12º	Intervalos de nubes y sol	Precip. 3 %
jue. 31/10	15º / 12º	Algo de lluvia más tarde	Precip. 69 %
vie. 1/11	20º / 13º	Algo de lluvia; más cálido	Precip. 57 %
sáb. 2/11	18º / 13º	Algo de lluvia más tarde	Precip. 64 %
dom. 3/11	17º / 11º	Algunos chubascos en la tarde	Precip. 69 %

$$\left(\frac{d_H}{dt}+D\right)\frac{\partial p}{\partial \eta}+\frac{\partial}{\partial \eta}\left(\dot{\eta}\frac{\partial p}{\partial \eta}\right)=0$$

$$\frac{dT_k}{dt_k}=\left[\frac{\kappa T_v}{1+(\delta-1)q}\right]_k\left(\frac{\omega}{p}\right)_k+(P_T+K_T)_k,$$

$$\frac{\partial lnp_s}{\partial t}=-\frac{1}{p_s}\sum_{j=1}^{N}\nabla_H.\{(\mathbf{v}_H)_j\Delta p_j\}$$

$$\frac{d\mathbf{v}_k}{dt_k}=[-f\mathbf{k}\times\mathbf{v}-\nabla\Phi-R_dT_v\nabla lnp]_k+(\mathbf{P_u}+\mathbf{K_u})_k.$$

$$\left(\frac{dq}{dt}\right)_k=(P_q+K_q)_k$$

$$\left(\frac{dm}{dt}\right)_k=(P_m+K_m)_k$$

$$\Phi_k=\Phi_s+R_d\sum_{j=k+1}^{N}(T_v\Delta lnp)_j+R_d(\alpha T_v)_k,$$

$$\left(\frac{d_H}{dt}+D\right)\frac{\partial p}{\partial \eta}+\frac{\partial}{\partial \eta}\left(\dot{\eta}\frac{\partial p}{\partial \eta}\right)=0$$

$$\frac{dT_k}{dt_k}=\left[\frac{\kappa T_v}{1+(\delta-1)q}\right]_k\left(\frac{\omega}{p}\right)_k+(P_T+K_T)_k,$$

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mar. 29/10	20° / 14°	Nubosidad variable	Precip. 40 %
mié. 30/10	17° / 12°	Intervalos de nubes y sol	Precip. 3 %
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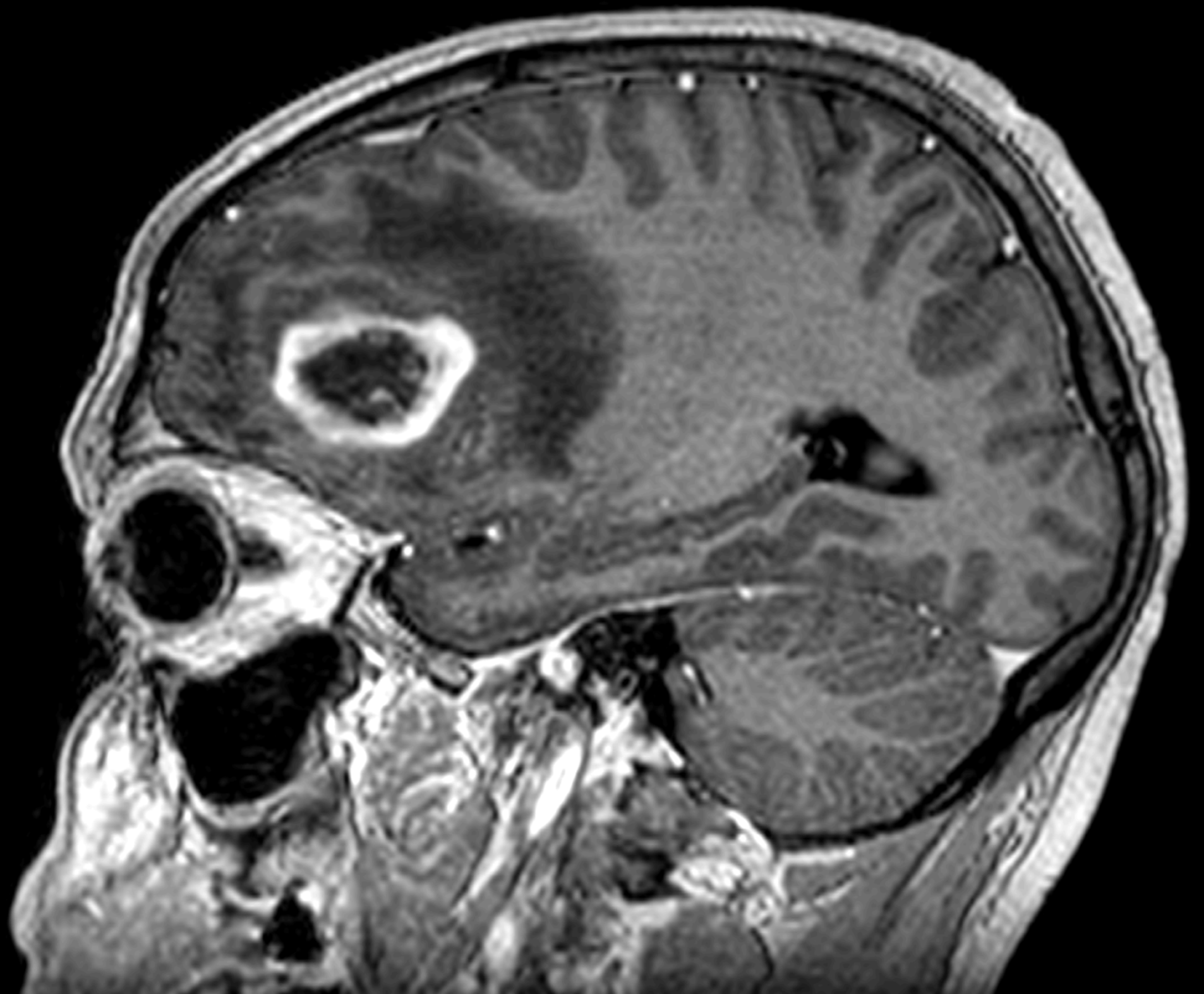
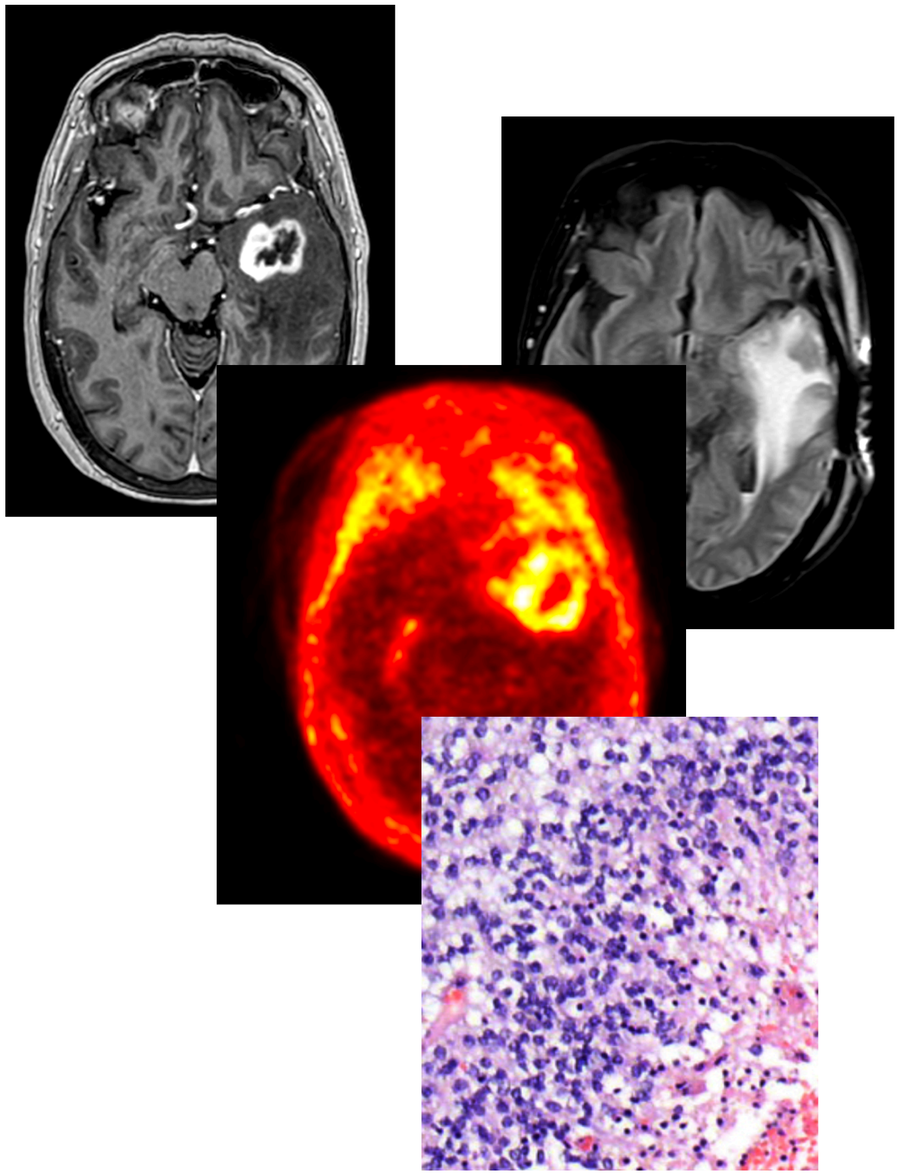
vie. 1/11	20° / 13°	Algo de lluvia; más cálido	Precip. 57 %
sáb. 2/11	18° / 13°	Algo de lluvia más tarde	Precip. 64 %
dom. 3/11	17° / 11°	Algunos chubascos en la tarde	Precip. 69 %

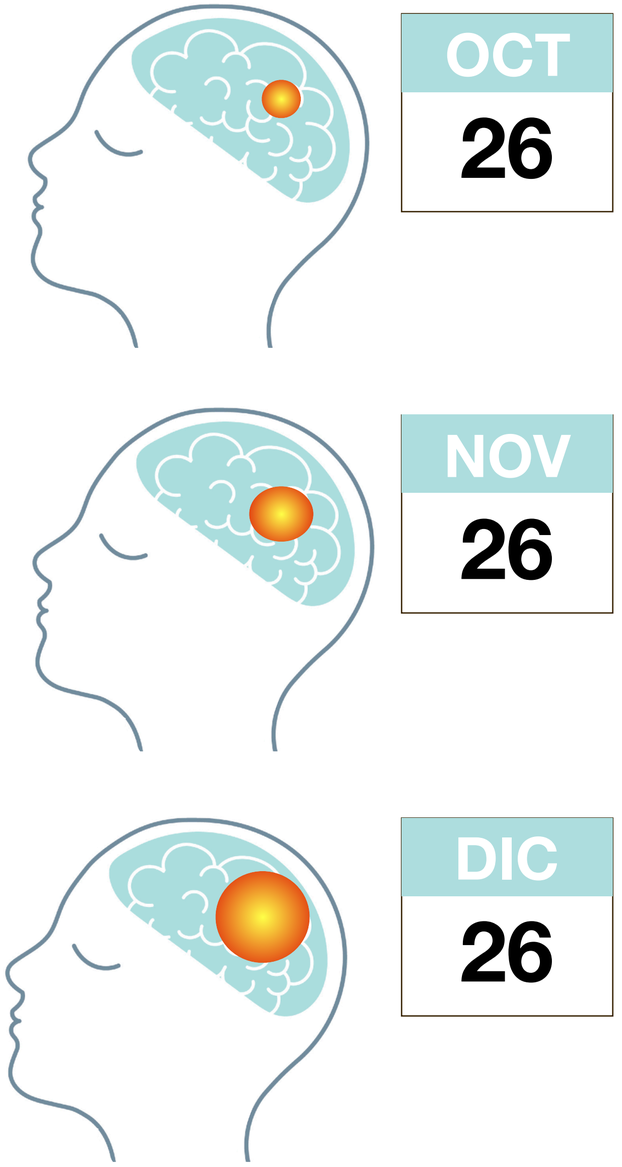
Glioblastoma

Tumor cerebral primario
más frecuente y maligno

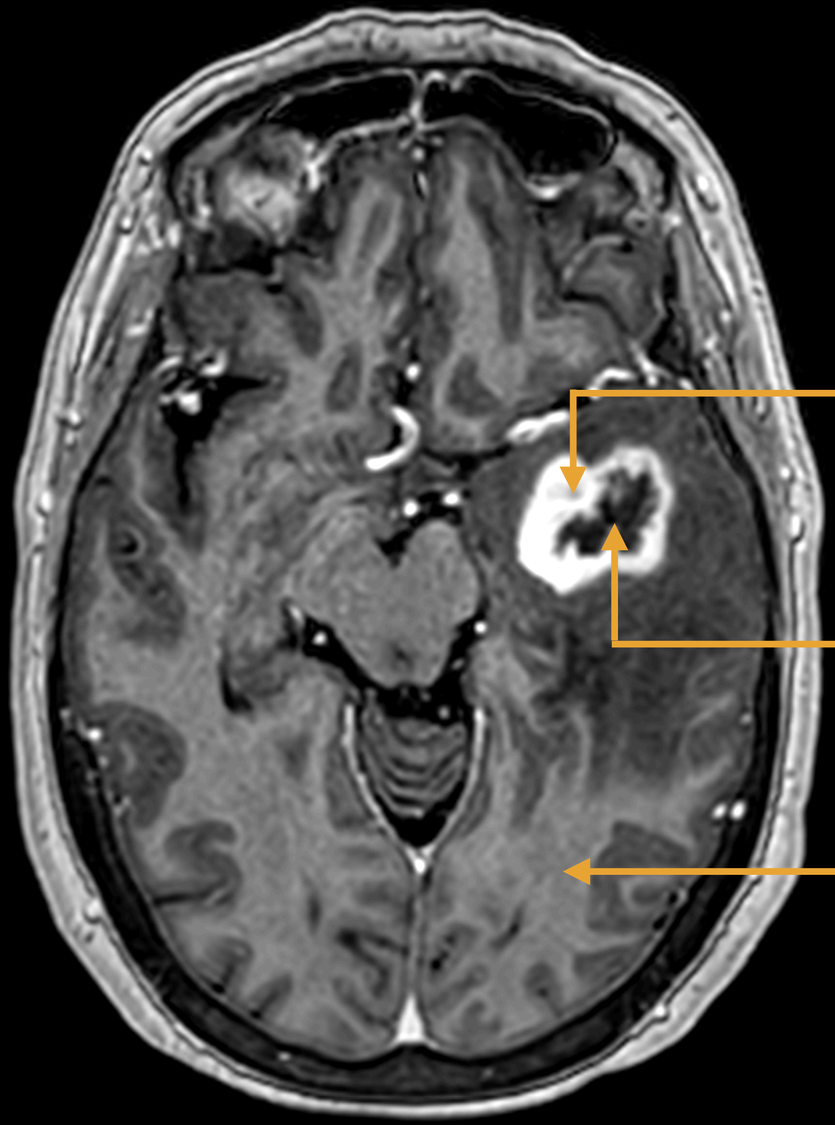




Pronóstico
Predicción
Personalización



Estudio(s) **retrospectivo**(s) **con 1400 pacientes** (500 útiles)

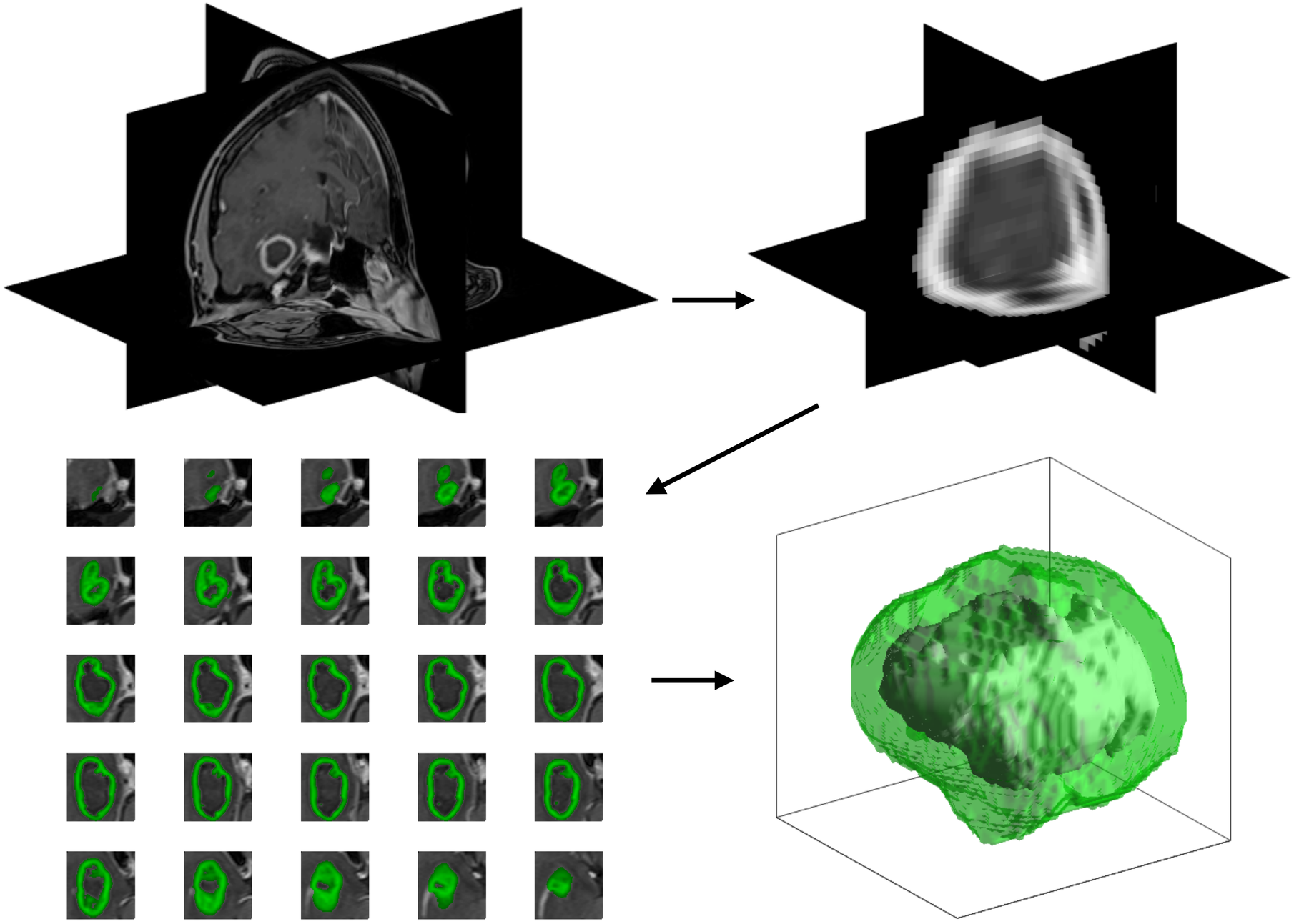


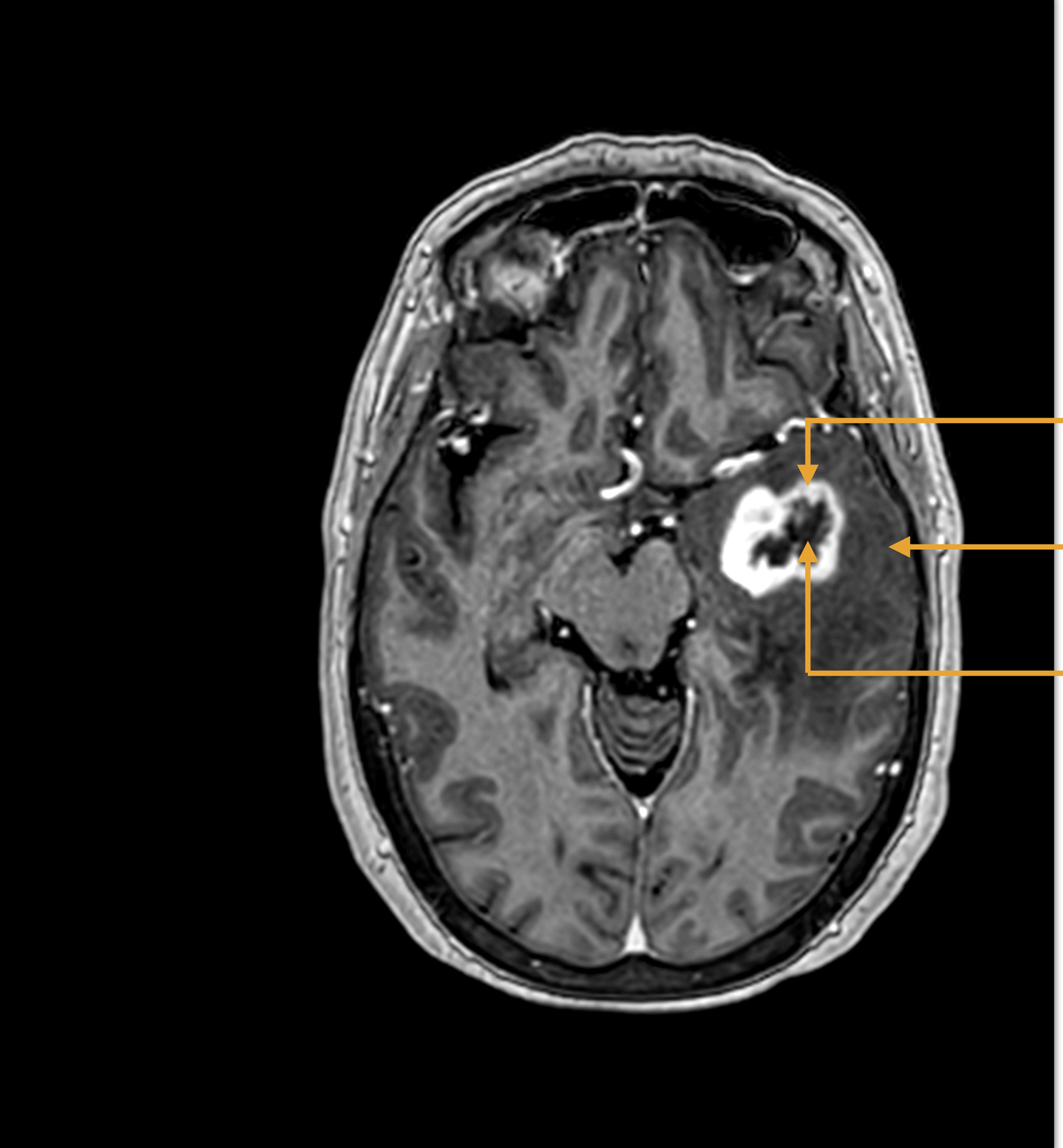
T1w con contraste pretratamiento

Tumor

Necrosis

Tejido sano

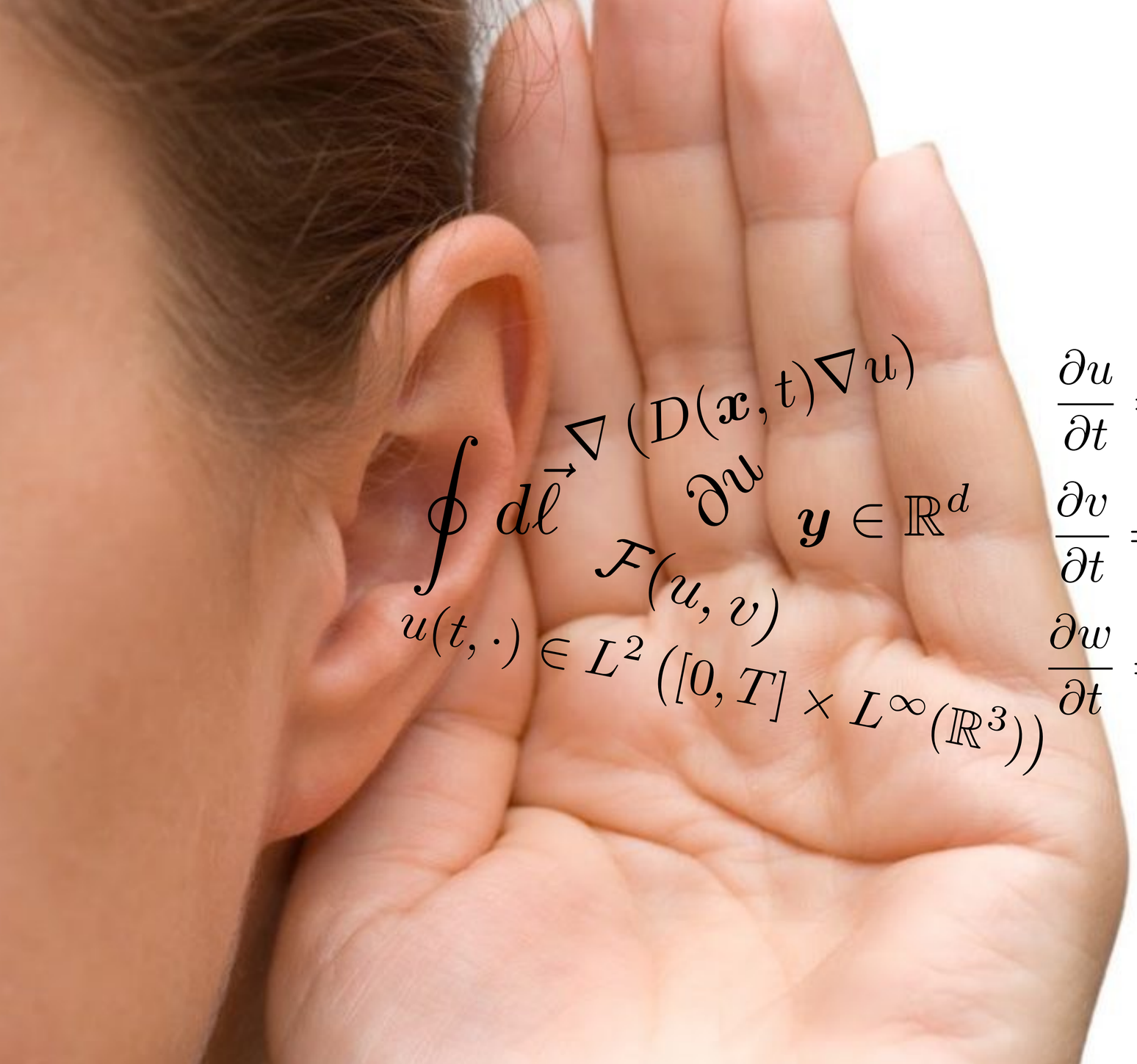




$$\frac{\partial u}{\partial t} = D\triangle u - \alpha u + \rho(u_* - u - v - w)u$$

$$\frac{\partial v}{\partial t} = -\mathcal{F}(u, v)$$

$$\frac{\partial w}{\partial t} = \alpha u + \mathcal{F}(u, v)$$



$$\oint d\vec{\ell} \nabla \left(\mathrm{D}(\boldsymbol{x}, \mathrm{t}) \nabla u \right)$$

$$\frac{\partial u}{\partial t} = D \triangle u - \alpha u + \rho(u_* - u - v - w)u$$

$$\frac{\partial v}{\partial t} = -\mathcal{F}(u, v)$$

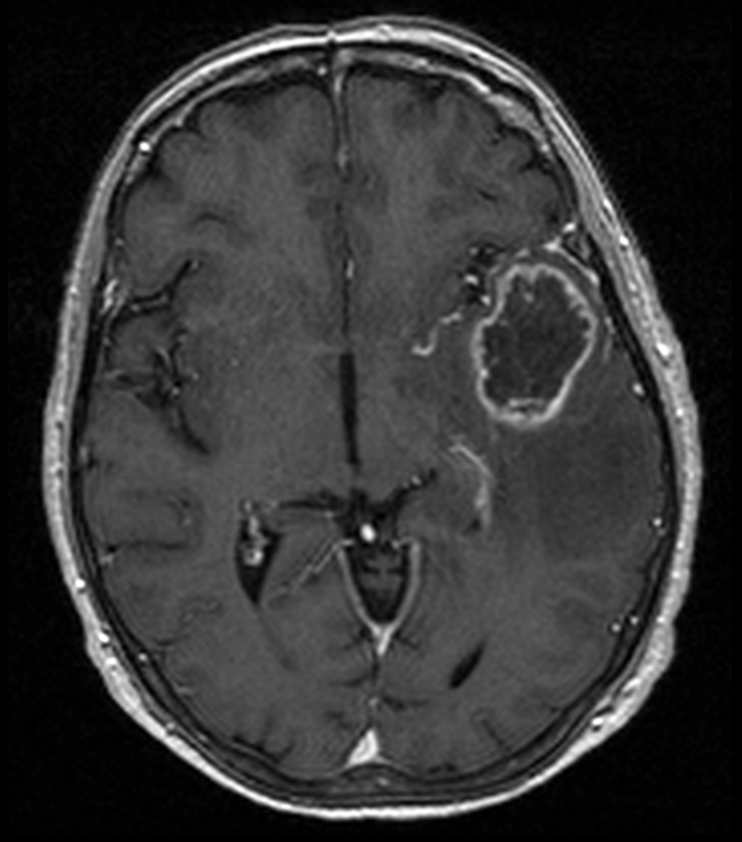
$$\frac{\partial w}{\partial t} = \alpha u + \mathcal{F}(u, v)$$

$$\mathcal{F}(u, v)$$

$$\boldsymbol{y} \in \mathbb{R}^d$$

$$u(t, \cdot) \in L^2\left([0, T] \times L^\infty(\mathbb{R}^3)\right)$$

Hipótesis basada en el modelo matemático



Estrecho
‘Lento’

Ancho
‘Rápido’

European Radiology (2019) 29:1968–1977
https://doi.org/10.1007/s00330-018-5758-7

HEAD AND NECK

Morphological MRI-based features provide pretreatment survival prediction in glioblastoma

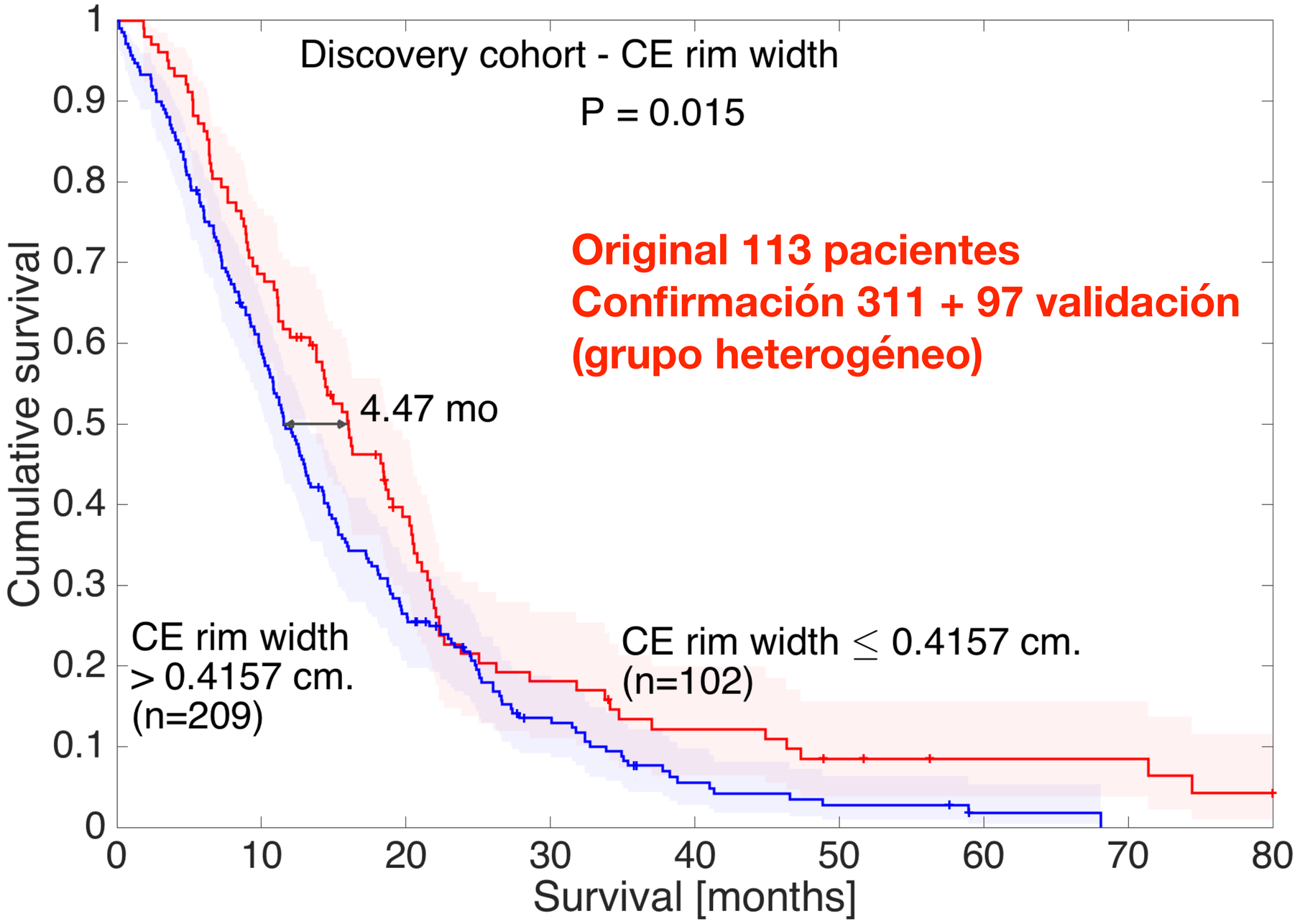
Julián Pérez-Beteta[1] · David Molina-García[1] · Alicia Martínez-González[1] · Araceli Henares-Molina[1] · Mariano Amo-Salas[1] · Belén Luque[1] · Elena Arregui[2] · Manuel Calvo[2] · José M. Borrás[3] · Juan Martino[4] · Carlos Velásquez[4] · Bárbara Meléndez-Asensio[5] · Ángel Rodríguez de Lope[6] · Raquel Moreno[7] · Juan A. Barcia[8] · Beatriz Asenjo[9] · Manuel Benavides[10] · Ismael Herruzo[11] · Pedro C. Lara[12] · Raquel Cabrera[12] · David Albillo[13] · Miguel Navarro[14] · Luis A. Pérez-Romasanta[15] · Antonio Revert[16] · Estanislao Arana[17] · Víctor M. Pérez-García[1]

Received: 23 May 2018 / Revised: 19 August 2018 / Accepted: 12 September 2018 / Published online: 15 October 2018

Abstract

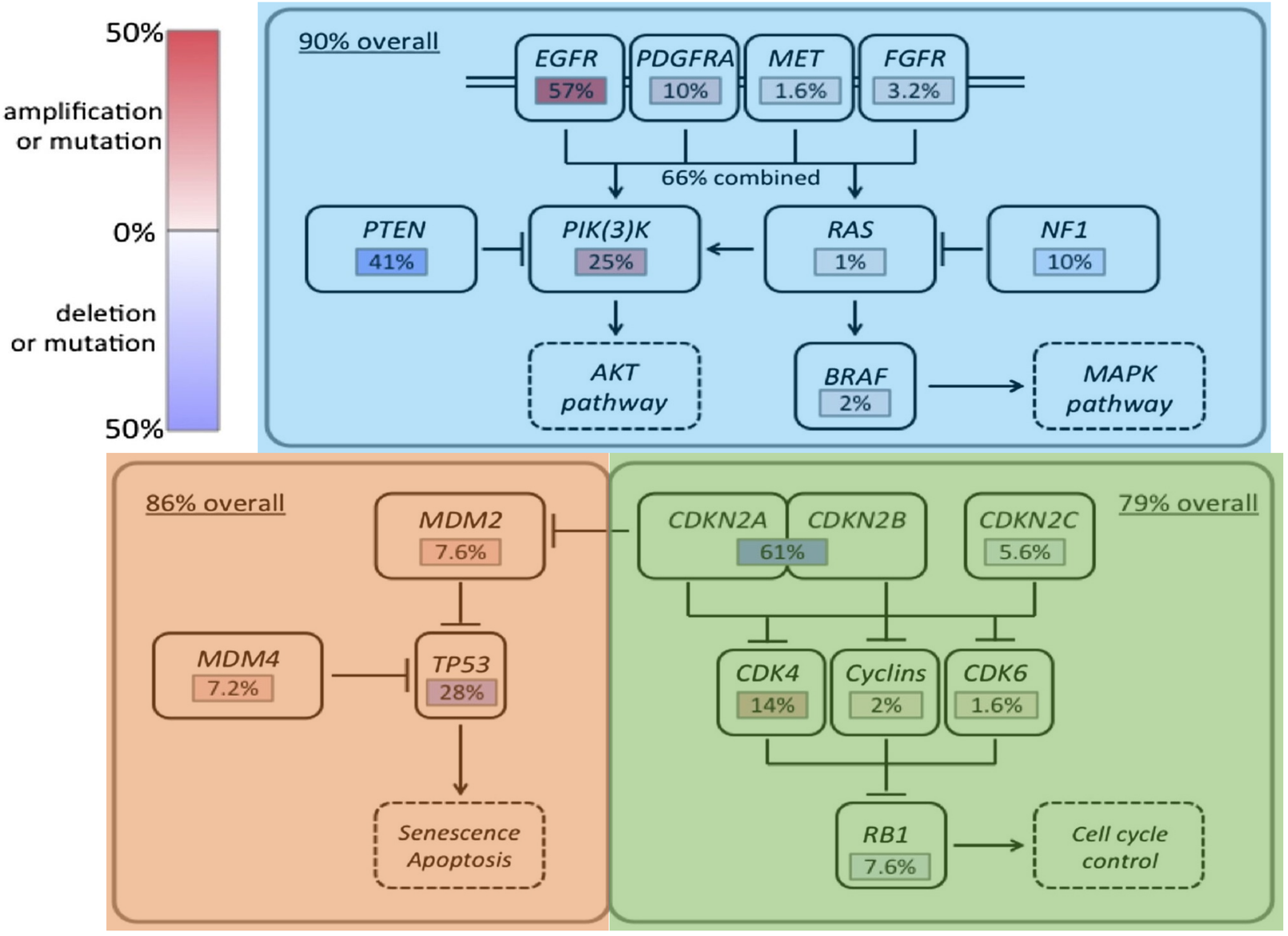
Objectives We wished to determine whether tumor morphology descriptors obtained from pretreatment magnetic resonance images and clinical variables could predict survival for glioblastoma patients.

Methods A cohort of 404 glioblastoma patients (311 discoveries and 93 validations) was used in the study. Pretreatment


Discovery cohort - CE rim width
P = 0.015
Original 113 pacientes
Confirmación 311 + 97 validación
(grupo heterogéneo)
4.47 mo
CE rim width
> 0.4157 cm.
(n=209)
CE rim width ≤ 0.4157 cm.
(n=102)
Cumulative survival
Survival [months]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80

El tamaño
sólo importa en los biopsiados

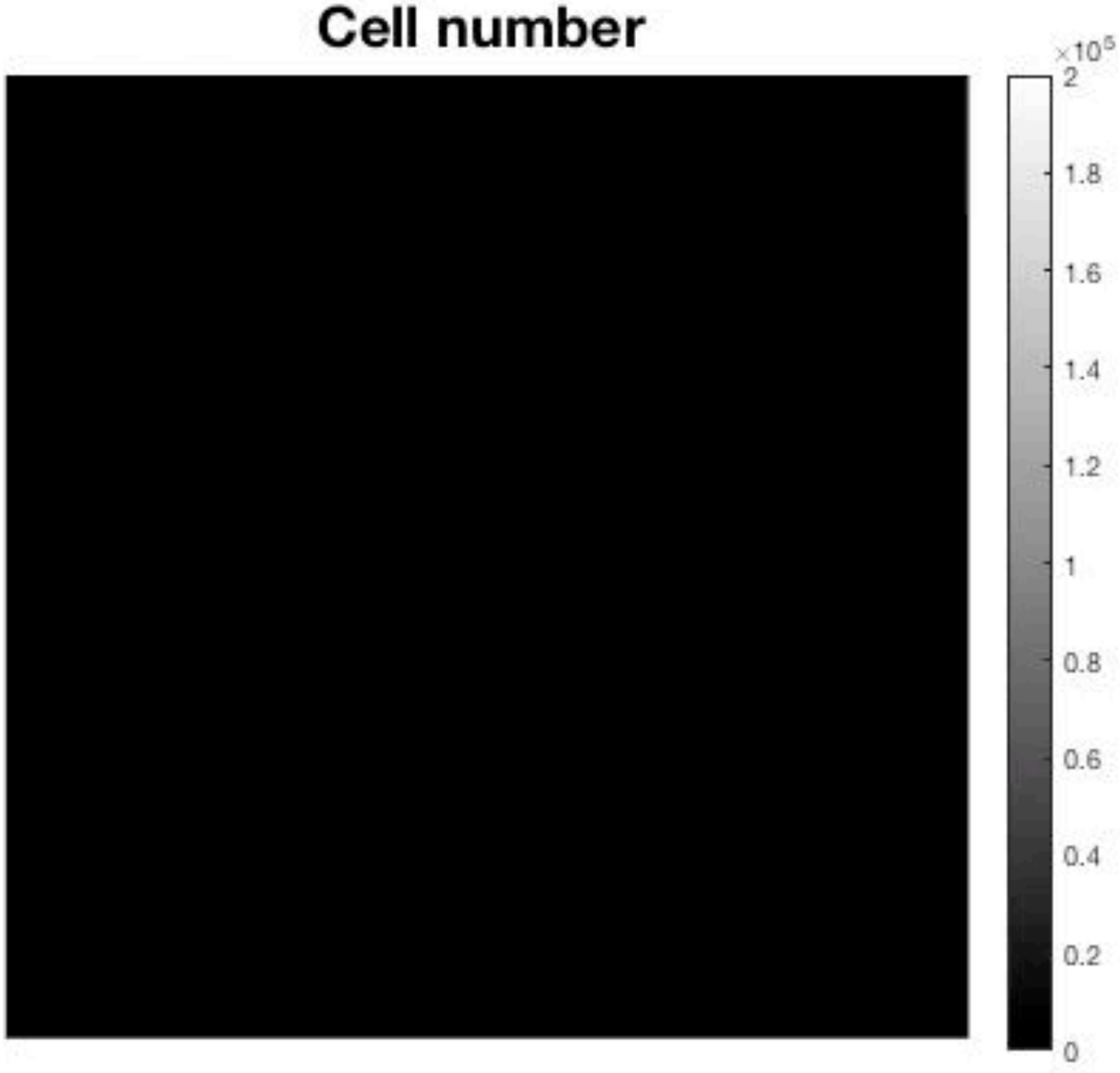
Volumen · Volumen captación · Necrosis · Diámetro · Superficie



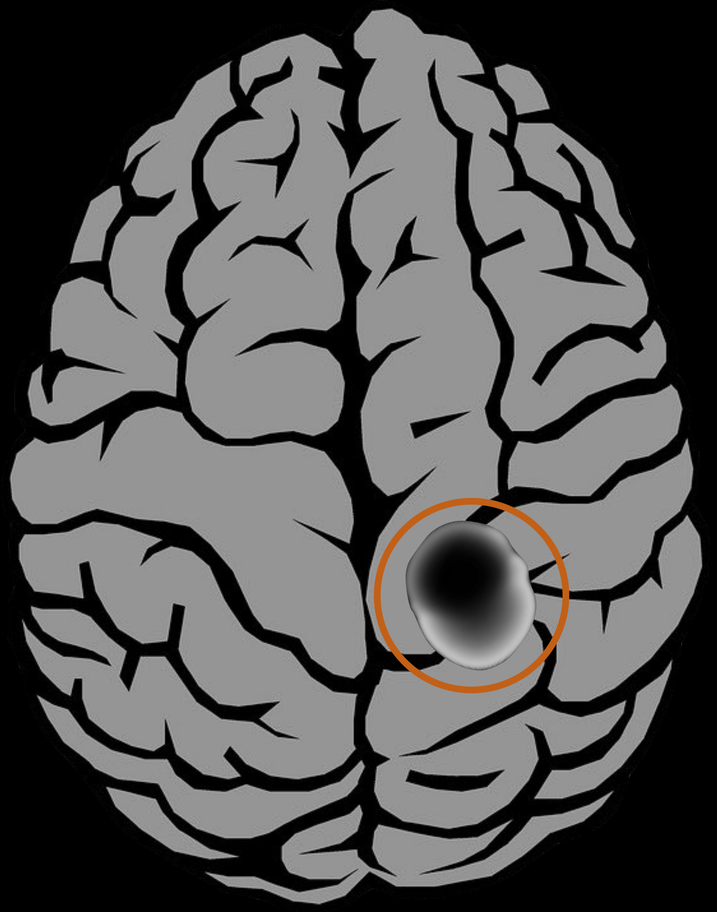
Brennan, C. W. et al. (2013) The somatic genomic landscape of glioblastoma. Cell 155(2), 462–477.

Time = 1 days

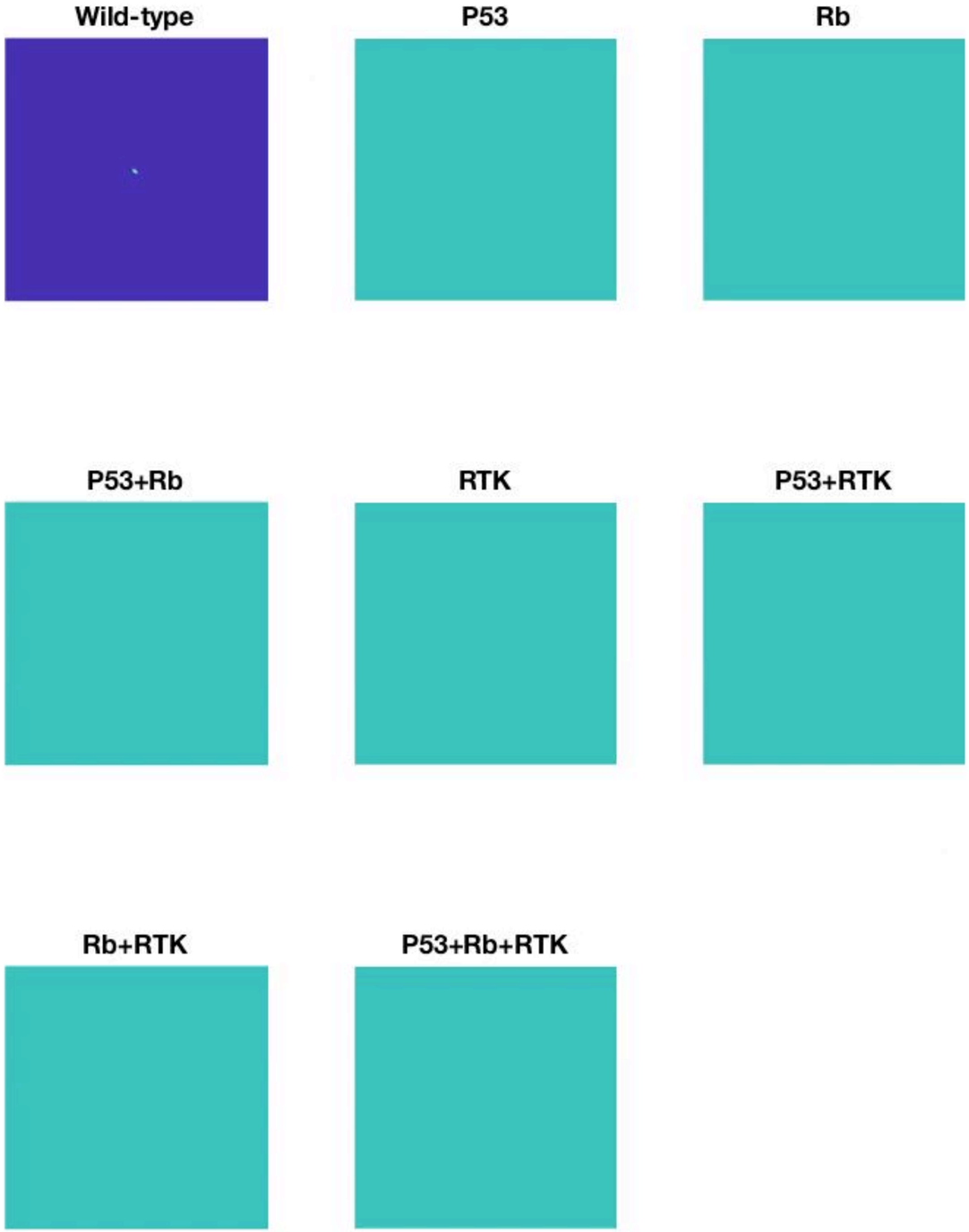
Volume = 0.004 cm^3


Cell number
×10^5
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0

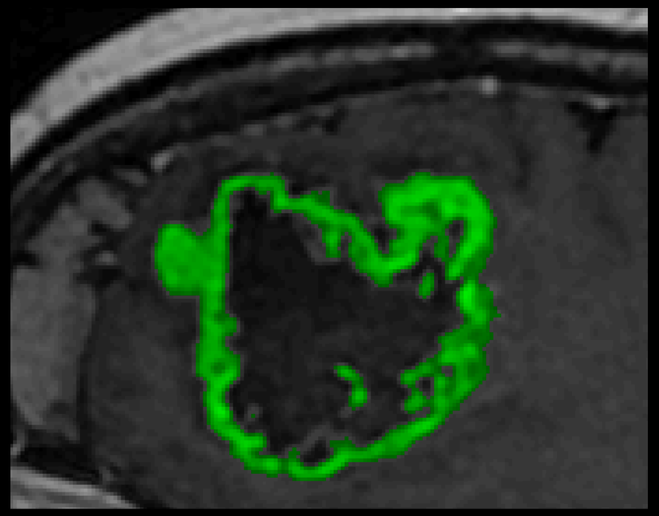
Real tumor



Simulation

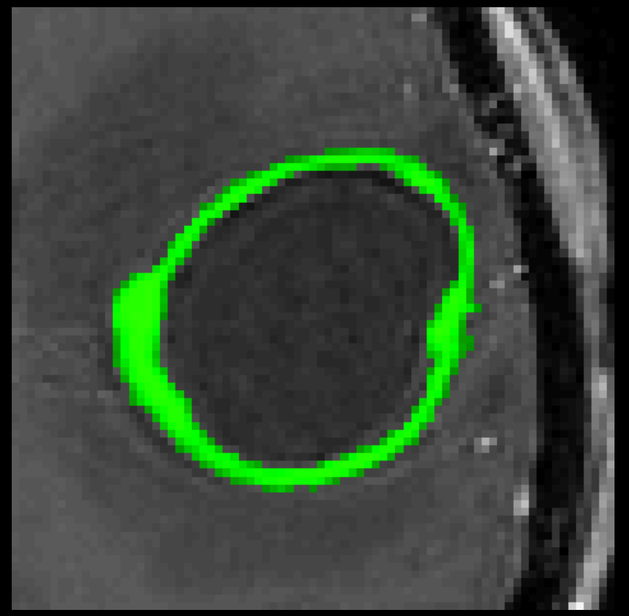

Wild-type
P53
Rb
P53+Rb
RTK
P53+RTK
Rb+RTK
P53+Rb+RTK

Otra hipótesis basada en modelos matemáticos



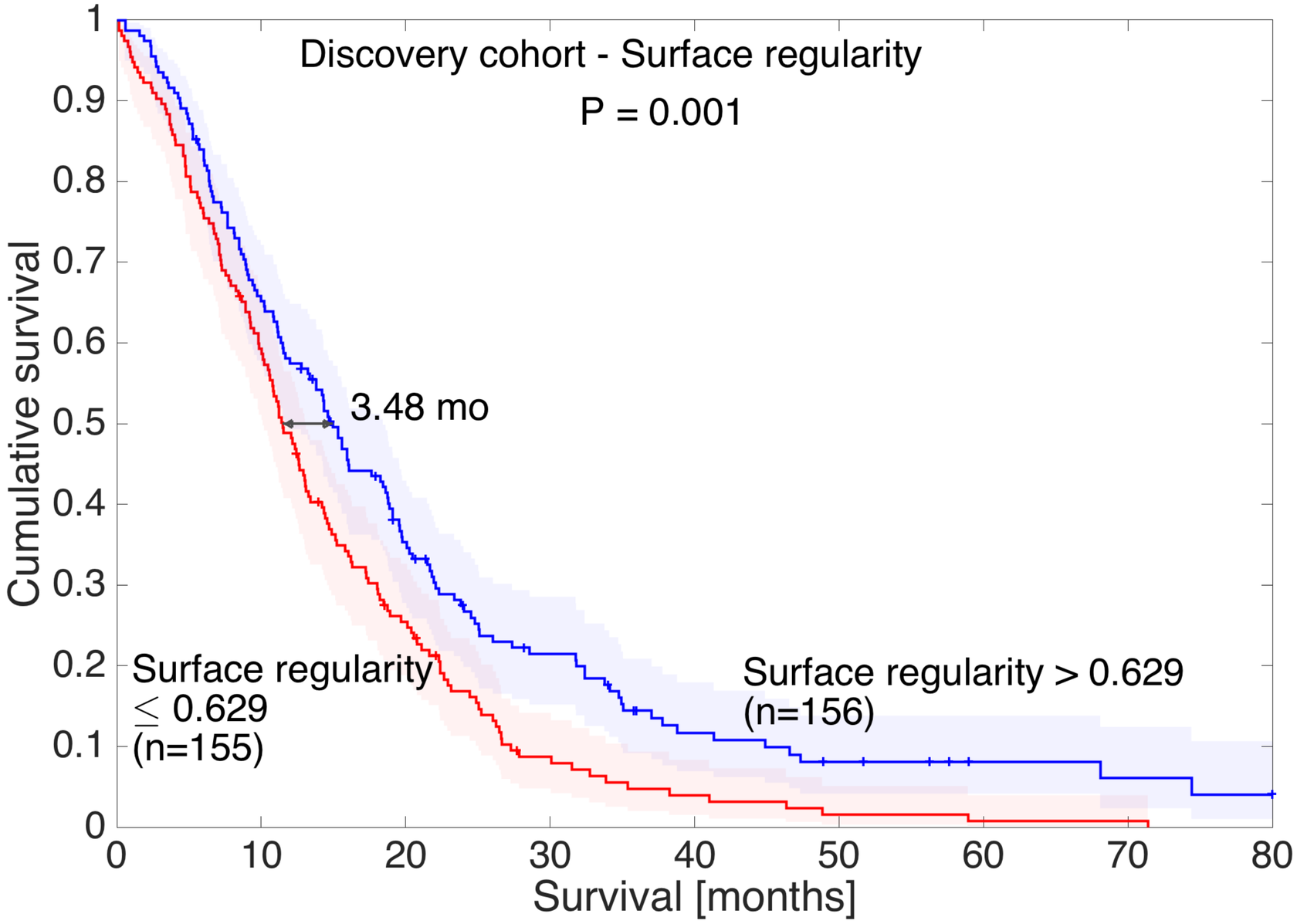
Irregular

‘Infiltrativo-Agresivo’



Regular

‘Nodular’

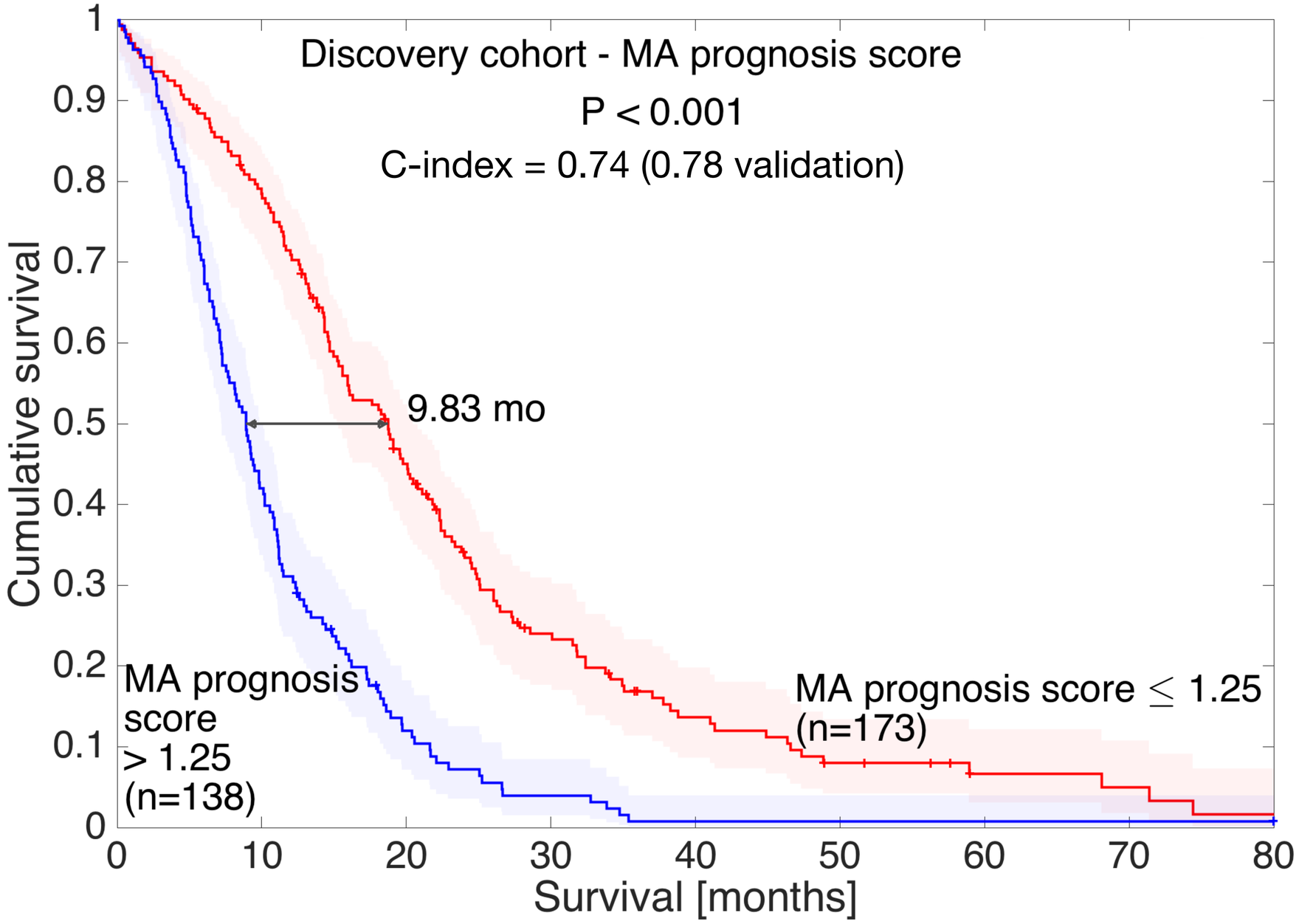

Discovery cohort - Surface regularity
P = 0.001
Cumulative survival
Survival [months]
3.48 mo
Surface regularity ≤ 0.629 (n=155)
Surface regularity > 0.629 (n=156)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80

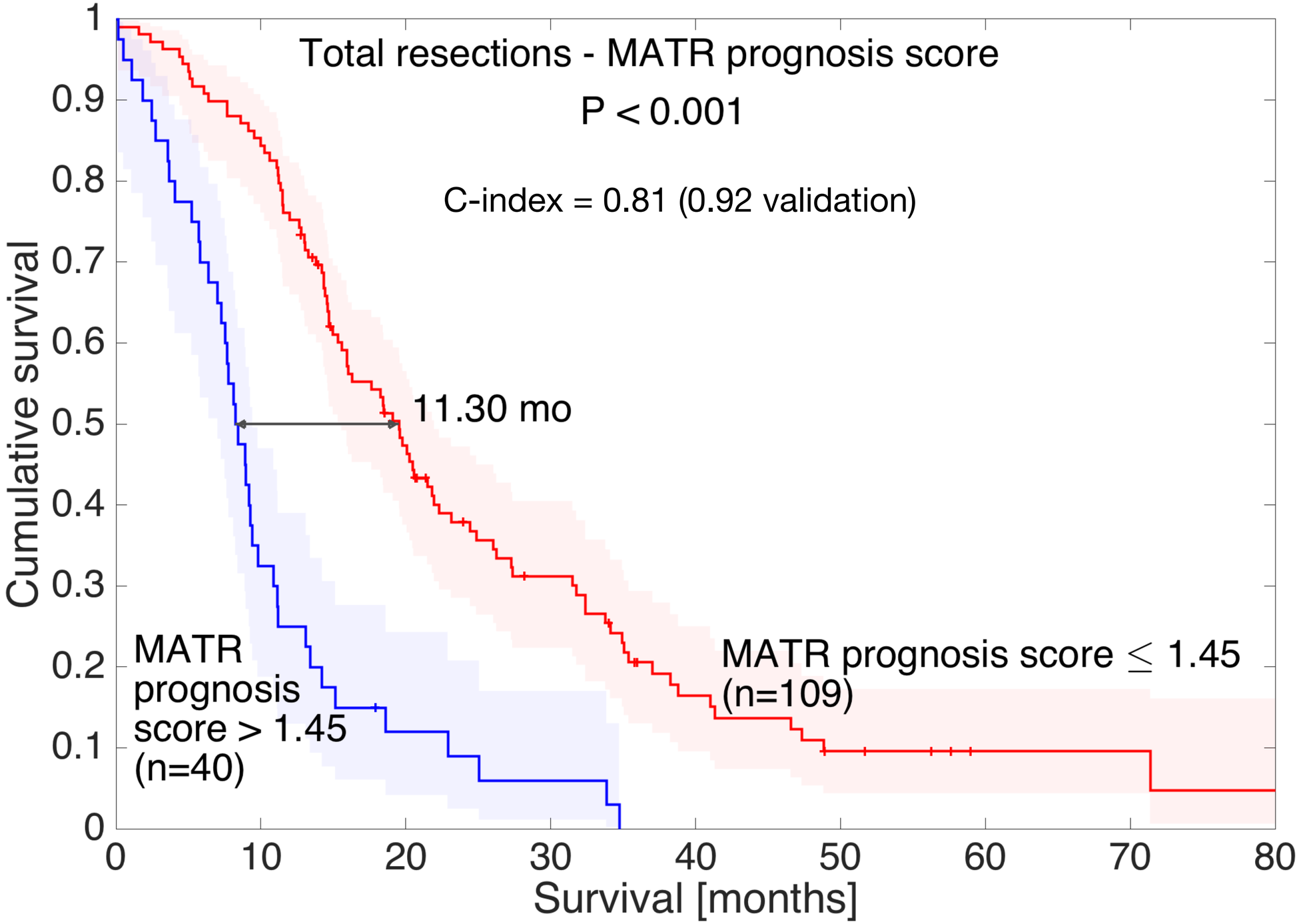
Edad

Ahora, ¡todos juntos!

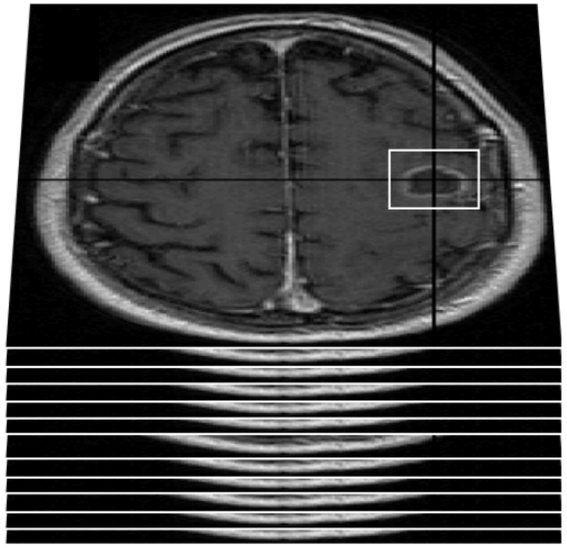
Anchura
Captación

Regularidad
Superficie


Discovery cohort - MA prognosis score
P < 0.001
C-index = 0.74 (0.78 validation)
9.83 mo
MA prognosis score > 1.25 (n=138)
MA prognosis score ≤ 1.25 (n=173)
Cumulative survival
Survival [months]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80


Total resections - MATR prognosis score
P < 0.001
C-index = 0.81 (0.92 validation)
11.30 mo
MATR prognosis score ≤ 1.45 (n=109)
MATR prognosis score > 1.45 (n=40)
Cumulative survival
Survival [months]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80

Edad
Ancho anillo
Regularidad
Cirugía completa

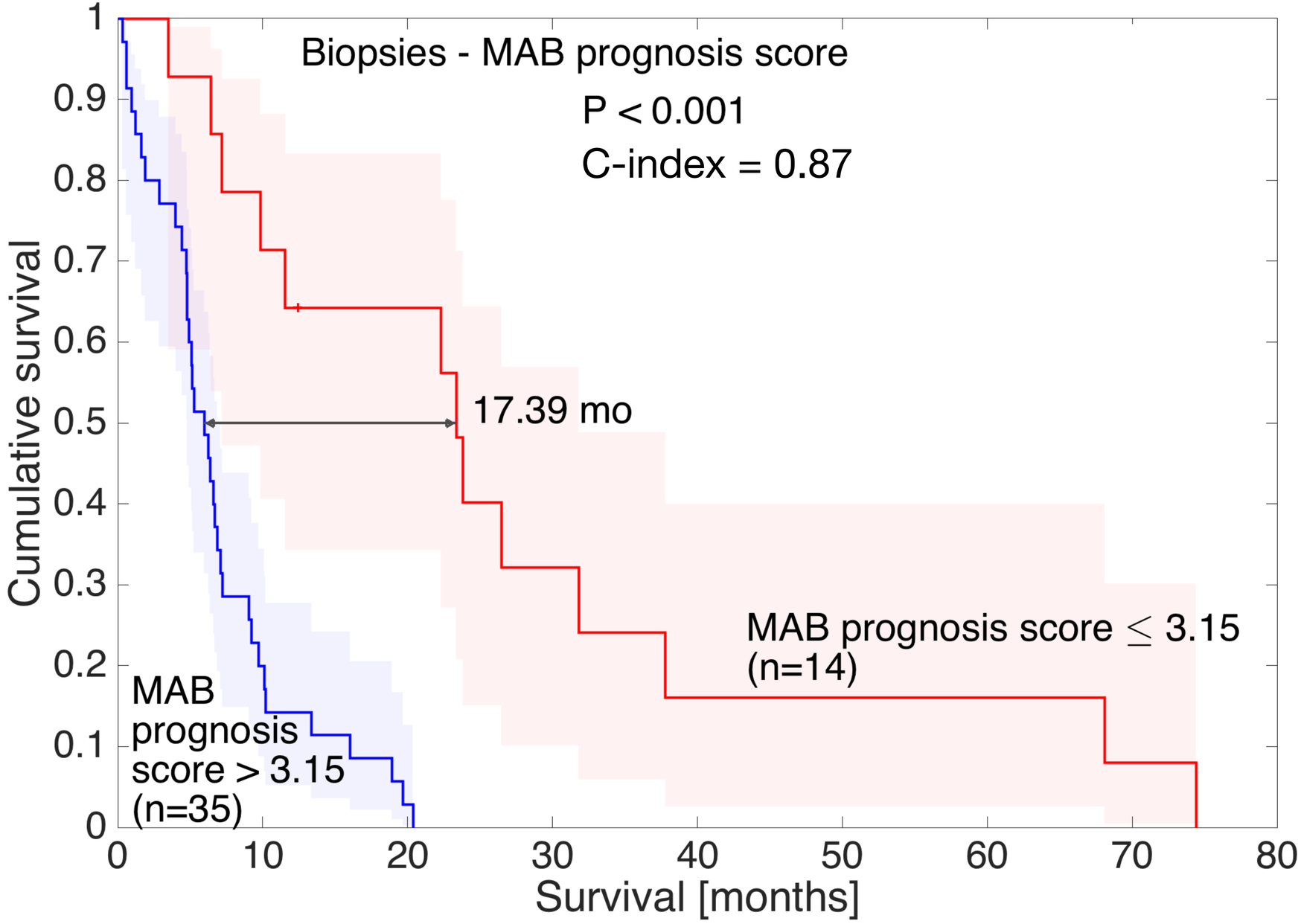


Riesgo estándar

20 meses

Riesgo alto

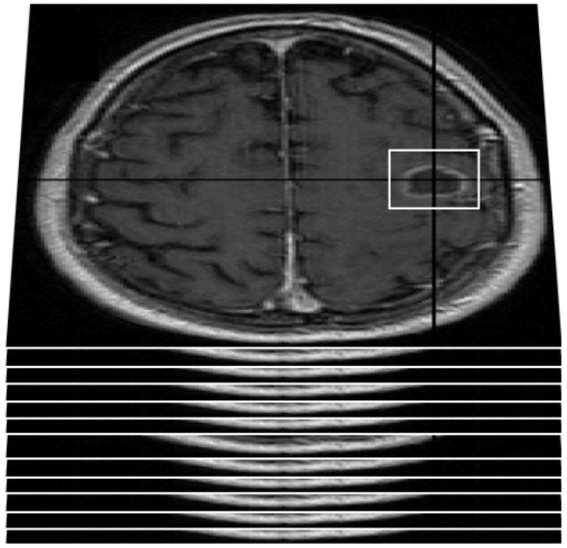
9 meses


Biopsies - MAB prognosis score
P < 0.001
C-index = 0.87
17.39 mo
MAB prognosis score ≤ 3.15
(n=14)
MAB
prognosis
score > 3.15
(n=35)
Cumulative survival
Survival [months]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80

Edad

Volumen de captación

Biopsia



Riesgo bajo

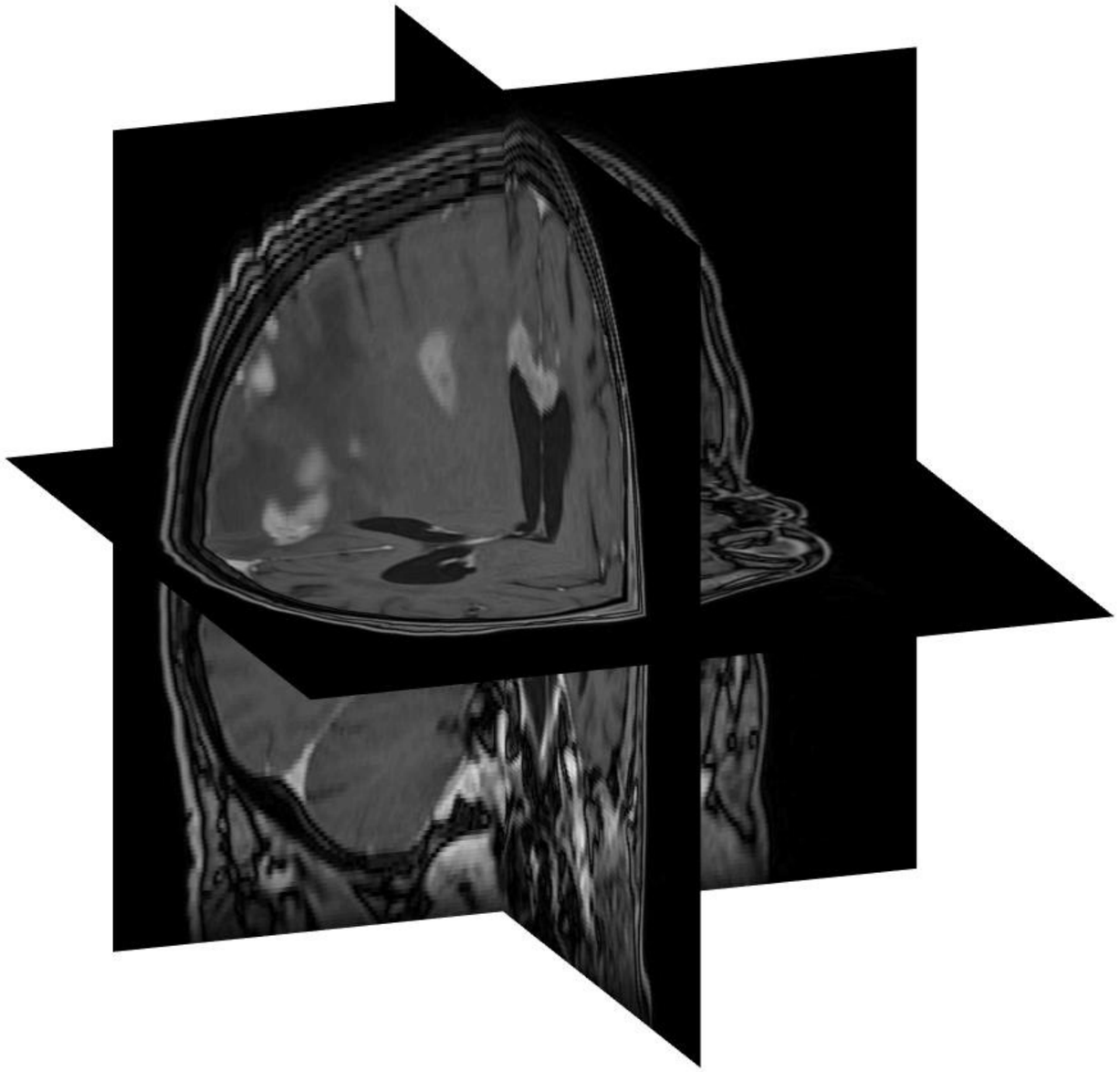
25 meses?

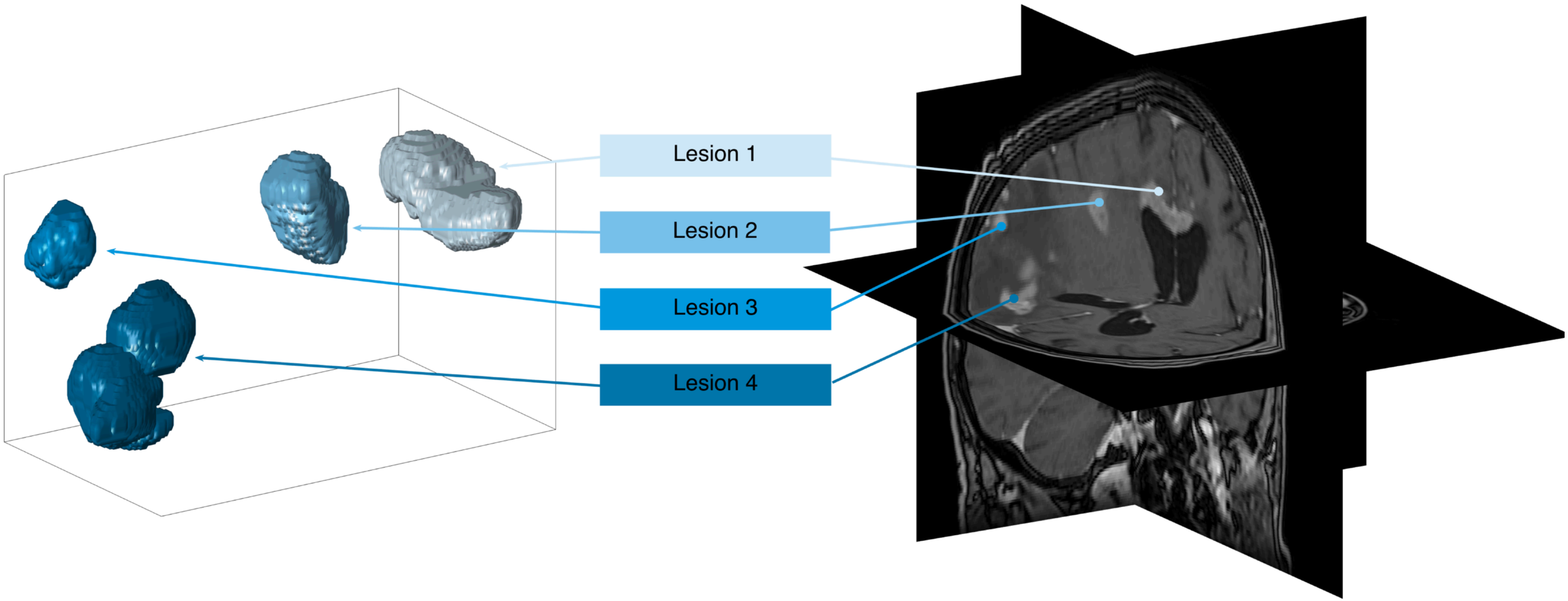
Riesgo alto

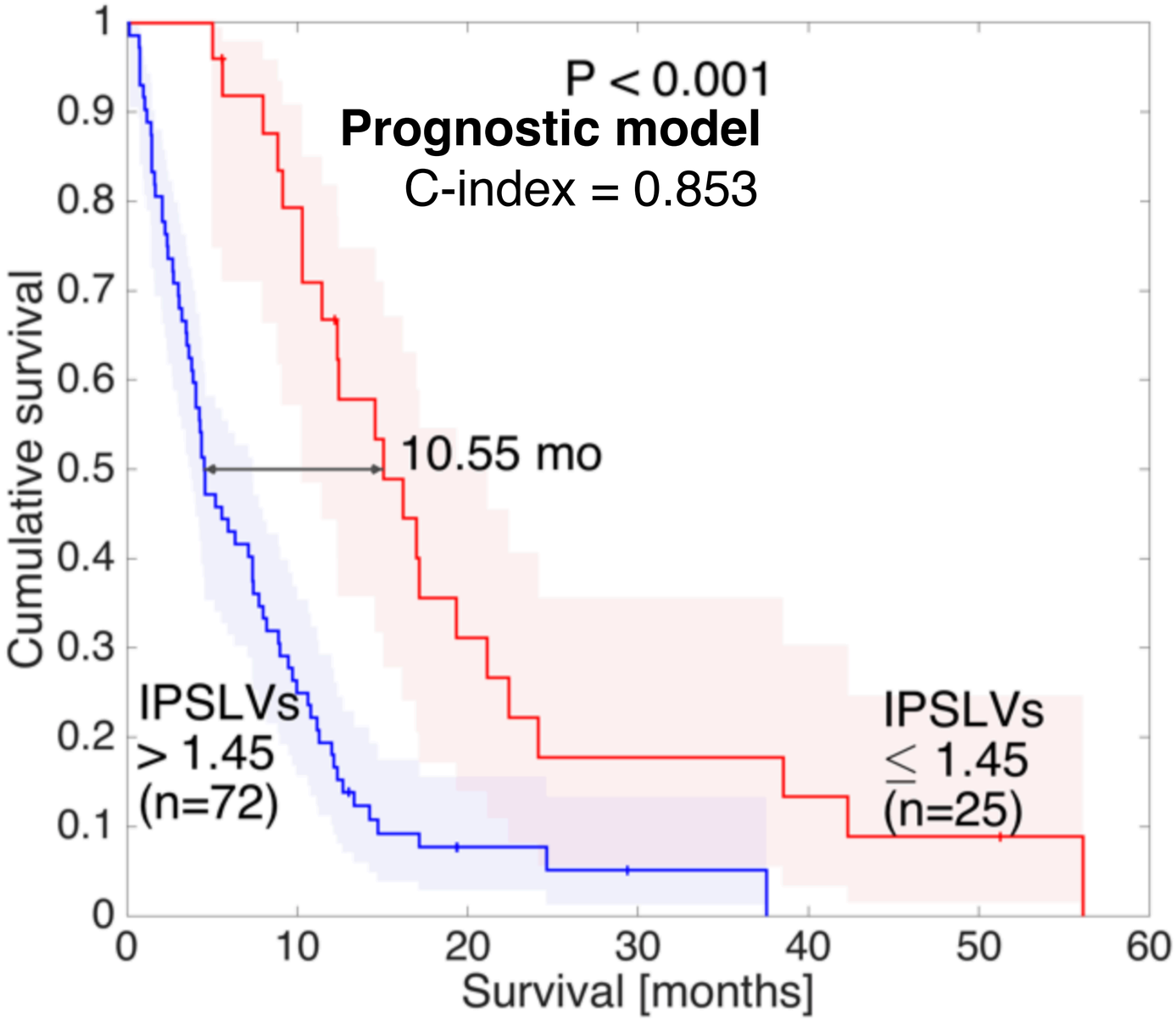
7 meses

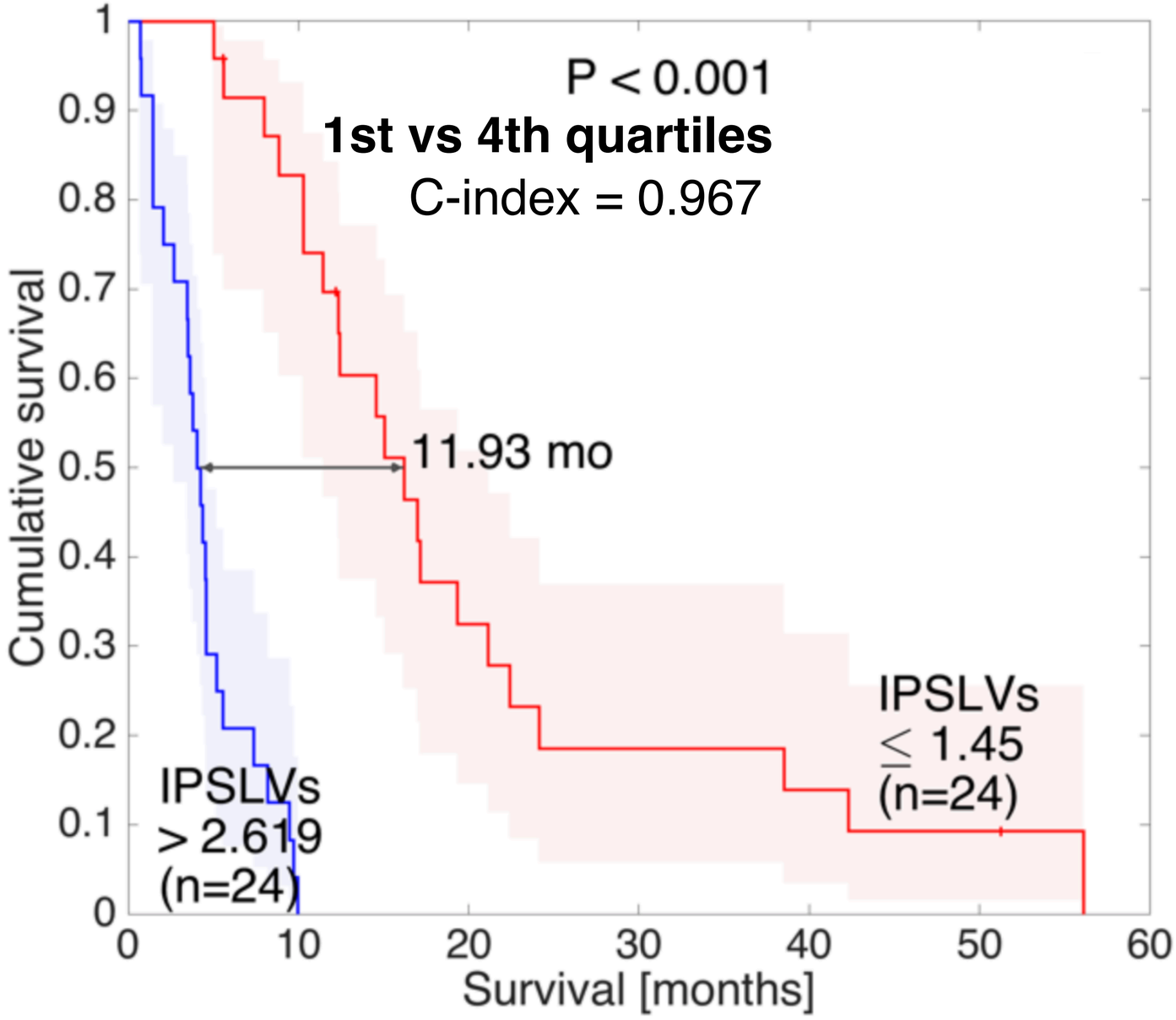
Glioblastoma multifocal

Supervivencia 8 meses



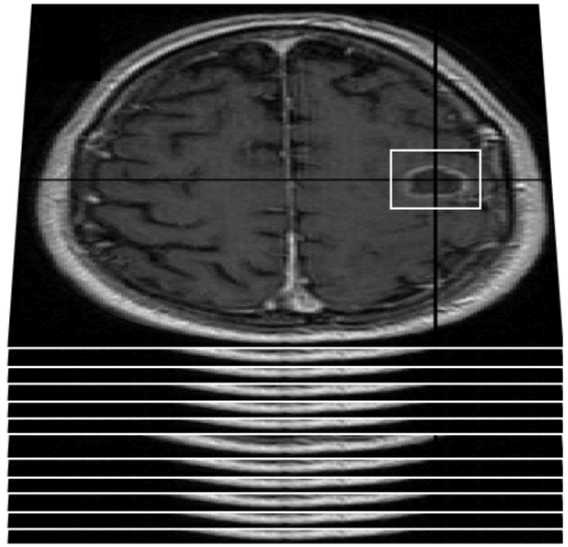

Lesion 1
Lesion 2
Lesion 3
Lesion 4


P < 0.001
Prognostic model
C-index = 0.853
10.55 mo
IPSLVs
> 1.45
(n=72)
IPSLVs
≤ 1.45
(n=25)
Cumulative survival
Survival [months]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60


P < 0.001
1st vs 4th quartiles
C-index = 0.967
11.93 mo
IPSLVs
> 2.619
(n=24)
IPSLVs
≤ 1.45
(n=24)
Cumulative survival
Survival [months]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60

Age
Rim width
Surgery

8 months



Standard prognosis

15 months

High risk

4 months

Morphologic Features on MR Imaging Classify Multifocal Glioblastomas in Different Prognostic Groups

J. Pérez-Beteta, D. Molina-García, M. Villena, M.J. Rodríguez, C. Velásquez, J. Martino, B. Meléndez-Asensio, Á. Rodríguez de Lope, R. Morcillo, J.M. Sepúlveda, A. Hernández-Laín, A. Ramos, J.A. Barcia, P.C. Lara, D. Albillo, A. Revert, E. Arana, and V.M. Pérez-García

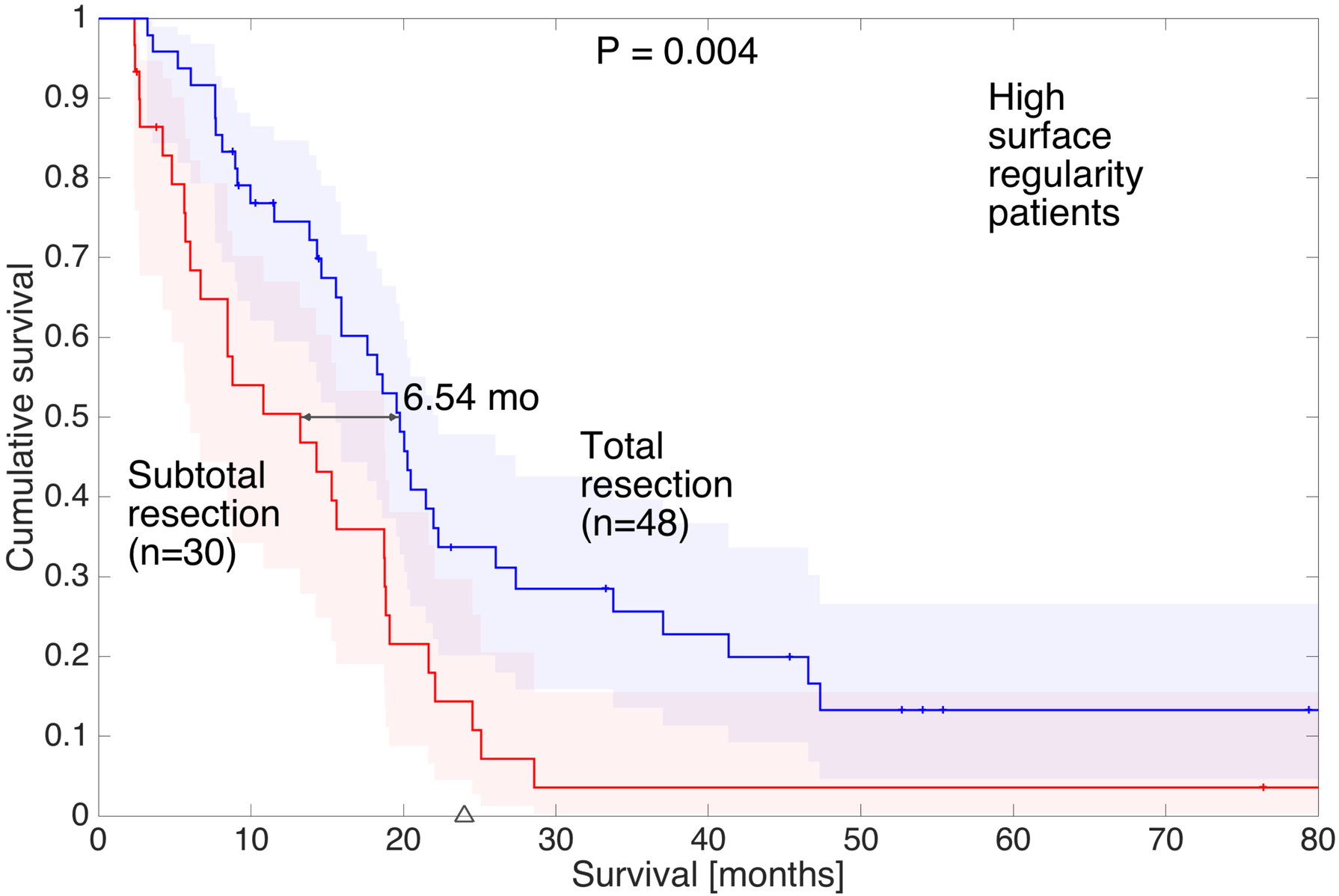
ABSTRACT

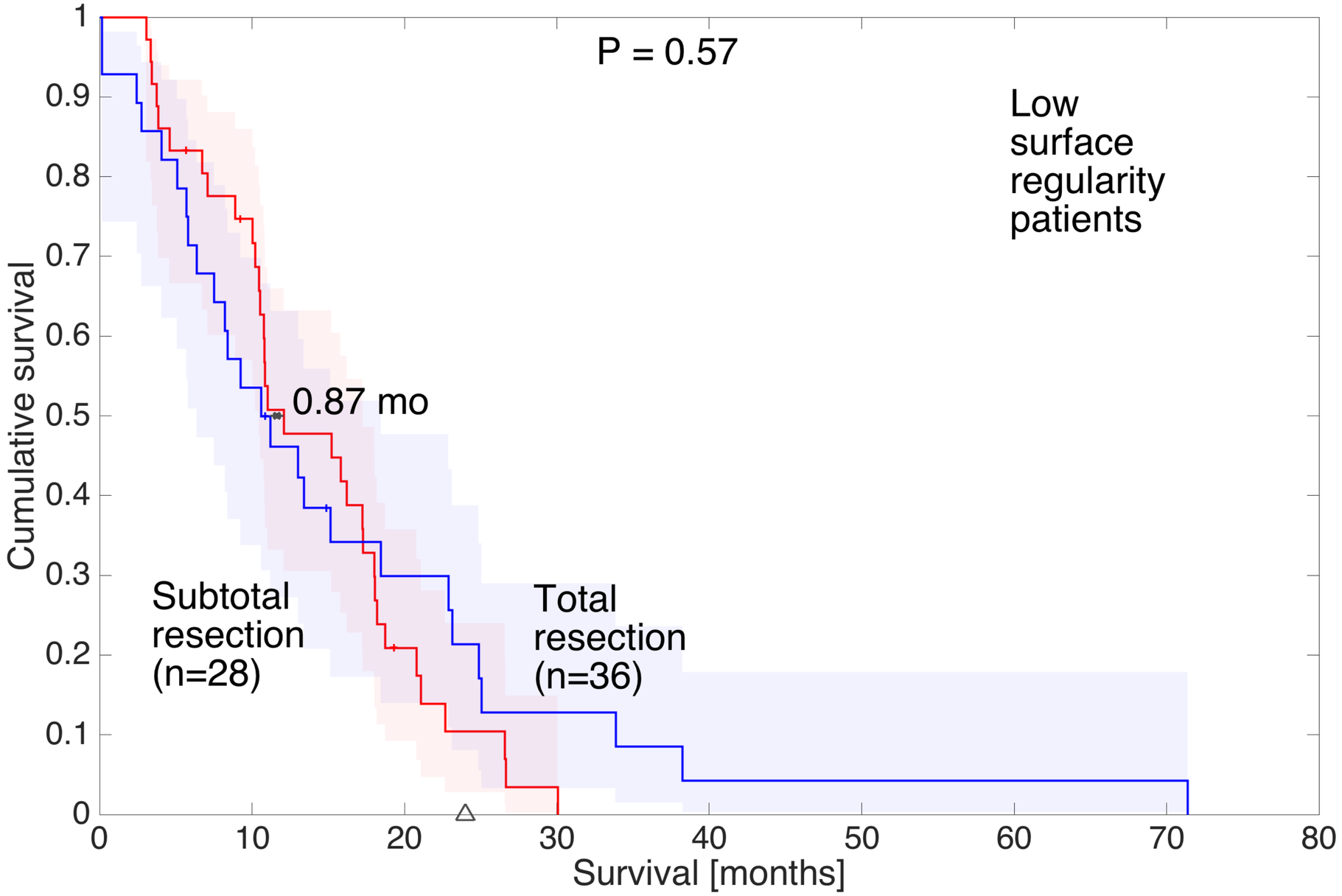
BACKGROUND AND PURPOSE: Multifocal glioblastomas (ie, glioblastomas with multiple foci, unconnected in postcontrast pretreatment T1-weighted images) represent a challenge in clinical practice due to their poor prognosis. We wished to obtain imaging biomarkers with prognostic value that have not been found previously.

MATERIALS AND METHODS: A retrospective review of 1155 patients with glioblastomas from 10 local institutions during 2006–2017 provided 97 patients satisfying the inclusion criteria of the study and classified as having multifocal glioblastomas. Tumors were segmented and morphologic features were computed using different methodologies: 1) measured on the largest focus, 2) aggregating the different foci as a whole, and 3) recording the extreme value obtained for each focus. Kaplan-Meier, Cox proportional hazards, correlations, and


$$\frac{\partial u}{\partial t} = D\triangle u - \alpha u + \rho(u_* - u - v - w)u$$
$$\frac{\partial v}{\partial t} = -\mathcal{F}(u, v)$$
$$\frac{\partial w}{\partial t} = \alpha u + \mathcal{F}(u, v)$$

Predicción de respuesta a cirugía


P = 0.004
High surface regularity patients
6.54 mo
Total resection (n=48)
Subtotal resection (n=30)
Cumulative survival
Survival [months]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80


P = 0.57
Low surface regularity patients
0.87 mo
Subtotal resection (n=28)
Total resection (n=36)
Cumulative survival
Survival [months]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80

No

¿Intentar cirugía (macroscópica) **completa?**

Sí

Tumor Surface Regularity at MR Imaging Predicts Survival and Response to Surgery in Patients with Glioblastoma

*Julián Pérez-Beteta, MSc** • *David Molina-García, PhD** • *José A. Ortiz-Alhambra, MSc* • *Antonio Fernández-Romero, MSc* • *Belén Luque, MSc* • *Elena Arregui, MD* • *Manuel Calvo, MD* • *José M. Borrás, MD* • *Bárbara Meléndez, PhD* • *Ángel Rodríguez de Lope, MD, PhD* • *Raquel Moreno de la Presa, MD* • *Lidia Iglesias Bayo, PhD* • *Juan A. Barcia, MD, PhD* • *Juan Martino, MD, PhD* • *Carlos Velásquez, MD* • *Beatriz Asenjo, MD, PhD* • *Manuel Benavides, MD, PhD* • *Ismael Herruzo, MD, PhD* • *Antonio Revert, MD, PhD* • *Estanislao Arana, MD, MHE, PhD* • *Víctor M. Pérez-García, PhD*

From the Mathematical Oncology Laboratory, Instituto de Matemática Aplicada a la Ciencia y la Ingeniería, Universidad de Castilla-La Mancha, Avenida de Camilo Jose Cela 3, 13071 Ciudad Real, Spain (J.P., D.M., J.A.O., A.F., B.L., V.M.P.); Departments of Radiology and Neurosurgery, Hospital General de Ciudad Real, Ciudad Real, Spain (E. Arregui, M.C., J.M.B.); Departments of Pathology, Radiology, and Neurosurgery, Hospital Virgen de la Salud, Toledo, Spain (B.M., Á.R.d.L., R.M.d.l.P.); Department of Neurosurgery, Hospital Clínico San Carlos, Madrid, Spain (L.I.B., J.A.B.); Department of Neurosurgery, Hospital Marqués de Valdecilla, Santander, Spain (J.M., C.V.); Department of Radiology, Complejo Hospitalario Universitario de Granada, Granada, Spain (B.A.); Department of Radiology, Hospital Carlos Haya, Málaga, Spain (M.B., I.H.); Department of Radiology, Hospital de Manises, Valencia, Spain (A.R.); and Department of Radiology, Instituto Valenciano de Oncología, Valencia, Spain (E. Arana). Received May 21, 2017; revision requested July 6; revision received December 27; final version accepted January 5, 2018. **Address correspondence to** V.M.P. (e-mail: *Victor.perezgarcia@uclm.es*).

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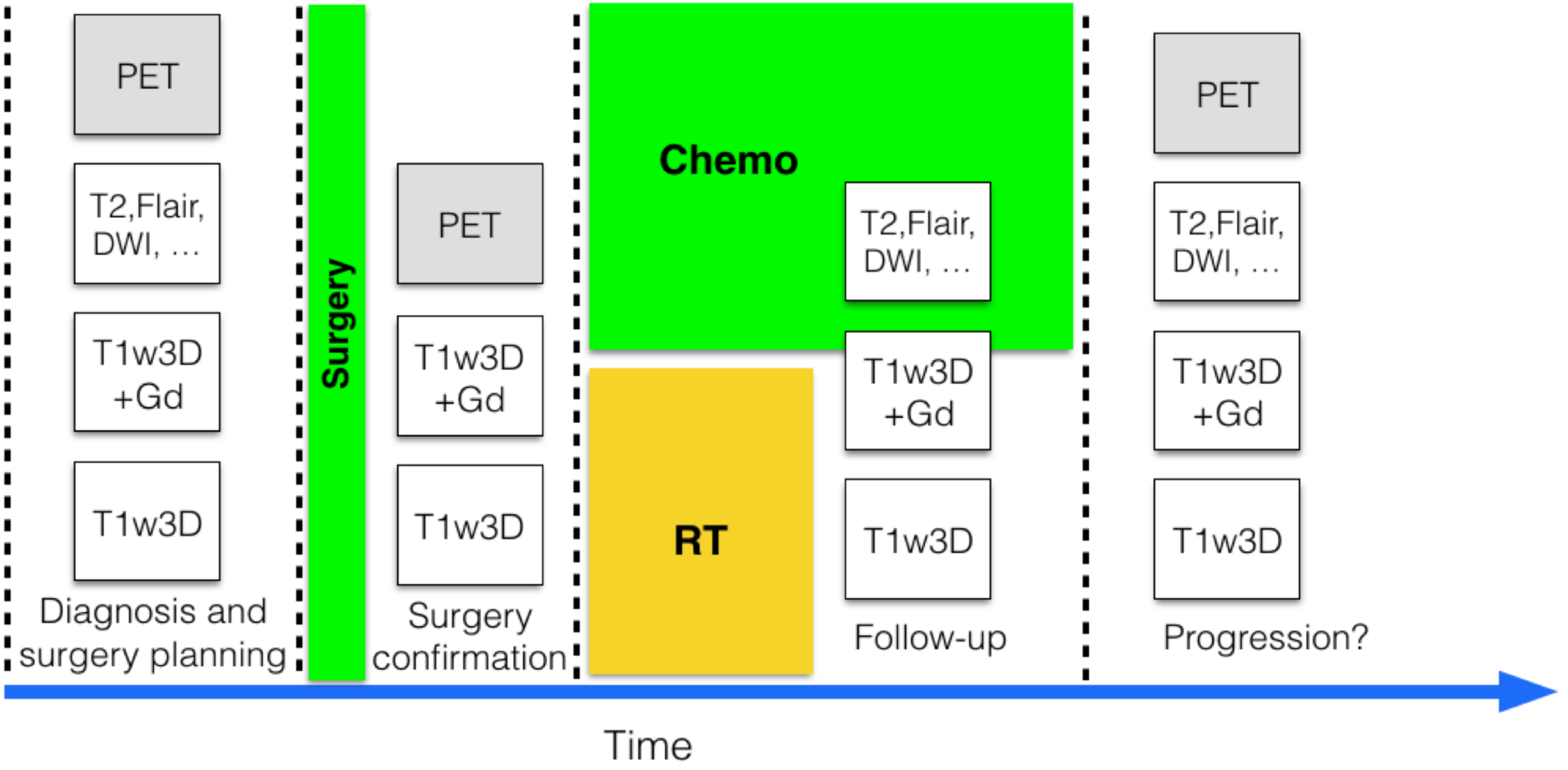
*J.P., and D.M. contributed equally to this work.

Conflicts of interest are listed at the end of this article.

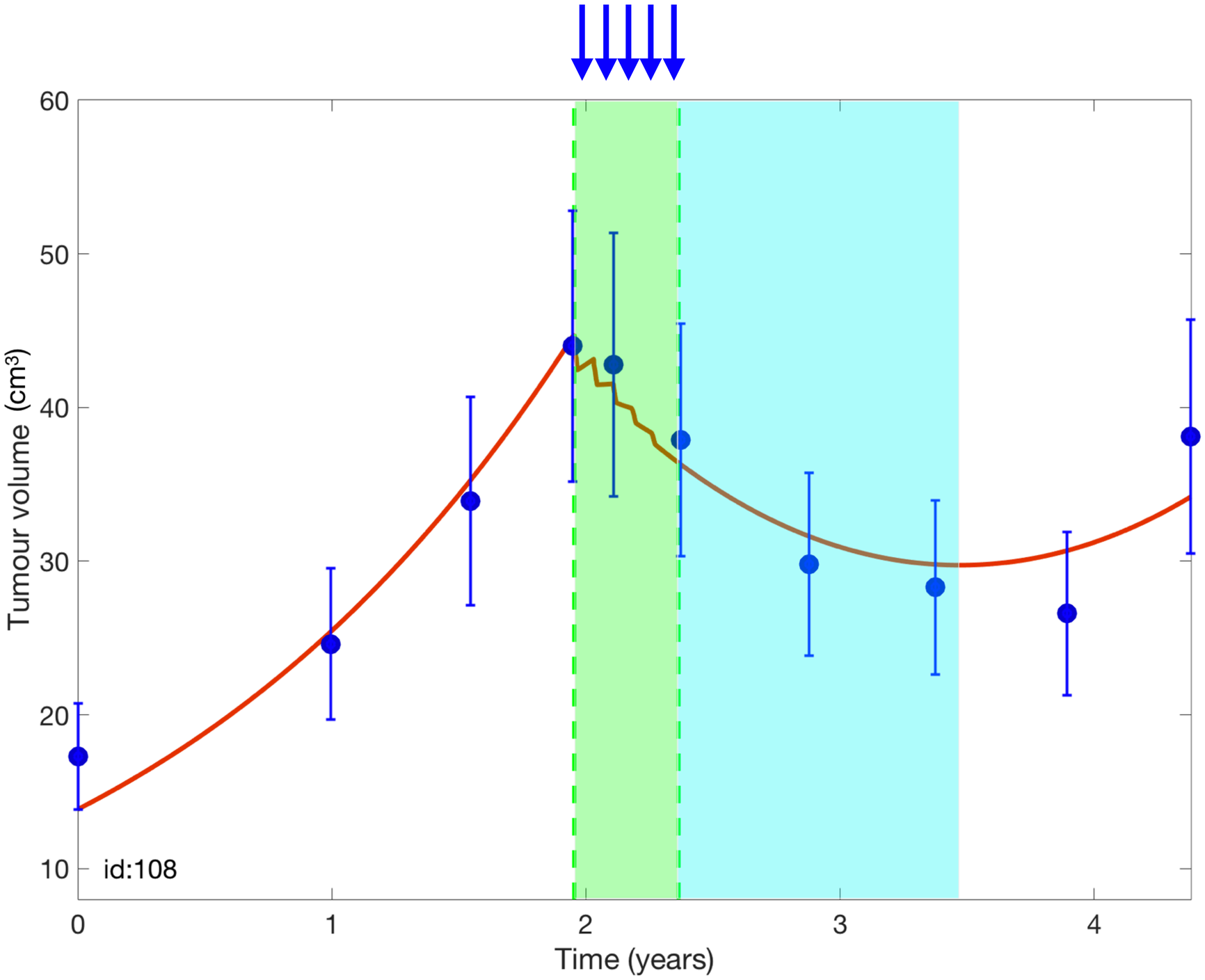
Radiology 2018; 288:218–225 • https://doi.org/10.1148/radiol.2018171051 • Content codes: MR NR

T1+Gd
pretratamiento
GBM

“Therapy optimization in glioblastoma: An integrative human-data based approach using mathematical models”
(James S. Mc. Donnell Foundation, USA)



Oligodendroglioma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Tumour volume (cm³)
id:108
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Time (years)


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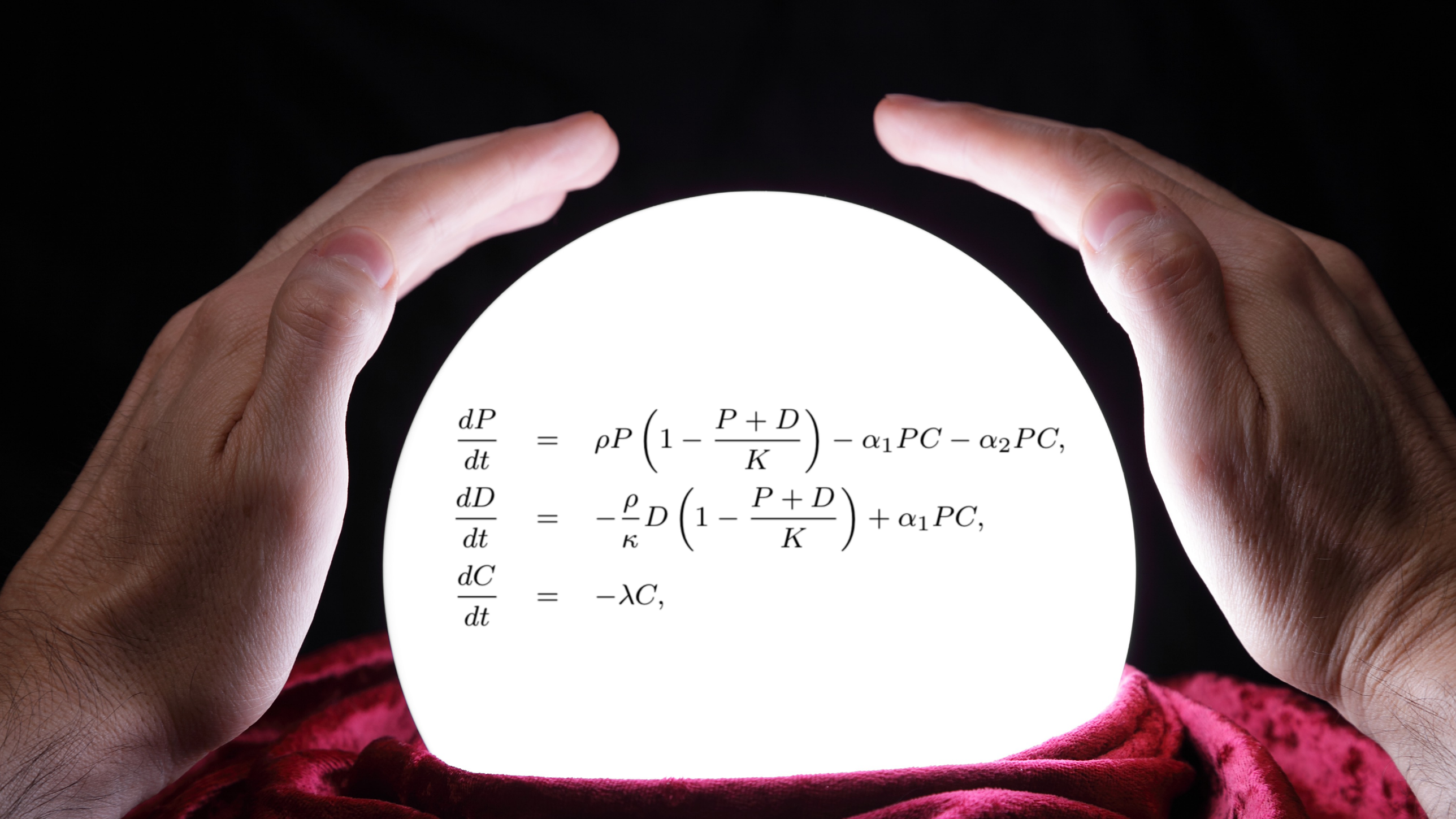
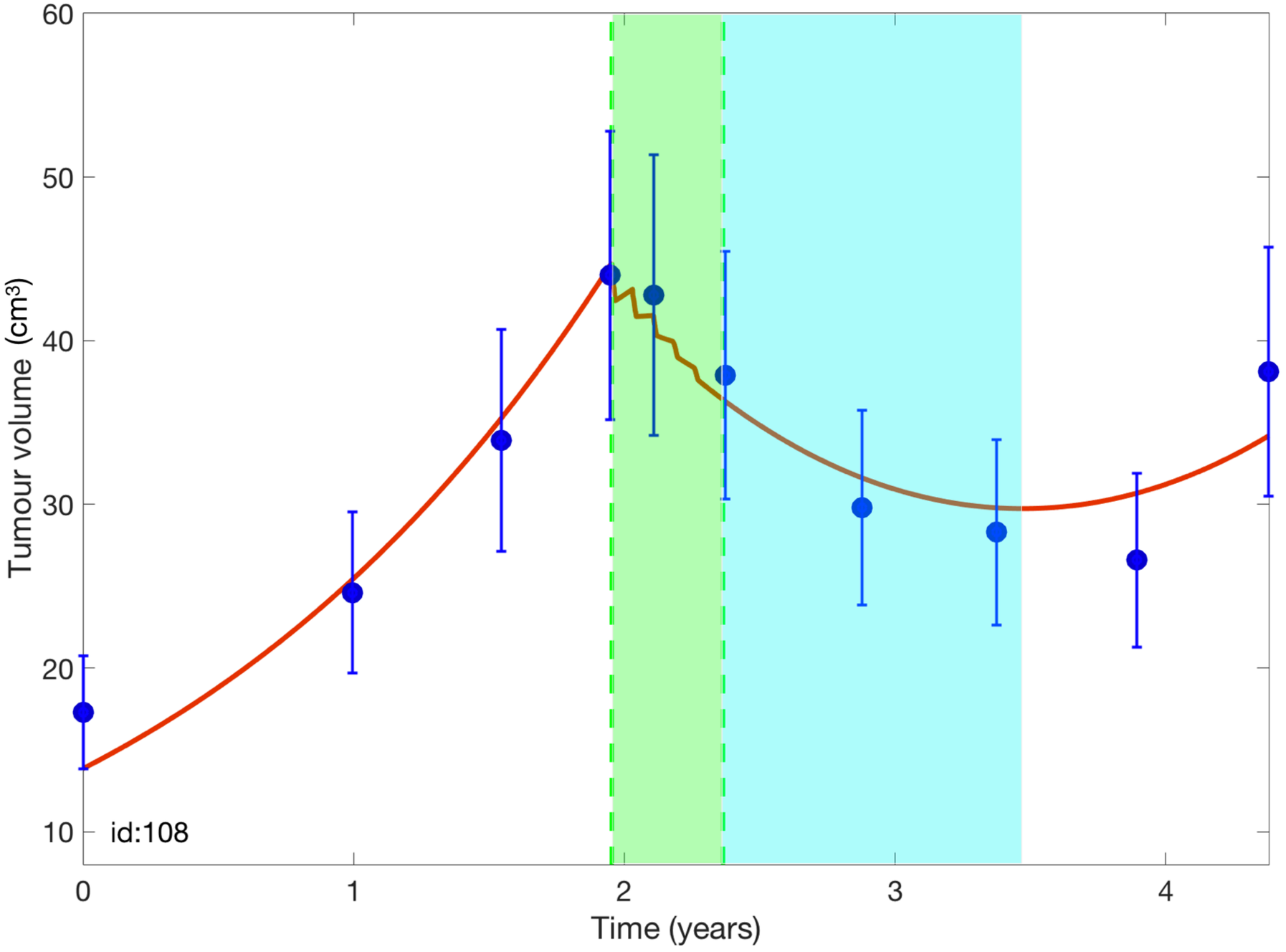
22 23 24 25 26 27 28
29 30 31


How can you find the best ...
for all patients?
for each individual patient?


Technical limitations — Ethical considerations — Time constraints



$$
\begin{aligned}
\frac{dP}{dt} &= \rho P\left(1-\frac{P+D}{K}\right)-\alpha_1 PC-\alpha_2 PC,\\
\frac{dD}{dt} &= -\frac{\rho}{\kappa}D\left(1-\frac{P+D}{K}\right)+\alpha_1 PC,\\
\frac{dC}{dt} &= -\lambda C,
\end{aligned}
$$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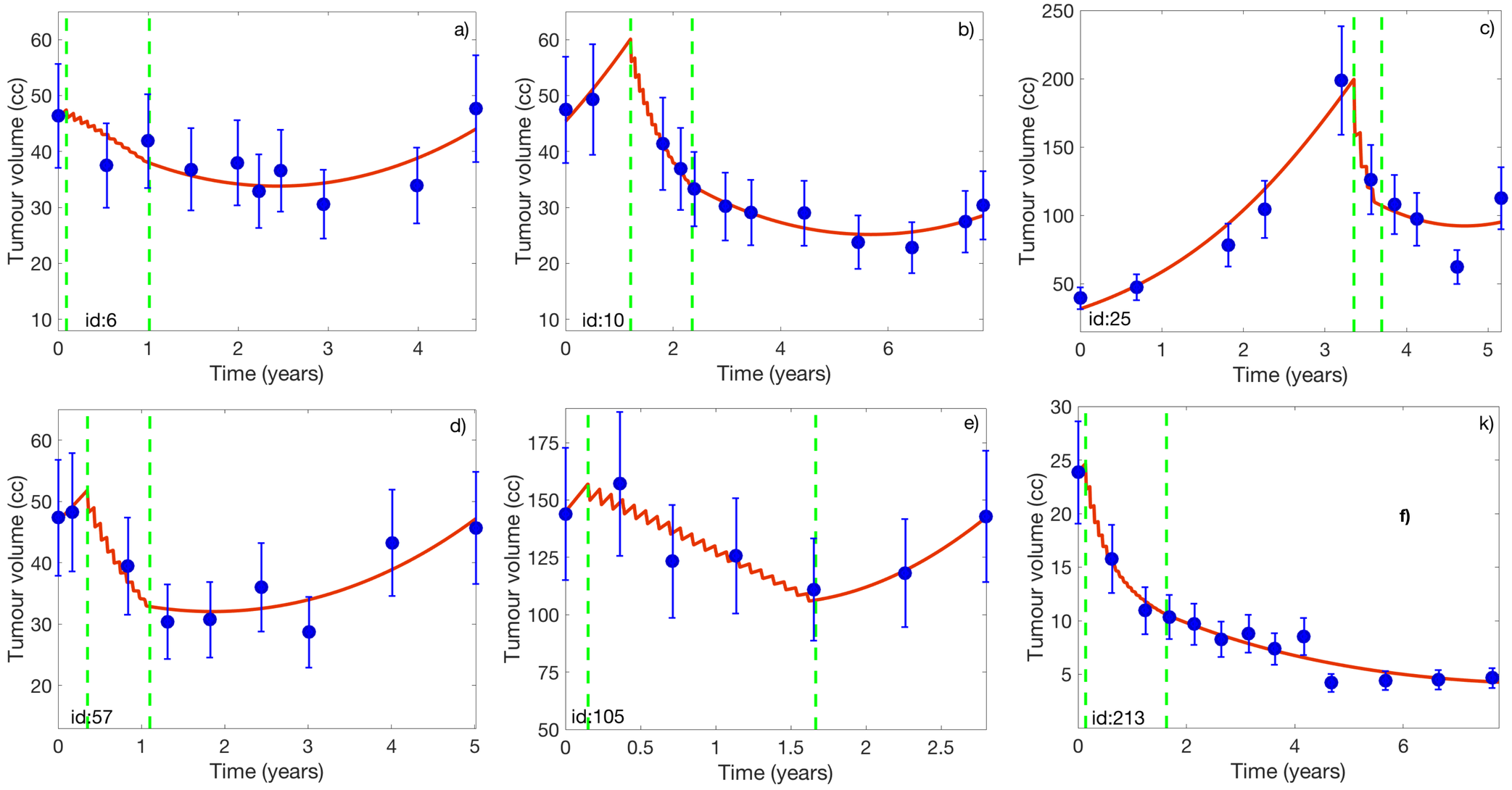
Tumour volume (cm³)
id:108
0
1
2
3
4
Time (years)



Worked for 11 patients of Bern Hospital


A clone made out of equations living in a computer
BPM=23 HEART=11
00:00:17.494
01:03:32.500
BPM=23 HEART=11


Therapy Personalization
BPM=23 HEART=11
00:00:17.494
01:03:32.500

Finding better protocols using clones

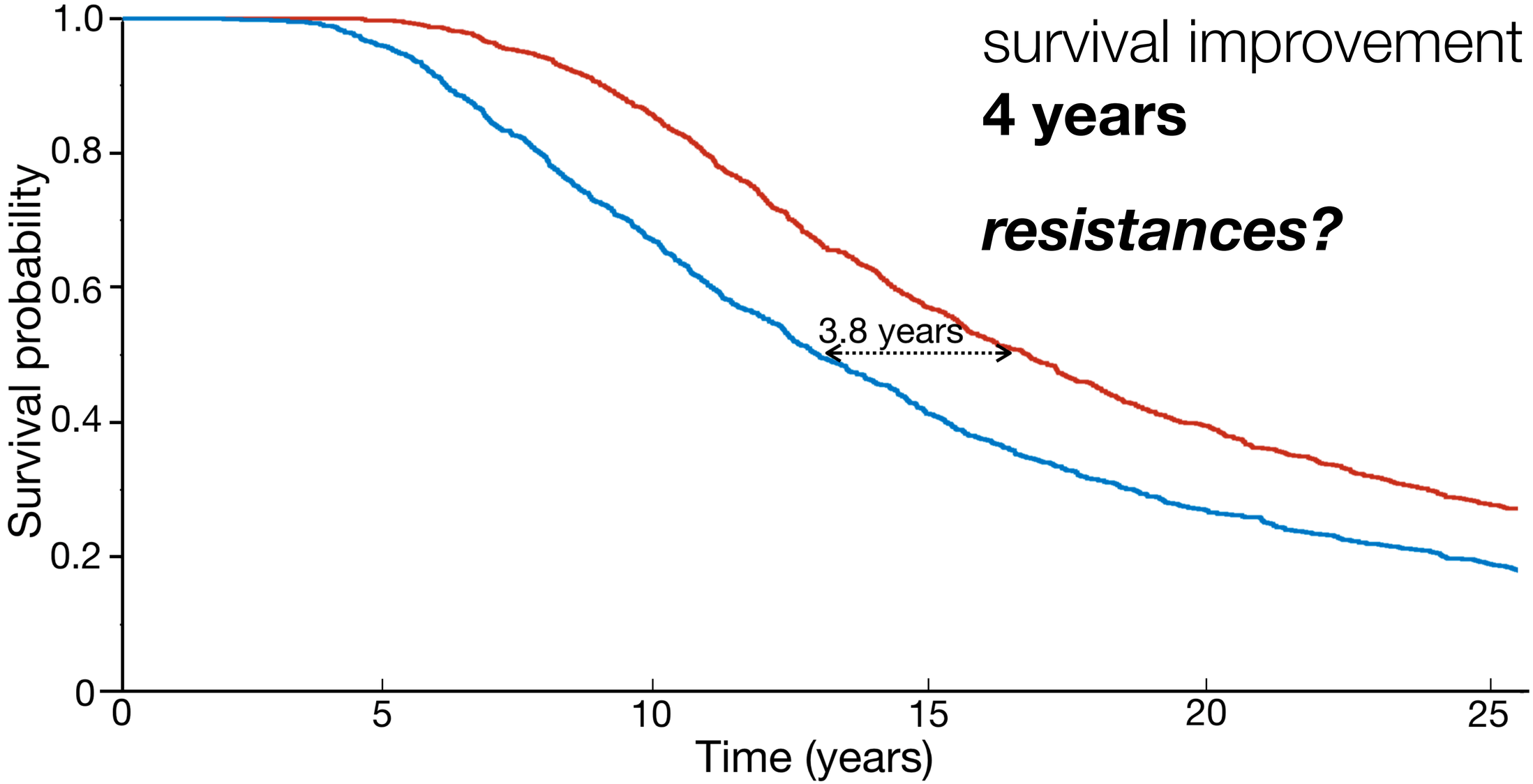
11 clones

1000 ‘brothers’

5
1 month

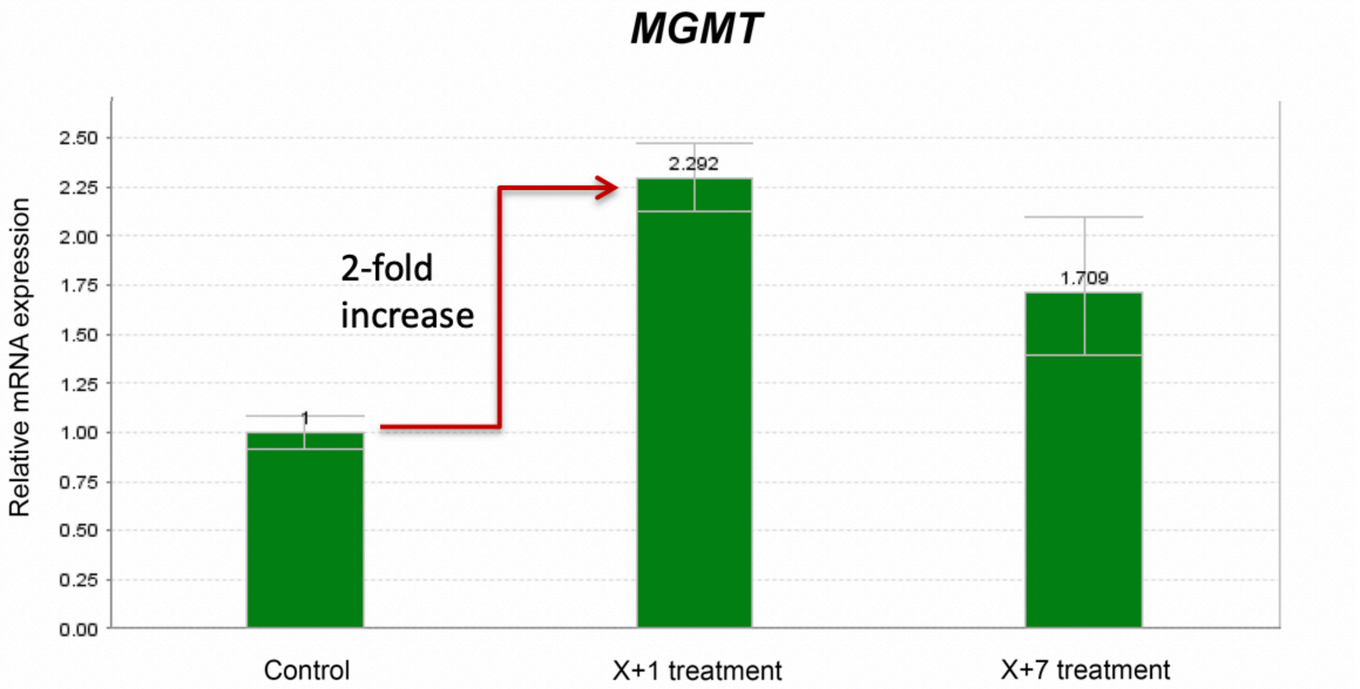
+

12
3 months

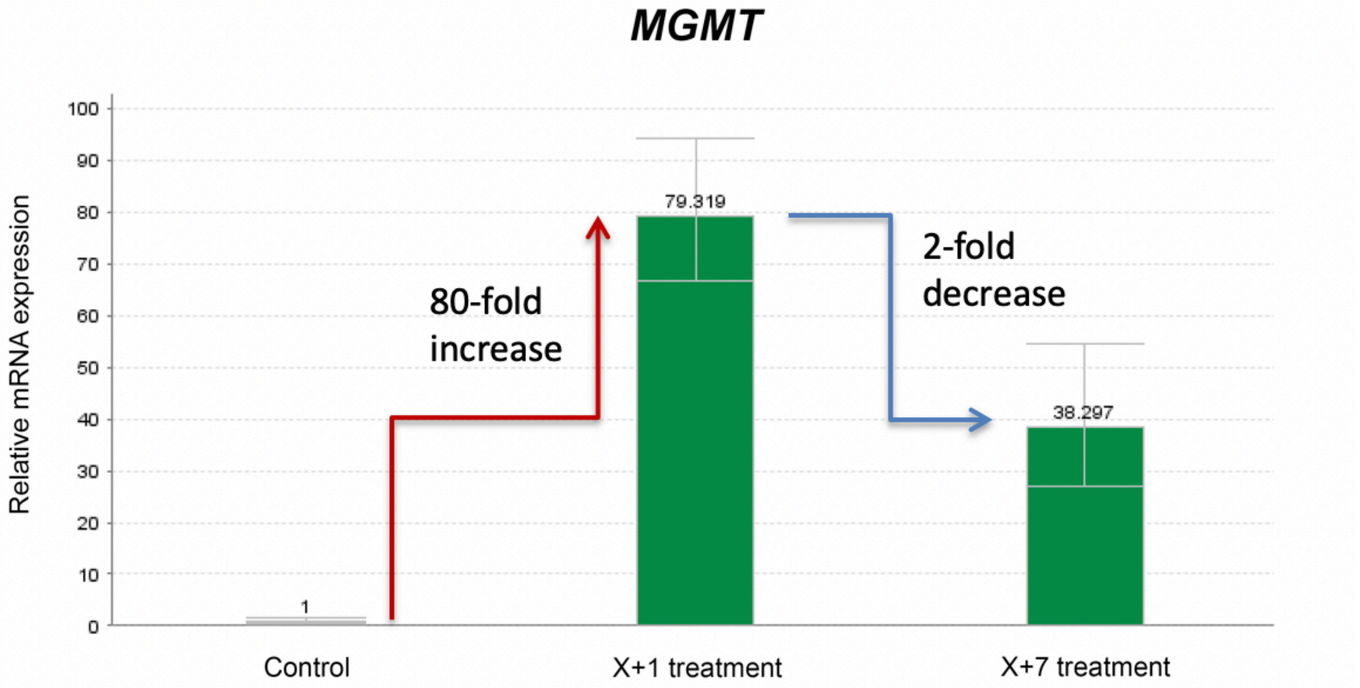

1.0
0.8
0.6
0.4
0.2
0
Survival probability
0
5
10
15
20
25
Time (years)
3.8 years
survival improvement
4 years
resistances?


Current approach
Shoot everything you've got
MakeAGIF.com


New one: wait till they are on target


MGMT
Relative mRNA expression
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
2.292
1.709
1
2-fold
increase
Control
X+1 treatment
X+7 treatment

U87


MGMT
Relative mRNA expression
100
90
80
70
60
50
40
30
20
10
0
79.319
38.297
1
80-fold
increase
2-fold
decrease
Control
X+1 treatment
X+7 treatment

U251

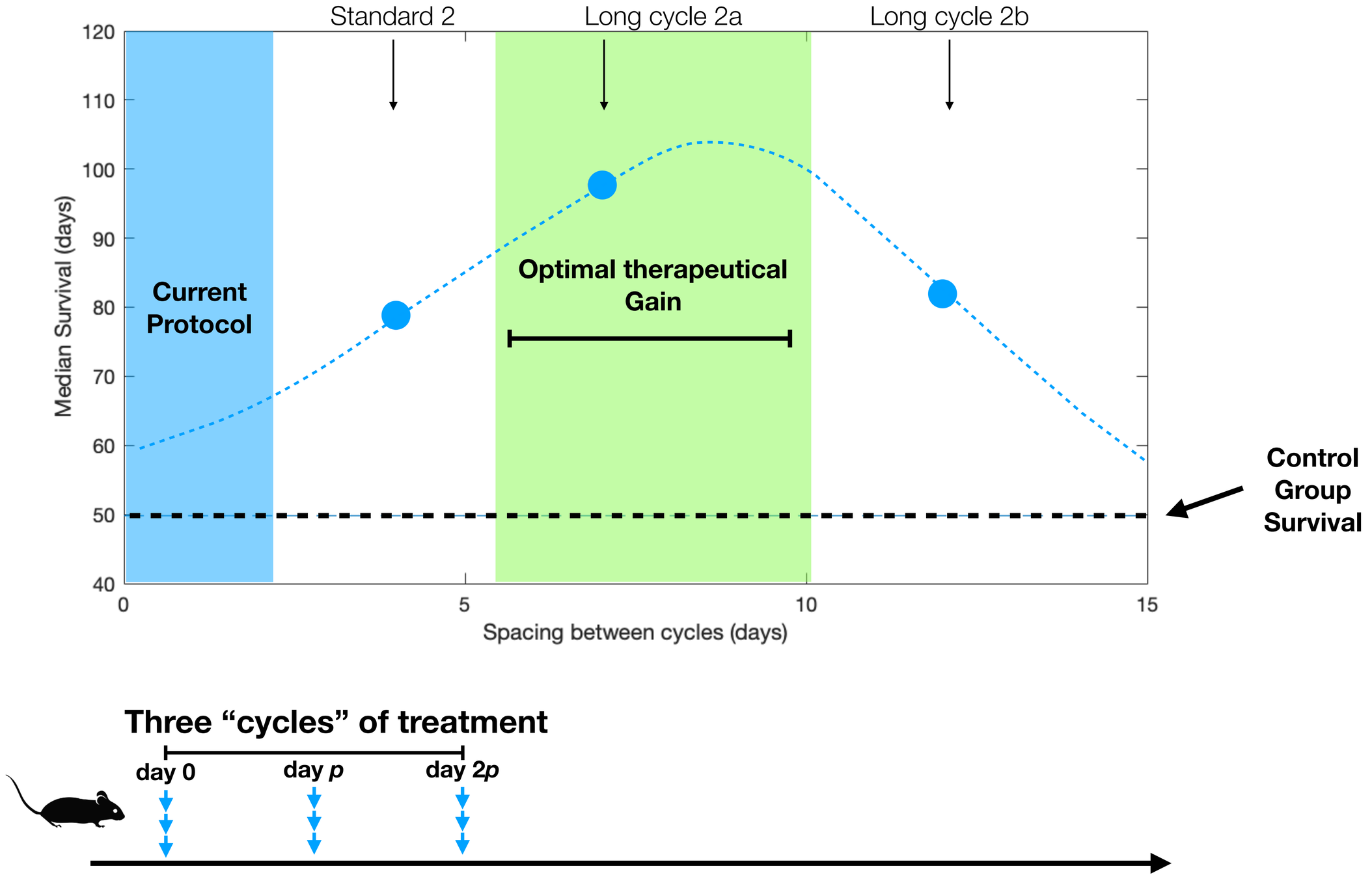

Standard 2
Long cycle 2a
Long cycle 2b
120
110
100
90
80
70
60
50
40
Median Survival (days)
Current Protocol
Optimal therapeutical Gain
Control Group Survival
0
5
10
15
Spacing between cycles (days)
Three “cycles” of treatment
day 0
day p
day 2p

Image-based Biomarkers

Maths for personalized treatment

Brain metastasis

PET imaging

Prostate cancer

Immunotherapy

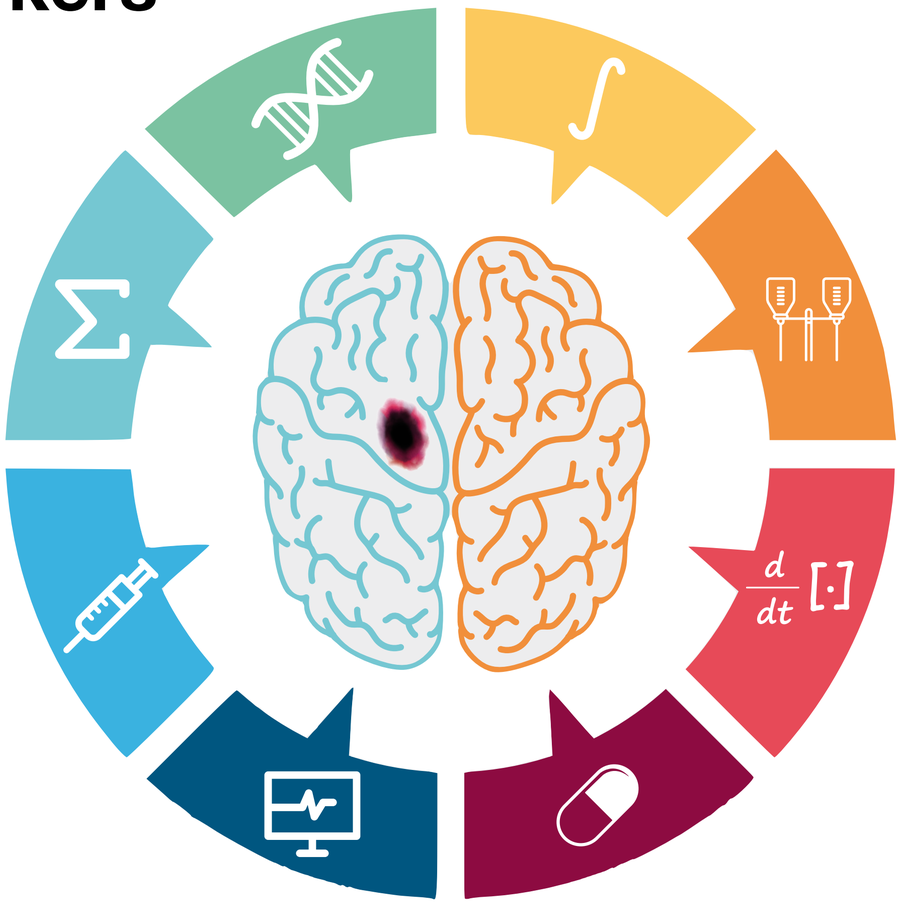
Hyperthermia

Acute lymphoblastic leukemia

Evolutionary dynamics

Novel administration protocols

Scaling laws



http://matematicas.uclm.es/molab


“Todo lo que uno puede imaginar
otros pueden hacerlo realidad”
Julio Verne

MATHEMATICAL
ONCOLOGY
LABORATORY

MATHEMATICAL
ONCOLOGY
LABORATORY

UCLM Universidad de Castilla-La Mancha

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FECYT FUNDACIÓN ESPAÑOLA PARA LA CIENCIA Y LA TECNOLOGÍA

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