

XVI CURSO NACIONAL DE NEURORRADIOLOGÍA

Neurorradiología en la Patología Tumoral Cerebral

20-21 febrero 2020 | Madrid



S.E.N.R.
Sociedad Española
de Neurorradiología

RADIOGENÓMICA: APROXIMACIÓN Y AVANCES “FENOTIPOS DE IMAGEN DE LOS GENOTIPOS DE GLIOMAS”

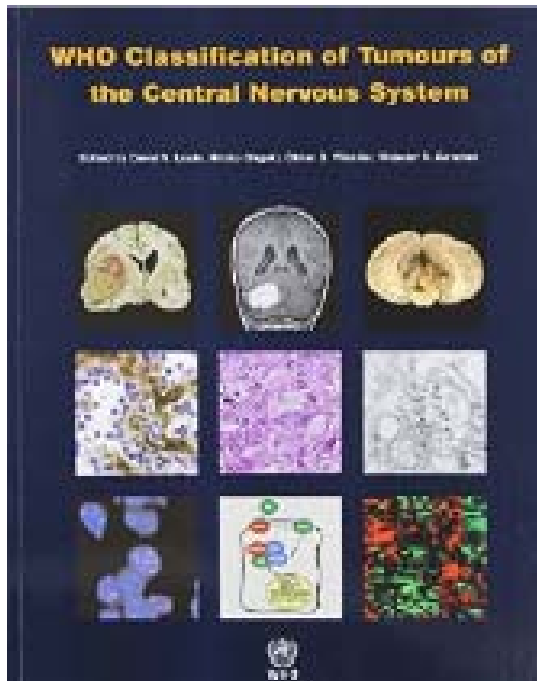
Cristina Auger Acosta

Unidad de RM. Servicio de Radiología.

Hospital General Universitario Vall D'Hebron

cristina.auger.idi@gencat.cat





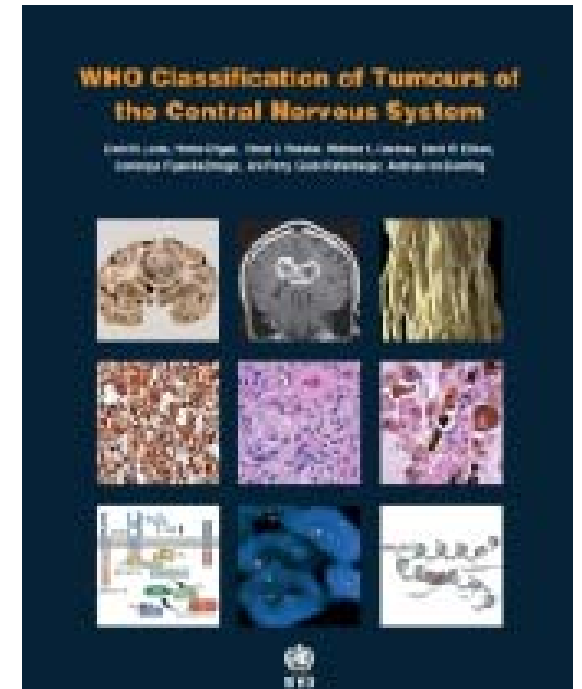
4ª edición

Acta Neuropathol (2007) 114:97–109
DOI 10.1007/s00401-007-0243-4

REVIEW

The 2007 WHO Classification of Tumours of the Central Nervous System

David N. Louis · Hiroko Ohgaki · Otmar D. Wiestler · Webster K. Cavenee · Peter C. Burger · Anne Jouvett · Bernd W. Scheithauer · Paul Kleihues



4ª edición revisada

Acta Neuropathol (2016) 131:803–820
DOI 10.1007/s00401-016-1545-1

REVIEW

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis¹ · Arie Perry² · Guido Reifenberger^{3,4} · Andreas von Deimling^{4,5} · Dominique Figarella-Branger⁶ · Webster K. Cavenee⁷ · Hiroko Ohgaki⁸ · Otmar D. Wiestler⁹ · Paul Kleihues¹⁰ · David W. Ellison¹¹

Table 1 The 2007 WHO Classification of Tumours of the Central Nervous

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours

Pilocytic astrocytoma	9421/1 ¹
Pilomyxoid astrocytoma	9425/3*
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3

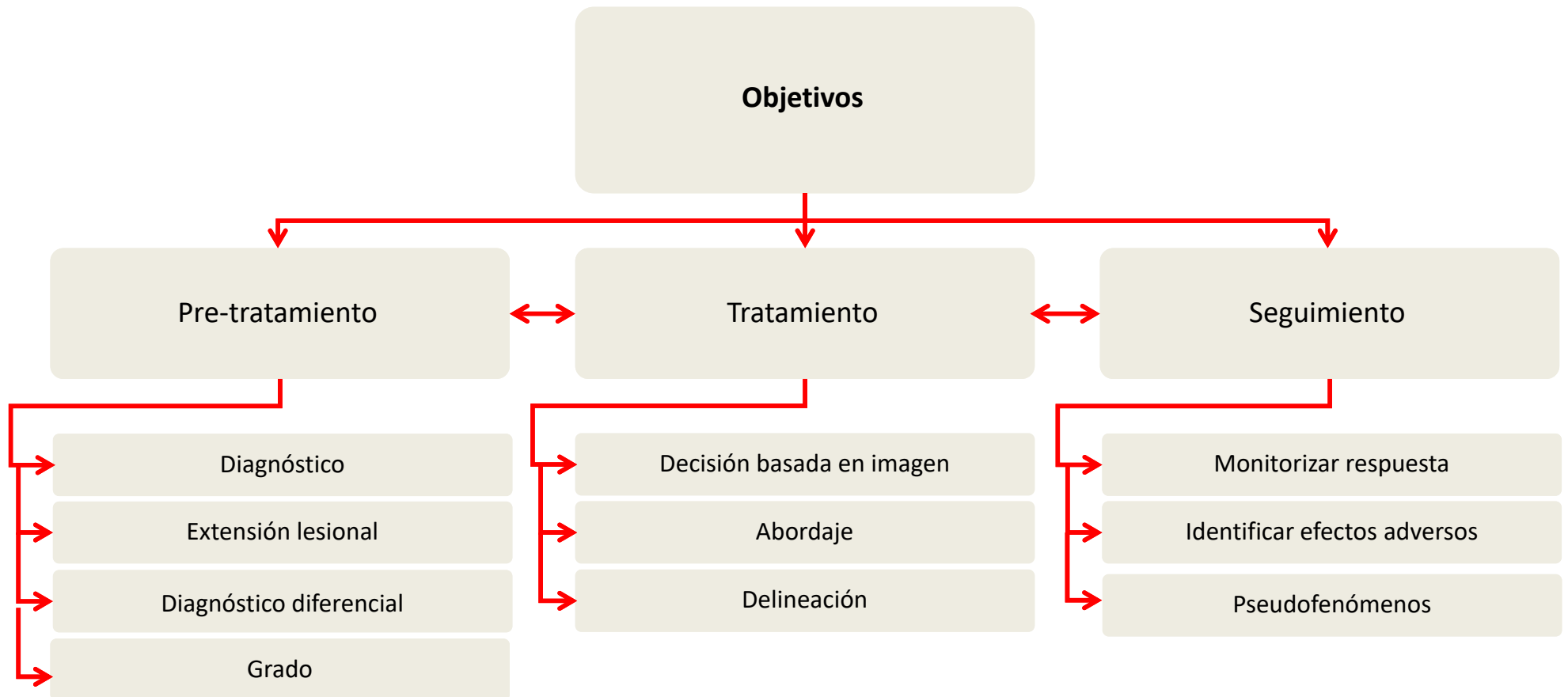
Diffuse astrocytic and oligodendroglial tumours

Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
<i>Diffuse astrocytoma, IDH-wildtype</i>	9400/3
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	
<i>Anaplastic astrocytoma, IDH-wildtype</i>	9401/3
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
<i>Epithelioid glioblastoma</i>	9440/3
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M-mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	
<i>Anaplastic oligodendroglioma, NOS</i>	9451/3
<i>Oligoastrocytoma, NOS</i>	9382/3
<i>Anaplastic oligoastrocytoma, NOS</i>	9382/3
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3

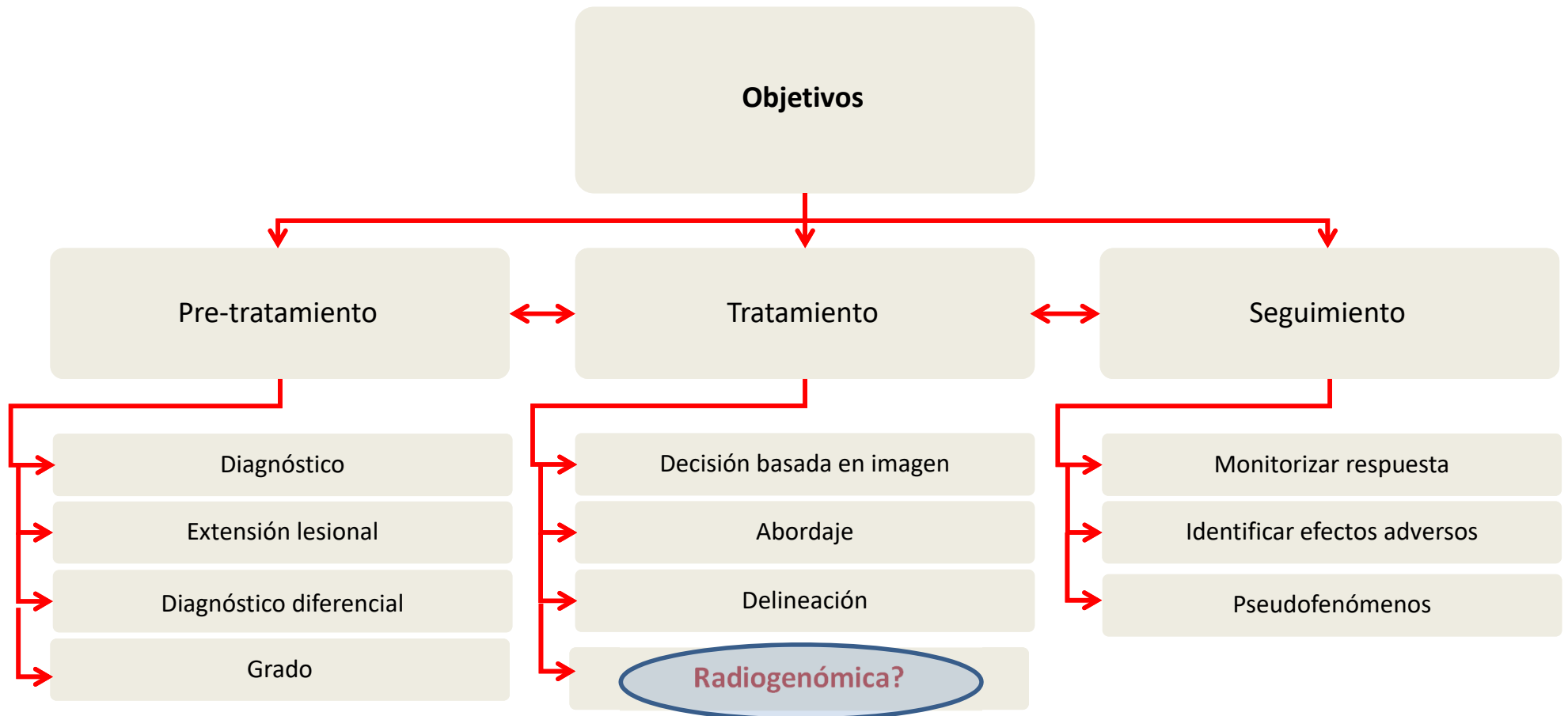
WHO 2007

WHO 2016

Objetivos de la NR en los tumores cerebrales



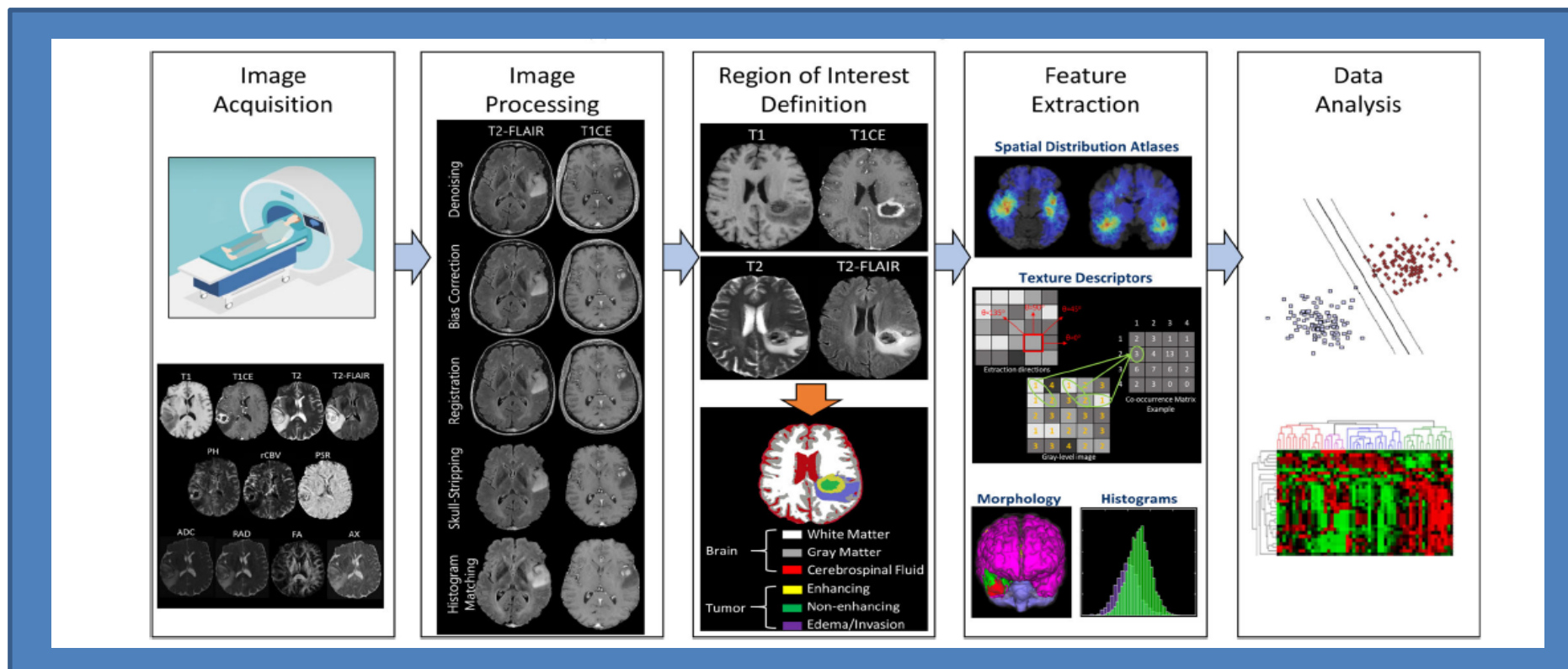
Objetivos de la NR en los tumores cerebrales



Relación entre la Imagen y Genómica en Tumores cerebrales (Radiogenómica)

Objetivo

- Comprender bases moleculares del cáncer a través de la aplicación de análisis genómico, histopatología e imagen
- Identificar características radiológicas que predigan genómica, (mutaciones, expresión)



astrocytoma oligoastrocytoma oligodendroglioma

IDH mutation

IDH-mutant

IDH-wildtype

1p/19q codeletion

TERT promoter, CIC,
and FUBP1 mutations

P53 mutation,
ATRX inactivation

If midline
location,
test for
H3F3A
K27M
mutations

**IDH-mutant,
1p/19q codeleted**

**IDH-mutant,
1p/19q non-codeleted**

IDH-wildtype

Oligodendroglioma, IDH-mutant
and 1p/19q-codeleted (grade II)

Anaplastic oligodendroglioma,
IDH-mutant and 1p/19q-
codeleted (grade III)

Diffuse astrocytoma,
IDH-mutant (grade II)

Anaplastic astrocytoma,
IDH-mutant (grade III)

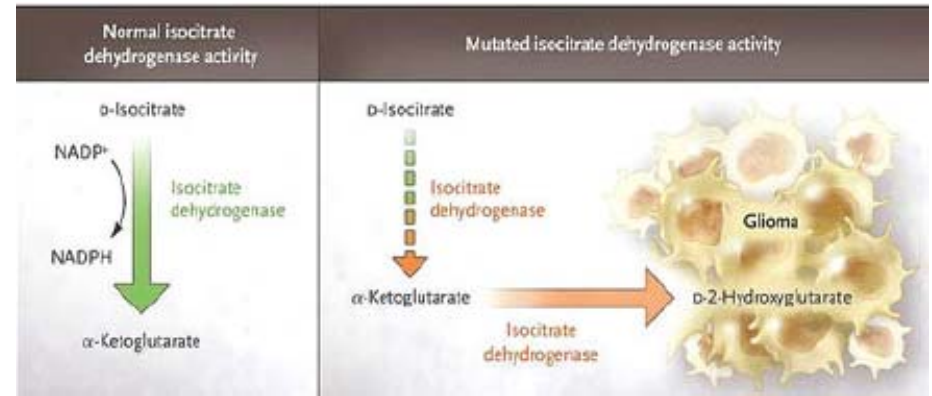
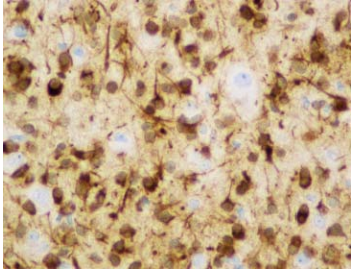
Diffuse astrocytoma,
IDH-wildtype (grade II)

Anaplastic astrocytoma,
IDH-wildtype (grade III)

Diffuse
midline
glioma, H3
K27M-
mutant
(grade IV)

Radiogenómica en gliomas

Isocitrato Deshidrogenasa 1&2



- **Responsable de la conversión del isocitrato a alfa-ketoglutarato.** Su mutación produce una reducción del alfa-ketoglutarato a 2-hidroxiglutarato

- **Presente en:**

Pacientes jóvenes

Gliomas grado II/III (>75%)

GBM secundarios (aprox 83%)

- **Asociado con un perfil de expresión génica (proneural)**

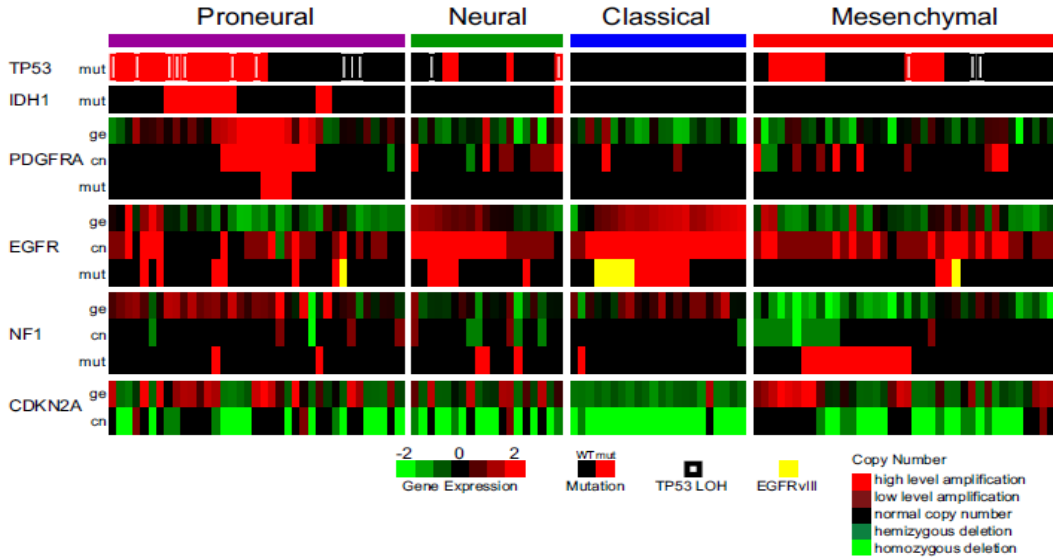
- **Mayor supervivencia (3,8 vs 1,1 años)**

Gliomas

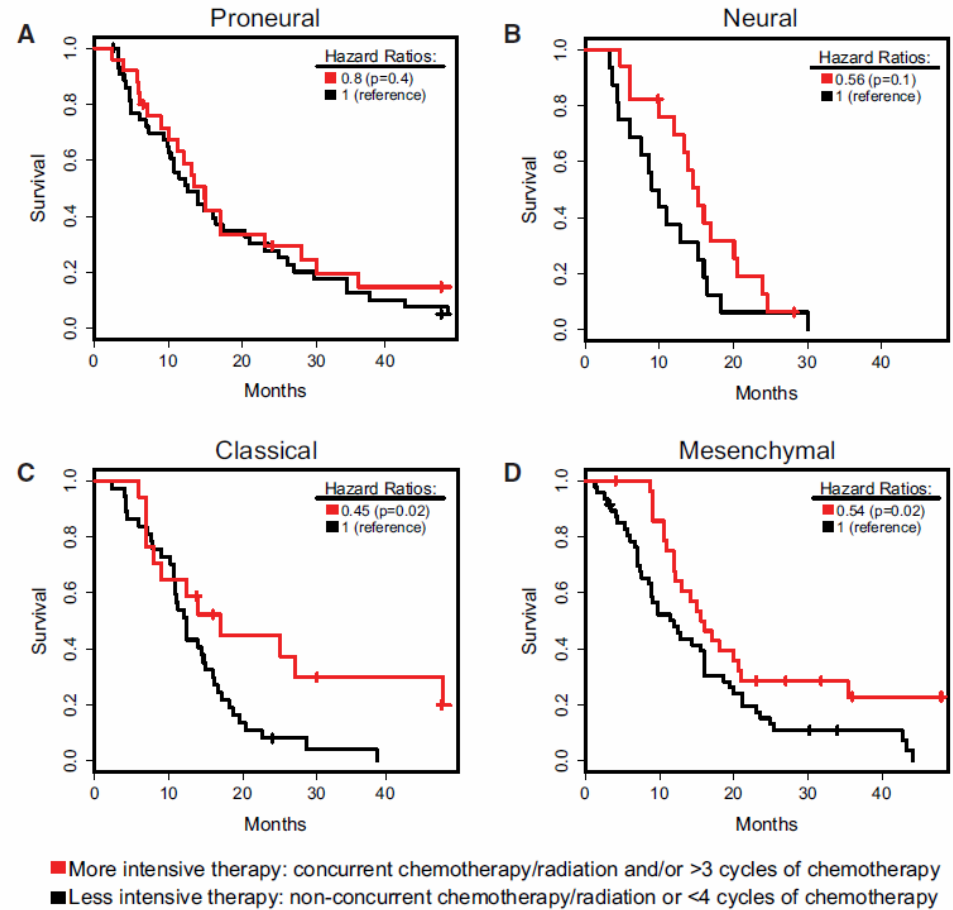
Clasificación basada en perfiles de expresión génica

Vías de señalización: *RTK/P13K/PTEN*; *P53*; *RB1*

GBM

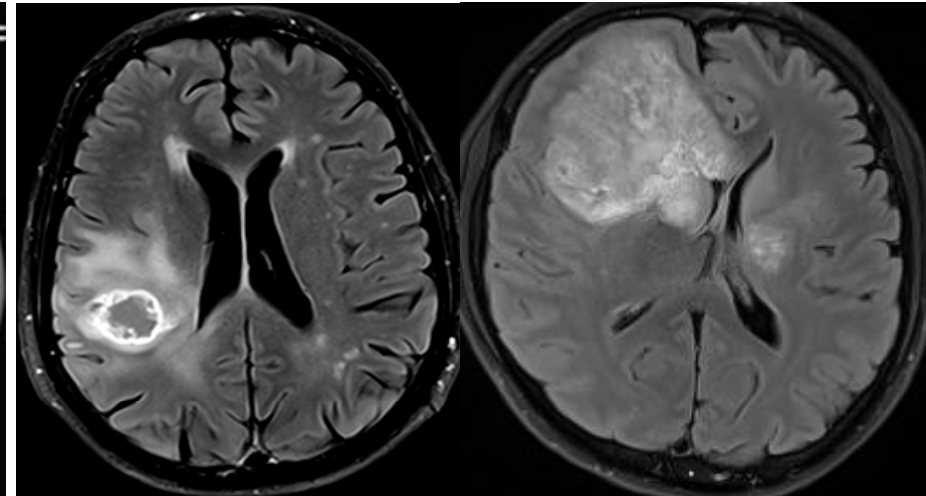
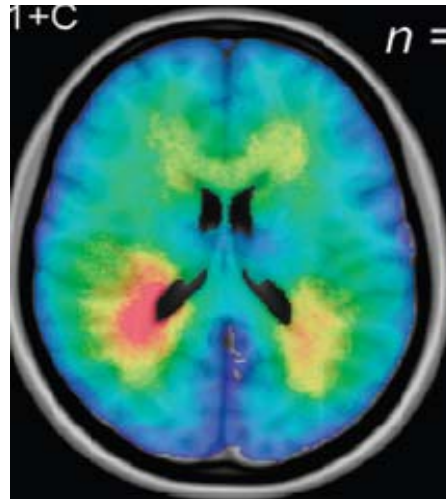
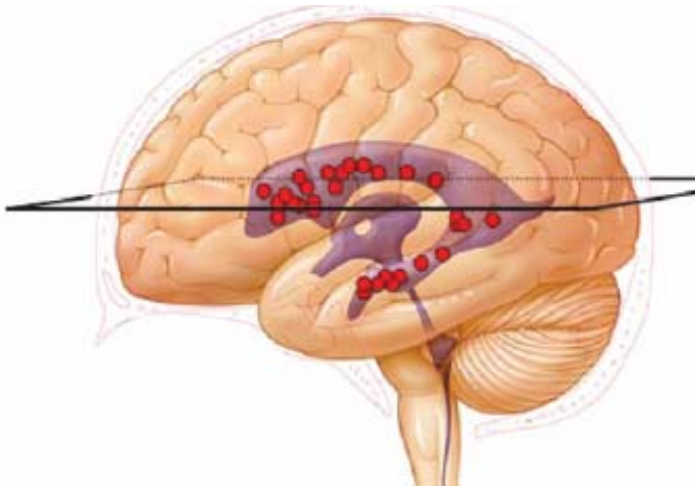


- Proneural (mejor pronóstico)
 - ✓ Menor volumen de realce tumoral
- Mesenquimal
 - ✓ Más necrosis



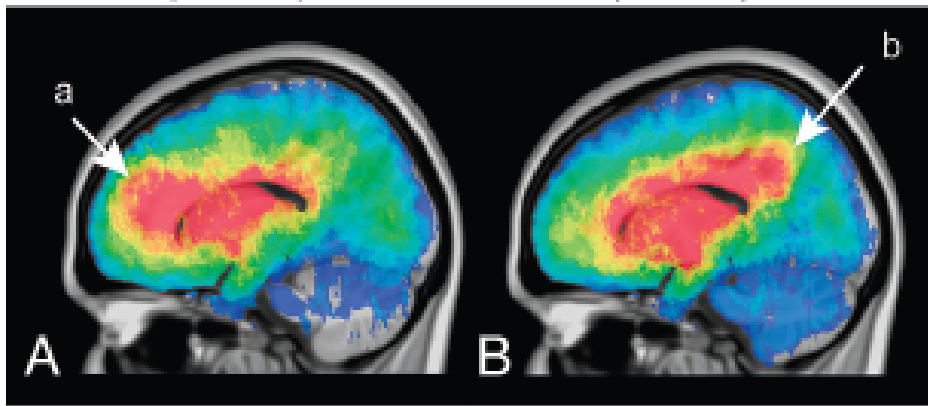
Radiogenómica en gliomas

Topografía y supervivencia



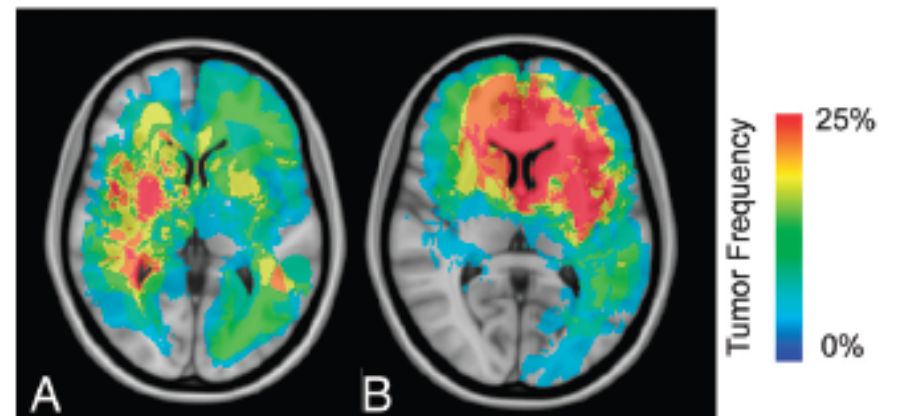
Age < 55 yo
(n = 179)

Age > 65 yo
(n = 160)



Mesenchymal
(n = 21)

Proneural+
Proliferative
(n = 22)



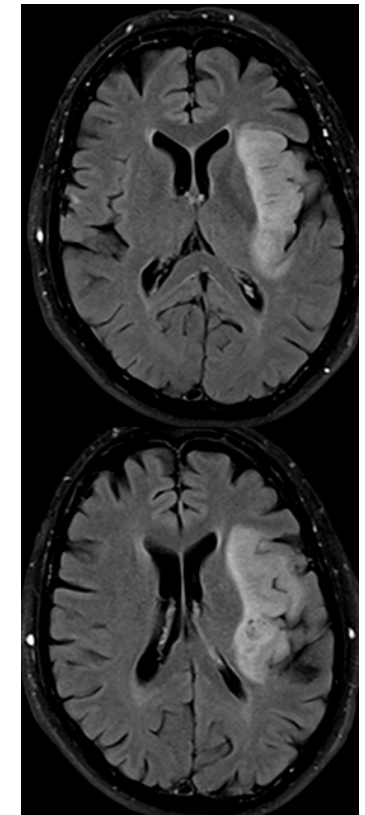
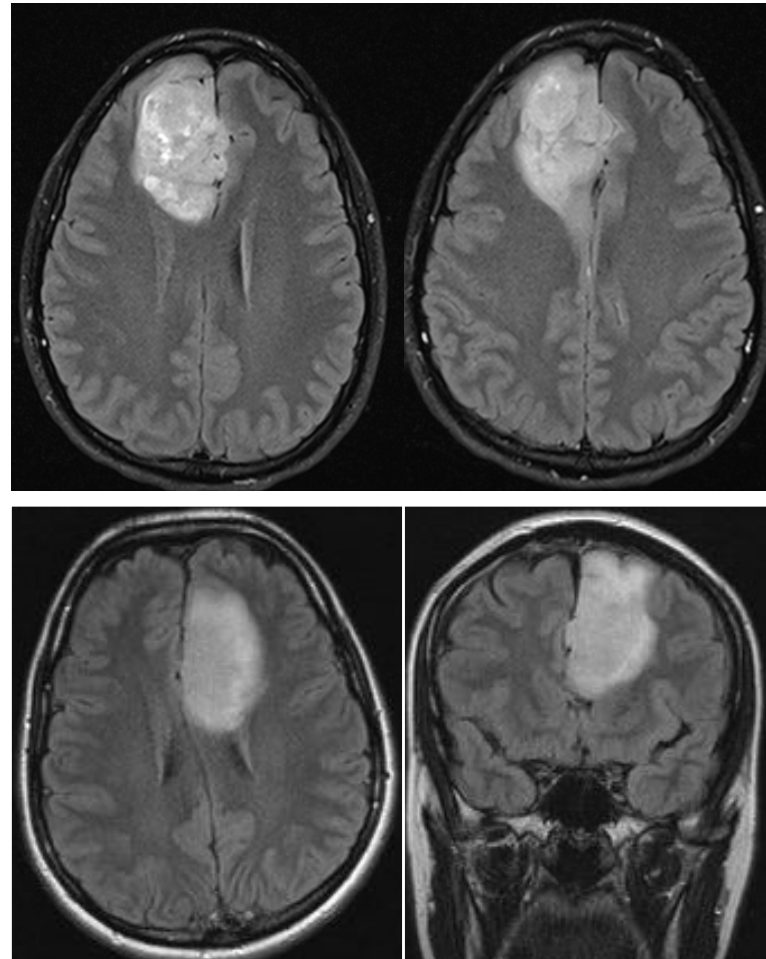
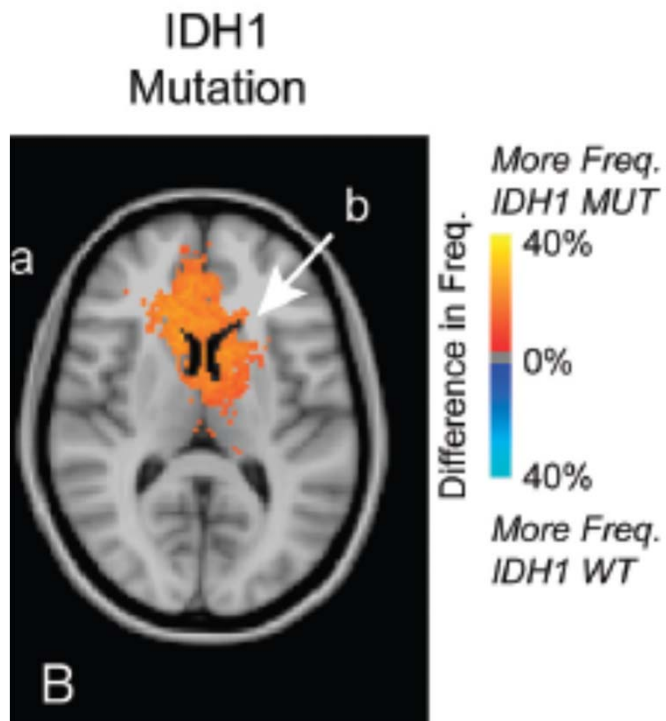
LOCALIZACIÓN

Lóbulo frontal
Unilobares

Radiogenómica en gliomas

Mutaciones IDH

- Hallazgos radiológicos predicen la mutación IDH1 (precisión 97,5%)



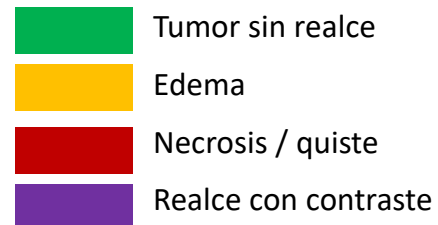
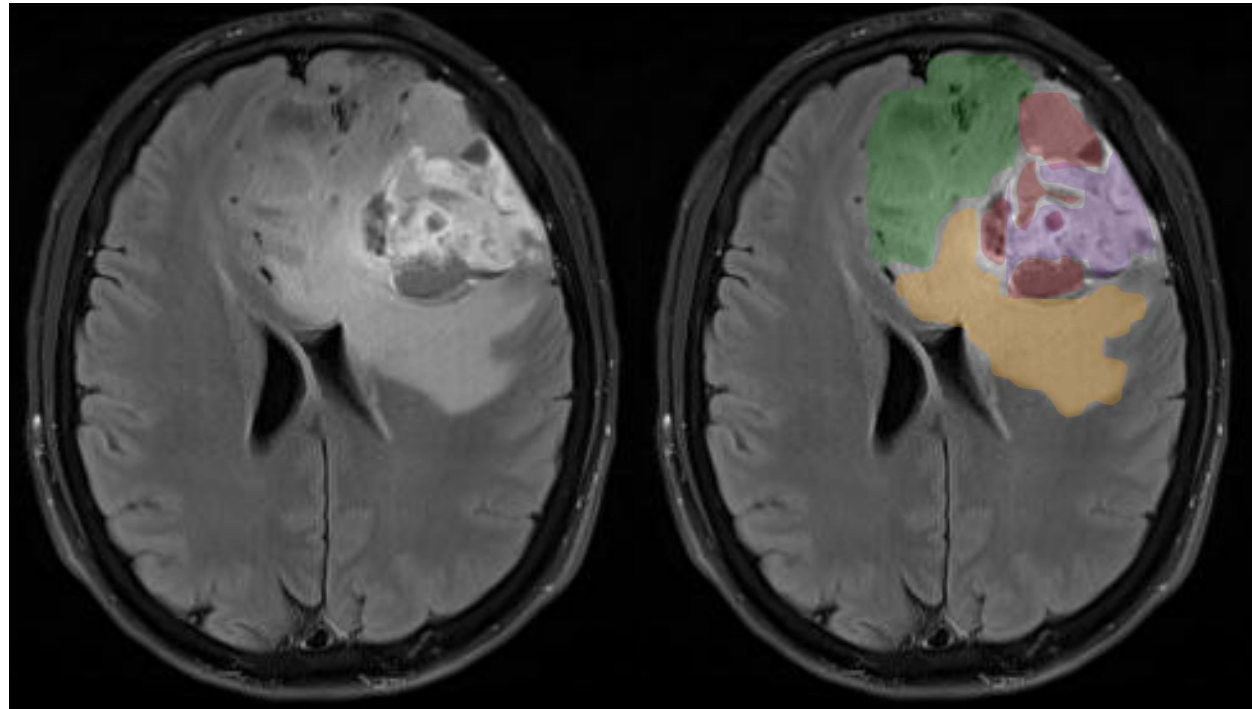
Radiogenómica en gliomas

Mutaciones IDH

- Hallazgos radiológicos predicen la mutación IDH1 (precisión 97,5%)

APARIENCIA

- Alto porcentaje sin realce
- Gran tamaño
- Presencia de quistes
- Presencia satélites



Invasión y migración celular



Supervivencia celular y antiapoptosis



Angiogénesis

Qi et al. Oncol Lett 2014

Carrillo et al. AJNR 2012

Wang et al. Eur J Neurol 2015

Radiogenómica en gliomas

Mutaciones IDH

Table II. Analyzing the frequency of *IDH1/2* mutations and tumor location according to anatomical structures.

Histology	F, n	T, n	P or O, n	Multilobes, n	I or BG, n	D or BS, n	CB, n
DA							
n	45	9	9	11	14	12	11
IDH mutation	38	7	8	3	6	1	9
IDH wild-type	7	2	1	8	8	11	2
AA							
n	21	16	8	17	4	14	2
IDH mutation	15	13	4	5	3	4	1
IDH wild-type	6	3	4	12	1	10	1
Overall							
n	66	25	17	28	18	26	13
IDH mutation	53	20	12	8	9	5	10
IDH wild-type	13	5	5	20	9	21	3

LOCALIZACIÓN

Lóbulo frontal
Unilobares

APARIENCIA

- Alto porcentaje sin realce
- Gran tamaño
- Presencia de quistes
- Presencia satélites

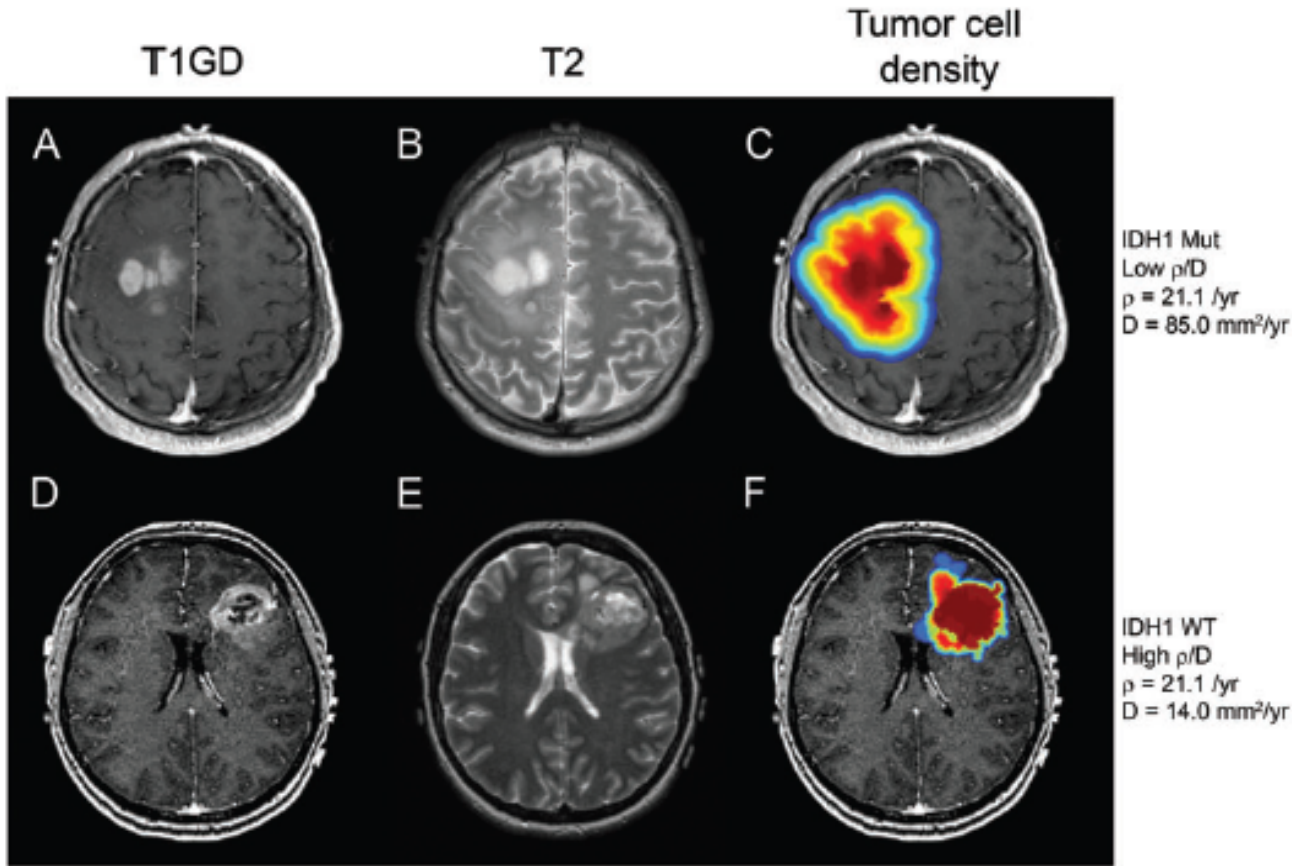
Table IV. Analyzing the frequency of *IDH1/2* mutations and different MRI features of gliomas.

MRI features	All ^a , n (%)	P-value	DA ^a , n (%)	P-value	AA ^a , n (%)	P-value
Pattern of growth		<0.001		0.007		0.001
Unilateral	116/178 (65.2)		71/104 (68.3)		45/74 (60.8)	
Bilateral	1/15 (6.7)		1/7 (14.3)		0/8 (0.0)	
Tumor margins		<0.001		0.001		0.012
Sharp	66/85 (77.6)		44/55 (80.0)		22/30 (73.3)	
Indistinct	51/108 (47.2)		28/56 (50.0)		23/52 (44.2)	
Tumor signal intensity		<0.001		0.003		<0.001
Homogeneous	70/89 (78.7)		45/58 (77.6)		25/31 (80.6)	
Heterogeneous	47/104 (45.2)		27/53 (50.9)		20/51 (39.2)	
Contrast enhancement		<0.001		0.001		0.003
Absent or slight	74/97 (76.3)		47/60 (78.3)		27/37 (73.0)	
Significant	43/96 (44.8)		25/51 (49.0)		18/45 (40.0)	
Mass effect		0.654		0.320		0.216
Absent or moderate	47/75 (62.7)		38/54 (70.4)		9/21 (42.9)	
Severe	70/118 (59.3)		34/57 (59.6)		36/61 (59.0)	
Edema		0.181		0.533		0.375
Absent or moderate	71/109 (65.1)		49/73 (67.1)		22/36 (61.1)	
Severe	46/84 (54.8)		23/38 (60.5)		23/46 (50.0)	

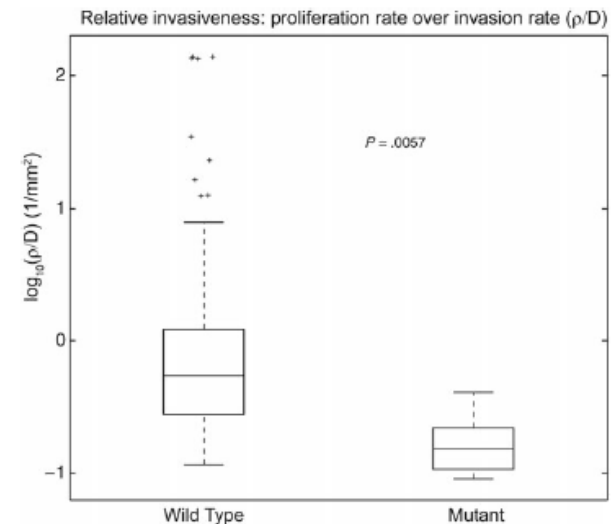
Radiogenómica en gliomas

IDHmut vs IDHwt

Ratio proliferación/Dispersión: ρ/D



IDHmut < IDHwt
↓
IDHmut: + difusos
- agresivos

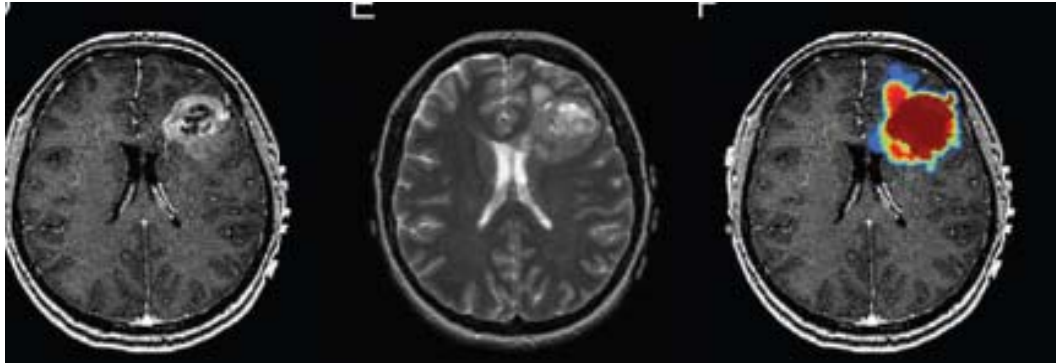


76% precisión

Radiogenómica en gliomas

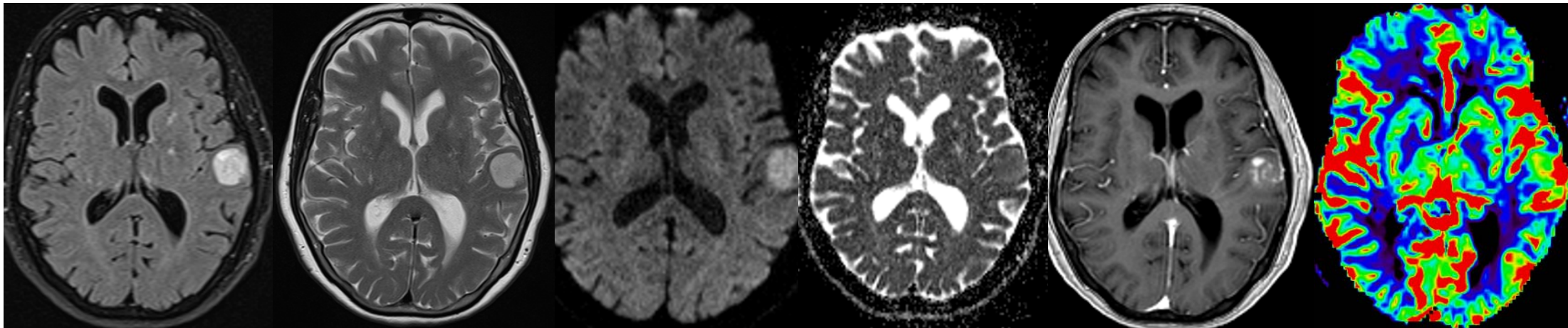
Baldock et al Neuro-Oncology 2014

Ratio proliferación/Dispersión: p/D ↑



IDH1 WT
High p/D
 $p = 21.1 /yr$
 $D = 14.0 \text{ mm}^2/yr$

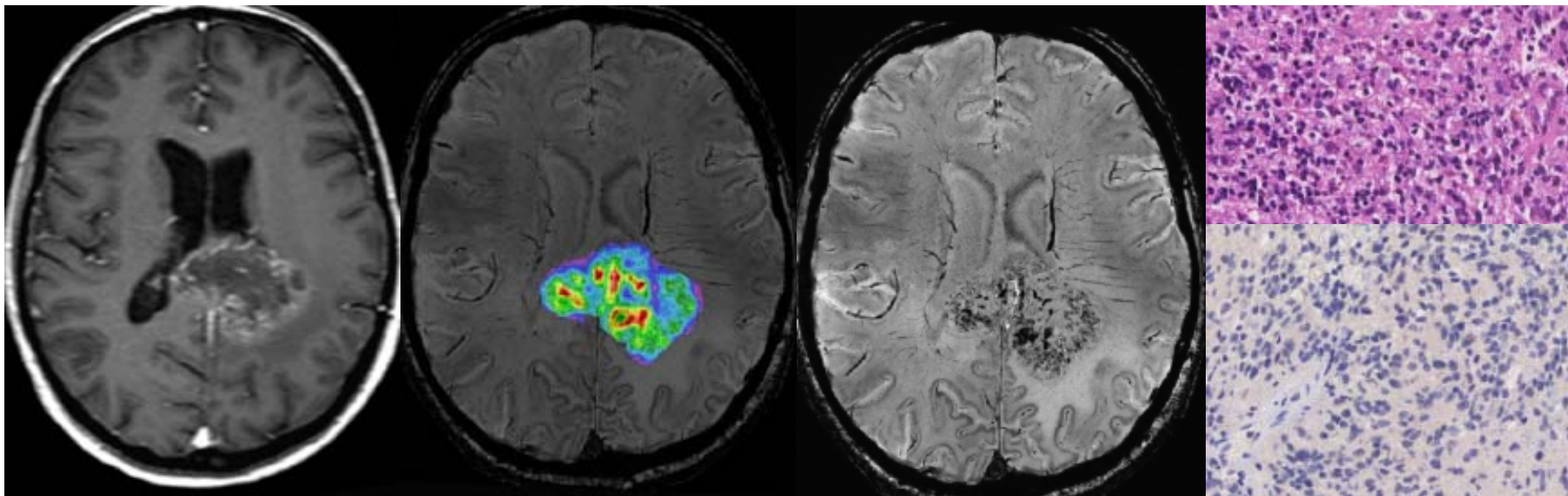
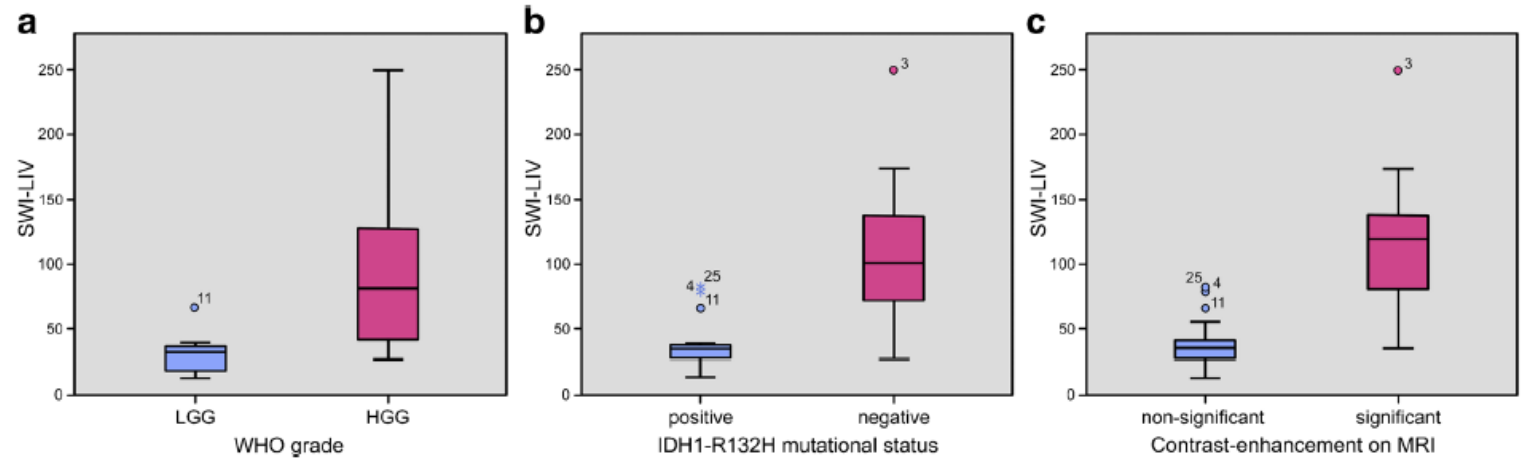
IDHwt



Vall d'Hebron

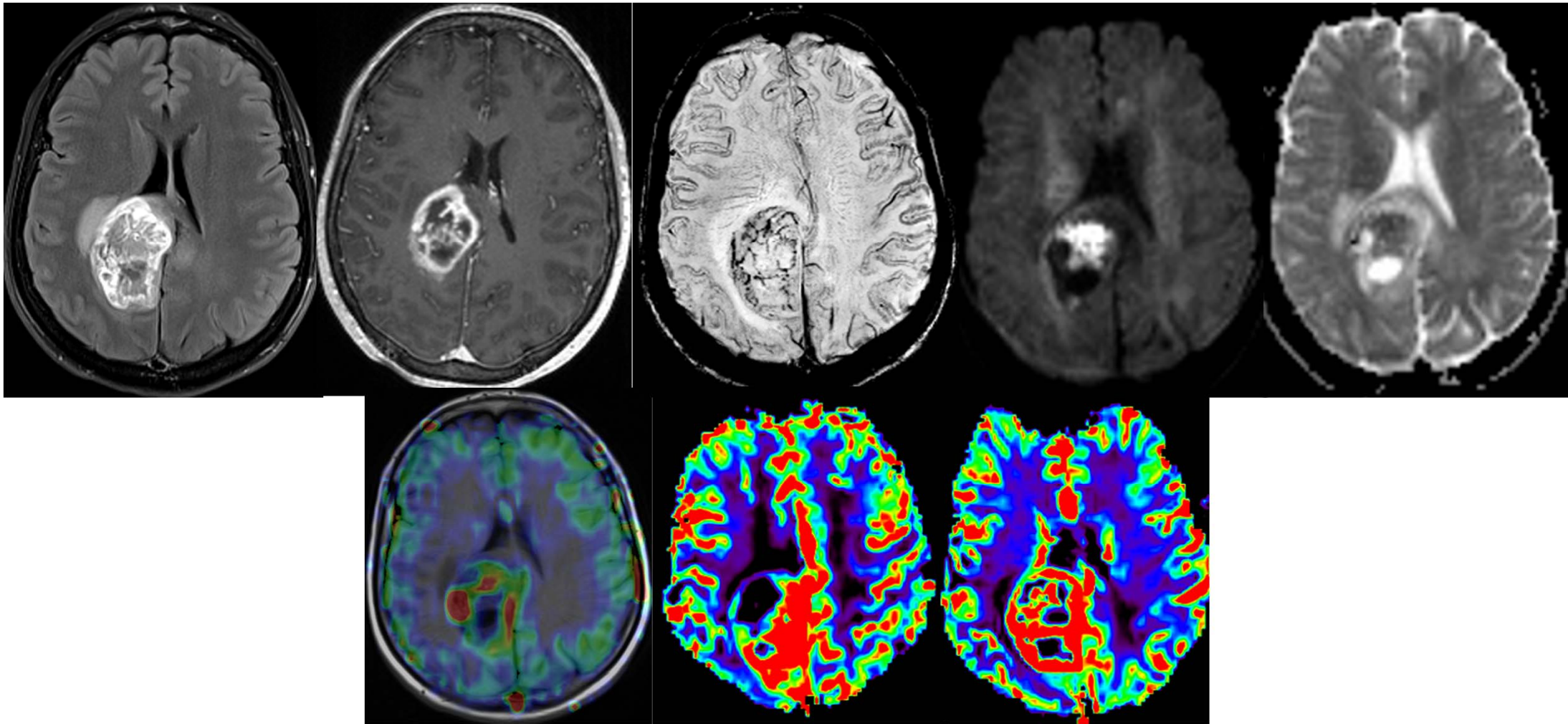
Mutaciones IDH1/Susceptibilidad magnética

30 pacientes
SWI 7T



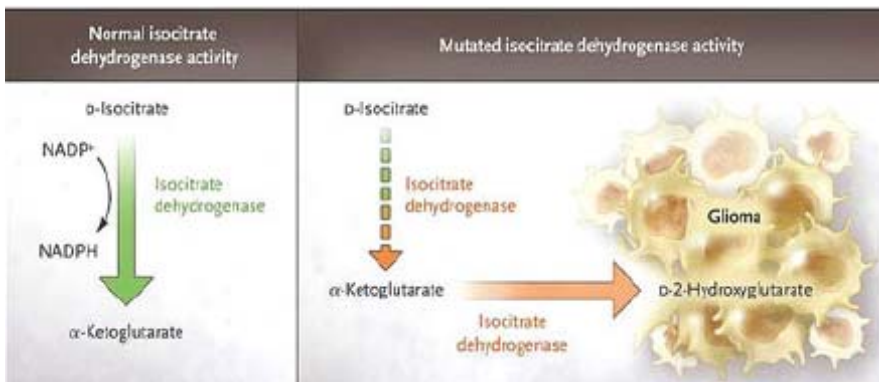
Radiogenómica en gliomas

IDHwt



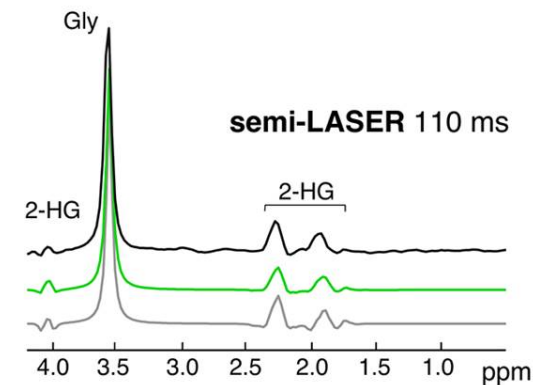
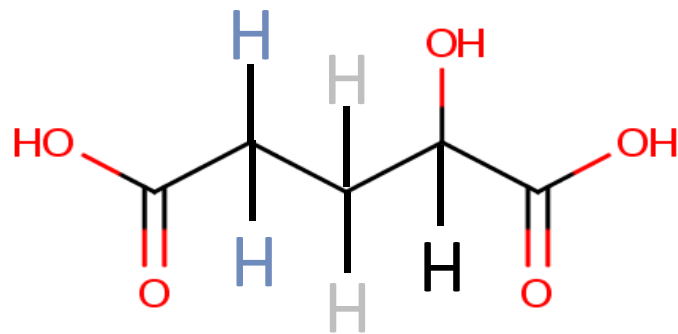
Radiogenómica en gliomas

Mutaciones IDH



Espectroscopia y 2-hidroxiglutarato (2-HG)

2-HG es una molécula estructuralmente compleja que da diferentes señales en espectro centradas sobre **1,9 , 2,25 y 4,02 ppm**



Estas señales se solapan con las debidas a otros metabolitos como el NAcc GABA, Glu, Gln, GSH, mIns.

Radiogenómica en gliomas

Mutaciones IDH

ERM 2-hidroxiglutarato (2-HG)

Técnicas para estudiar la presencia de 2-HG *“in vivo”*

técnica	Detección directa	ventajas	limitaciones
---------	-------------------	----------	--------------

SVS TE 30ms	NO “fitting”	comercial	“fitting”
-------------	-----------------	-----------	-----------

SVS TE 97ms	NO “fitting”	modificación secuencia comercial	“fitting”
-------------	-----------------	-------------------------------------	-----------

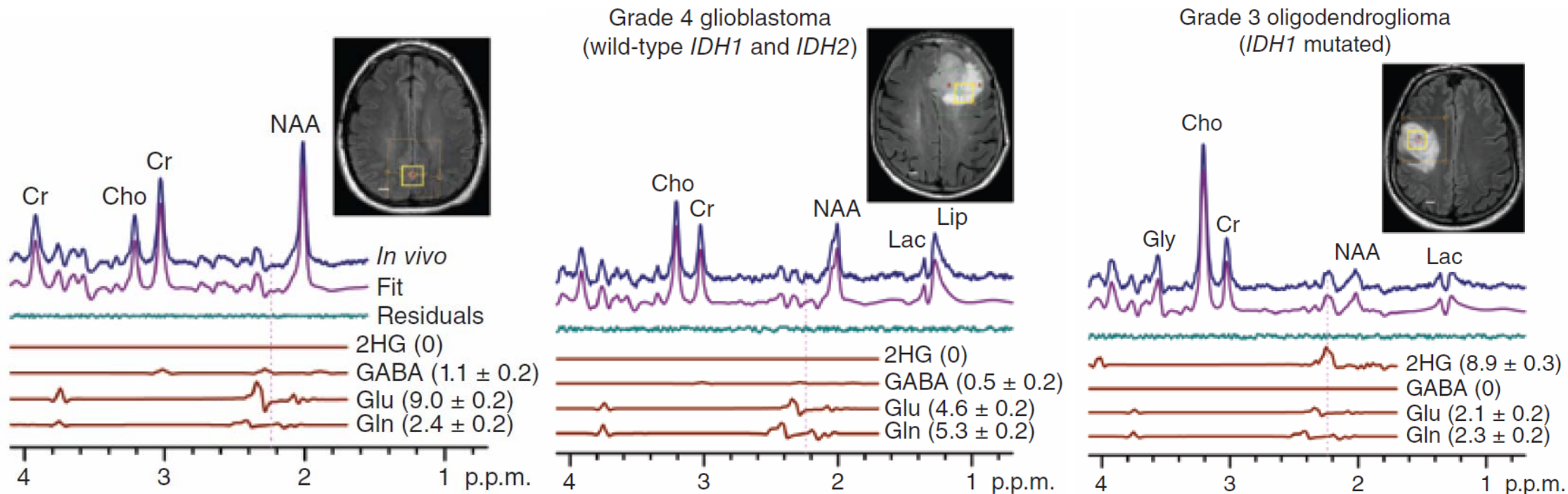
“editing” SVS o CSI	SI eliminación señales otros compuestos	detección 2-HG No falsos positivos	NO comercial Volumen y TA ↑
------------------------	-----------------------------------------------	---------------------------------------	--------------------------------

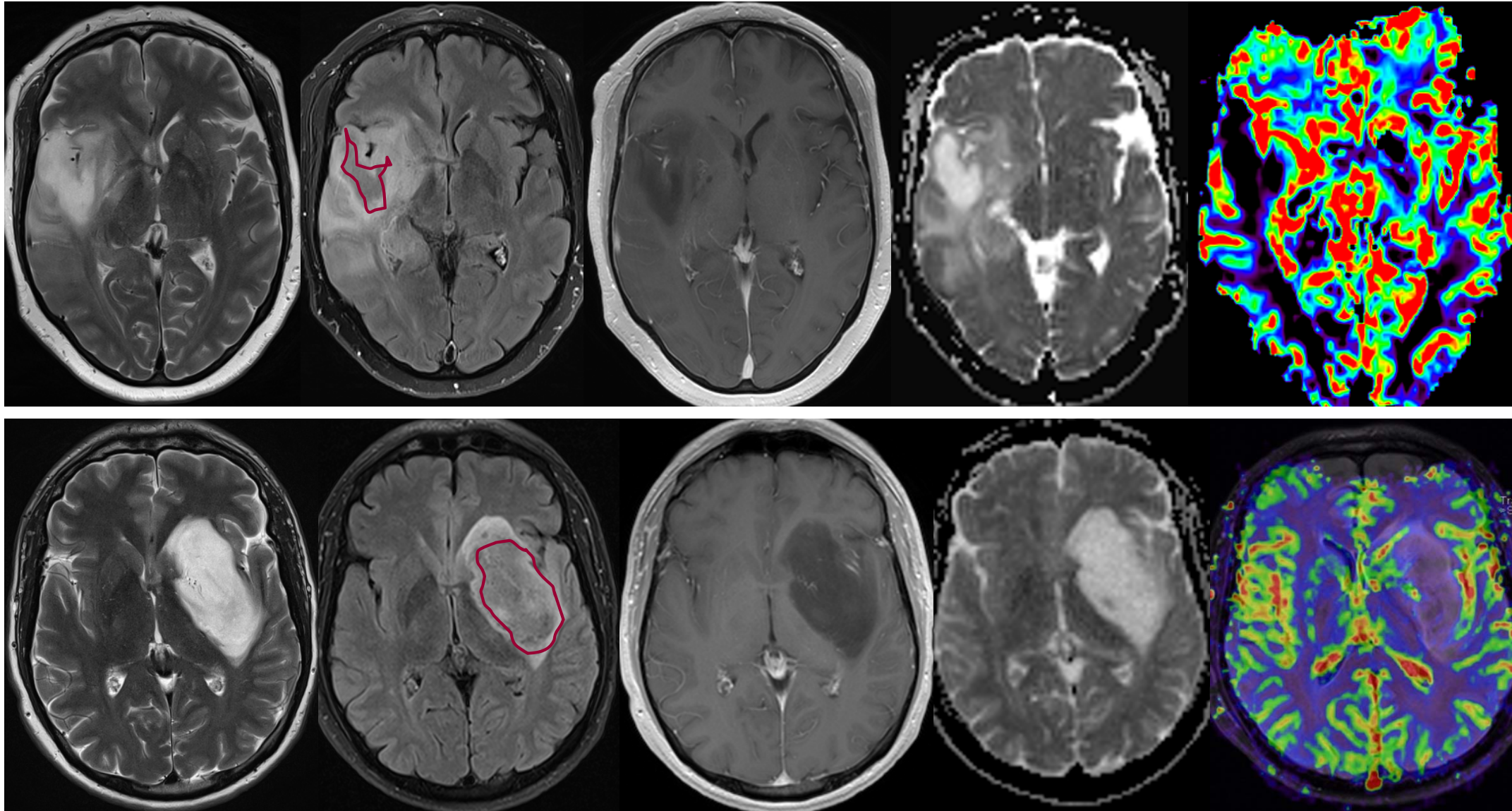
2D-COSY	SI presencia pico conexión	detección 2-HG No falsos positivos	NO comercial procesado cuantificación volumen y TA ↑
---------	----------------------------------	---------------------------------------	---------------------------------------------------------------

Radiogenómica en gliomas

Mutaciones IDH

- Marcador diagnóstico y pronóstico en gliomas (inmunohistoquímica)
- 2HG (2-hydroxyglutarate) se produce por todos los enzimas de la mutación *IDH*
- 2HG puede detectarse con espectroscopía (3Tesla) (2.25 ppm)





T2-FLAIR–mismatch sign

T2-FLAIR–mismatch sign

Mutaciones IDH

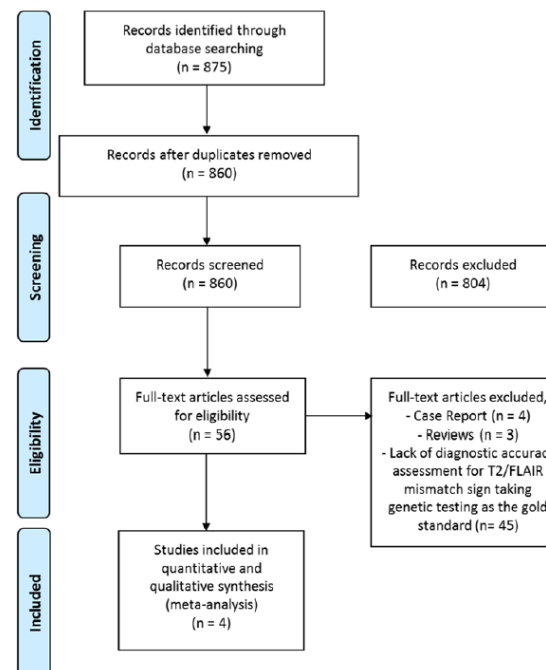
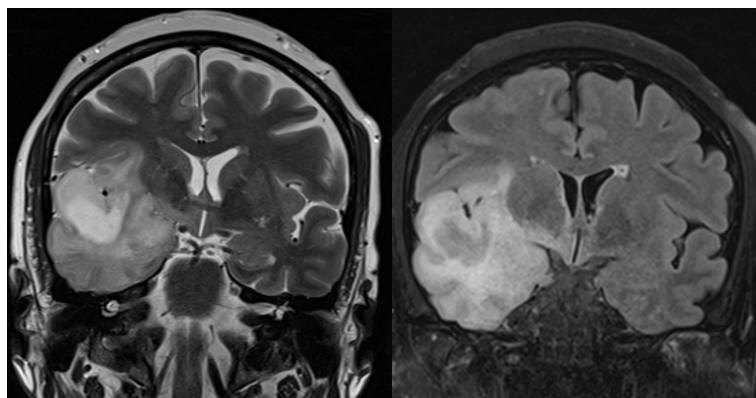


TABLE 2. Diagnostic performance of the T2-FLAIR–mismatch sign in predicting *IDH* mutation

Authors & Year	<i>IDH</i> Mutation Diagnostic Performance Parameter							
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR-	Posttest Probability (+), %*	Posttest Probability (-), %*
Patel et al., 2017 (cases)	14.7	100	100	20.9	14.7	0.9	98.3	77.7
Patel et al., 2017 (validation)	18.9	100	100	14.0	18.9	0.8	98.7	76.8
Lasocki et al., 2018	58.1	100	100	14.8	58.1	0.4	99.6	63.2
Broen et al., 2018	26.8	100	100	10.3	26.8	0.7	99.1	75.0
Overall	32.1	100	100	15.1	32.1	0.7	99.2	73.5

* Positive and negative posttest probabilities were determined using Bayes theorem with a pretest probability of 80.2%.

T2-FLAIR–mismatch sign

Mutaciones IDH

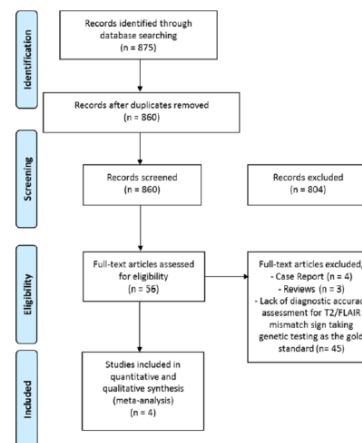
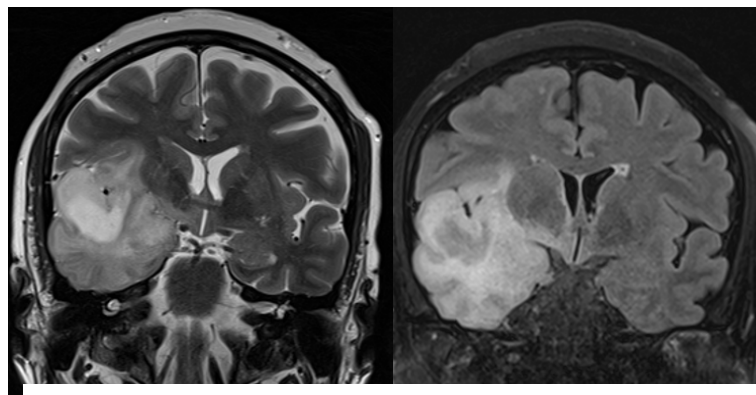


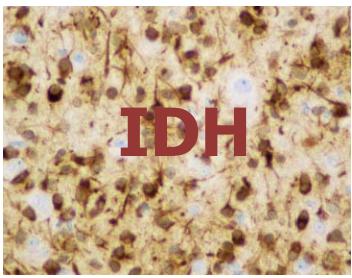
TABLE 4. Diagnostic performance of the T2-FLAIR–mismatch sign in predicting *IDHmut-Noncode1*

Authors & Year	<i>IDH</i> Mutation Diagnostic Performance Parameter							
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR-	Posttest Probability (+), %*	Posttest Probability (-), %*
Patel et al., 2017 (cases)	22.1	100	100	51.8	22.1	0.8	95.7	43.8
Patel et al., 2017 (validation)	45.5	100	100	76.0	45.5	0.5	97.8	35.3
Lasocki et al., 2018	31.4	87.5	78.6	46.7	2.5	0.8	71.5	43.9
Broen et al., 2018	50.7	100	100	68.1	50.7	0.5	98.1	33.0
Overall	33.7	98.5	95.5	60.7	22.5	0.7	95.7	40.2

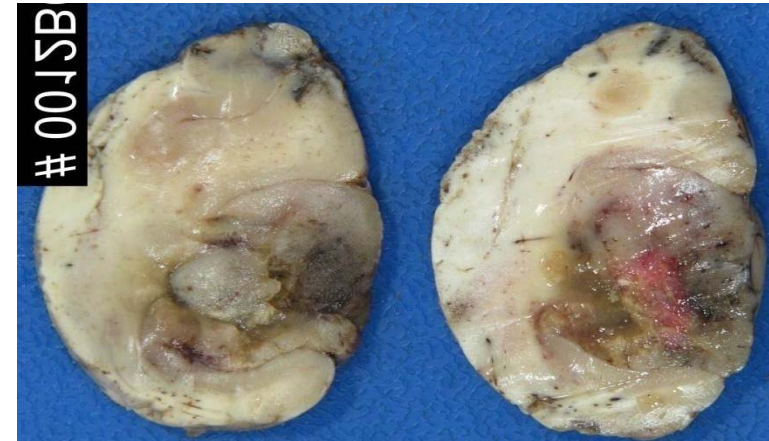
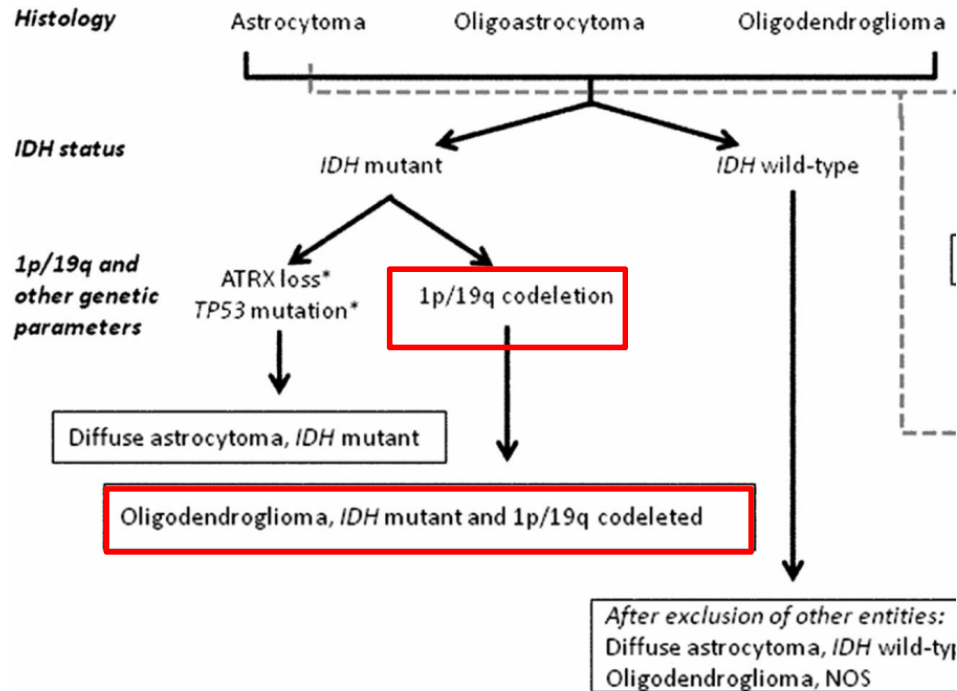
TABLE 3. Diagnostic performance of the T2-FLAIR–mismatch sign in predicting *IDHmut-Code1*

Authors & Year	<i>IDH</i> Mutation Diagnostic Performance Parameter							
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR-	Posttest Probability (+), %*	Posttest Probability (-), %*
Patel et al., 2017 (cases)	0.0	84.3	0.0	70.4	0.01	1.2	0.4	33.9
Patel et al., 2017 (validation)	0.0	65.5	0.0	38.0	0.01	29.9	0.4	39.8
Juratli et al., 2019	73.2	76.0	83.3	63.3	3.1	0.4	56.9	13.2
Broen et al., 2018	0.0	62.0	0.0	53.4	0.01	1.6	0.4	41.1
Overall	29.9	72.7	44.4	58.7	1.1	1.0	32.2	29.4

* Positive and negative posttest probabilities were determined using Bayes theorem with a pretest probability of 30.2%.



WHO2016



Moderada celularidad
Núcleos redondos
Halos perinucleares
Capilares finos ramificados
Degeneración mucoide/quística
Calcificaciones

80% Gliomas de bajo grado son IDH mut: 37-50% codelección
Son más sensibles al tratamiento

102 LGG IDH mut

Edad

Lóbulo frontal
Homogeneidad
T2/flair mismatch sign
T2* señal

Márgenes
Realce con contraste
Quistes
Necrosis
Diámetro máximo
Infiltración cortical
Edema
+ de 3 lóbulos
Desviación línea media
Hidrocefalia

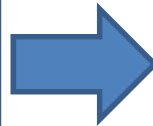
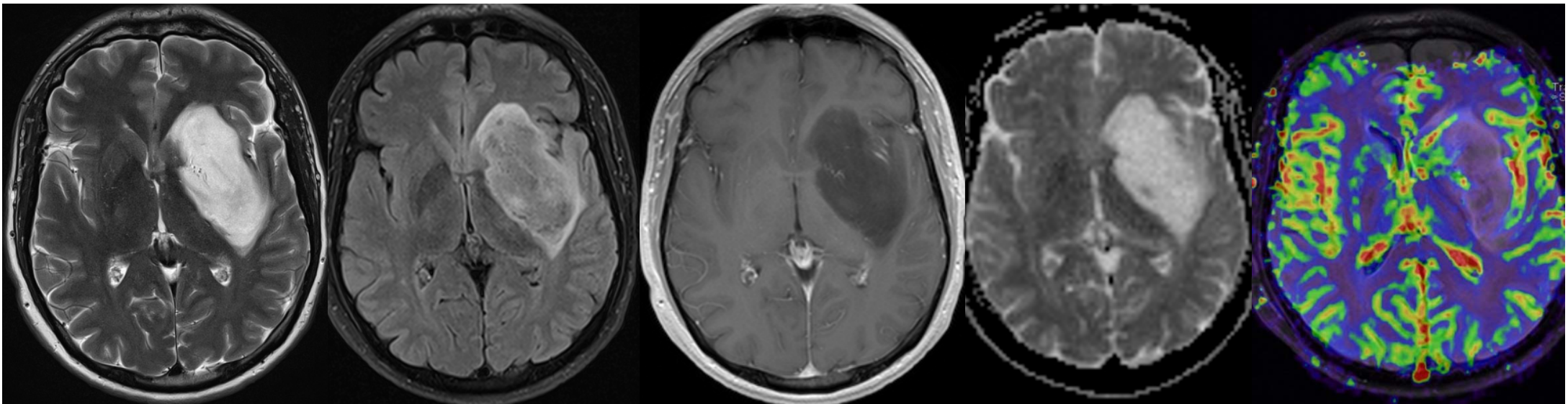
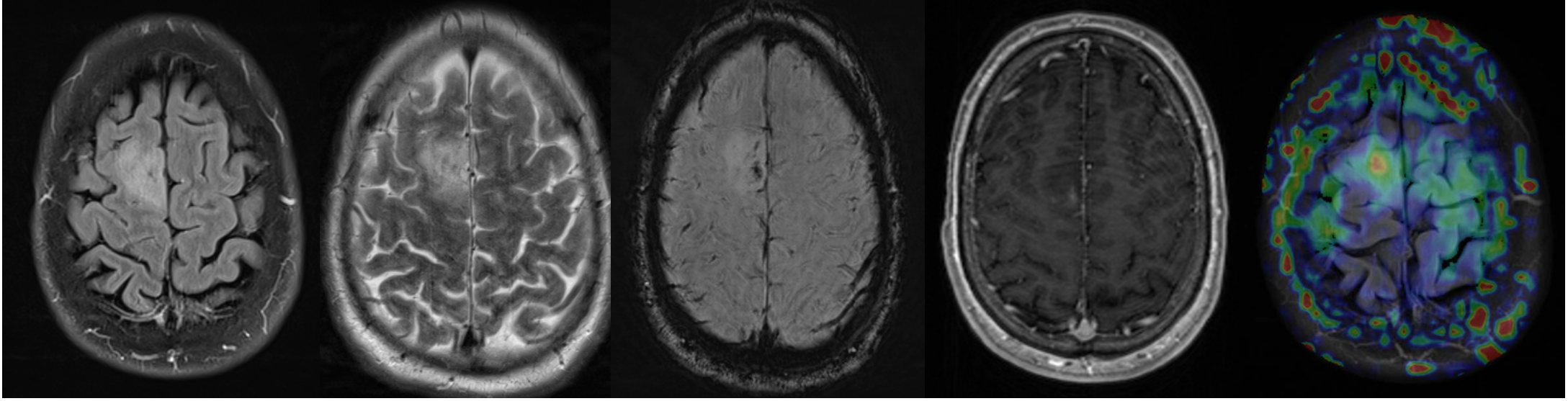


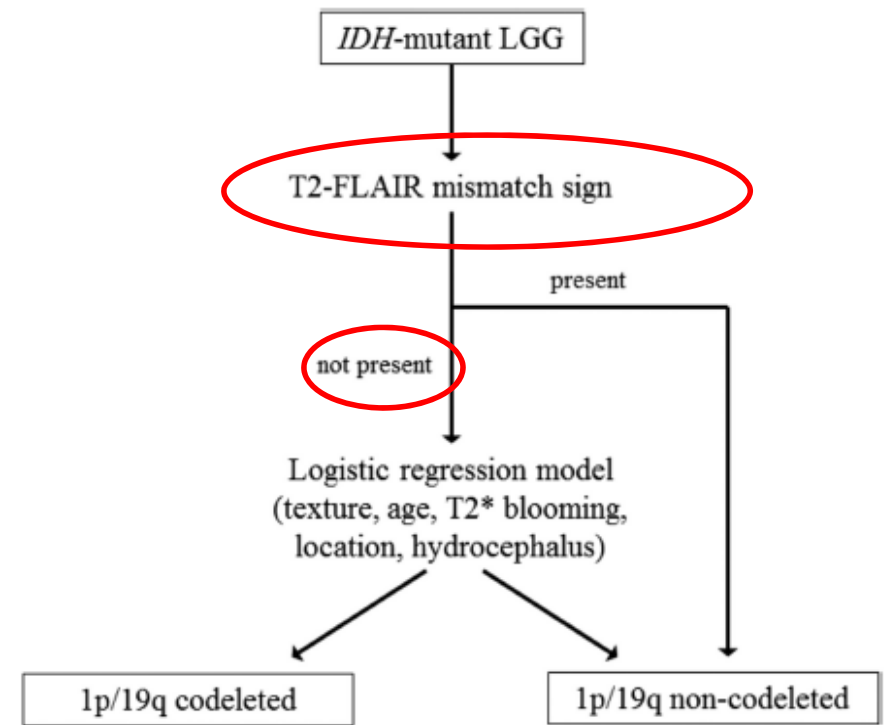
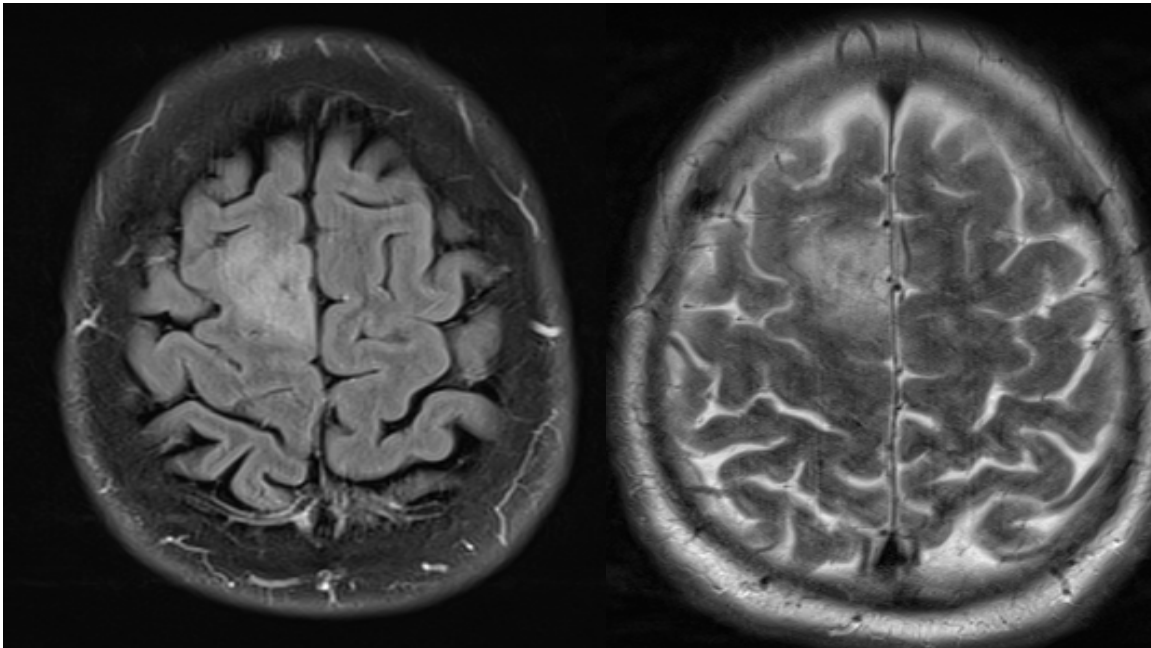
Table 1: Univariate logistic regression analyses for predicting 1p/19q codeletion among the training dataset

Predictor	Ratio	Odds Ratio (95% CI)	P Value
Maximum diameter (cm)	1st Quartile: 3rd quartile	1.33 (0.70–2.49)	.381
Margins	Irregular: sharp	1.04 (0.47–2.33)	.917
Texture	Homogeneous (<75%): homogeneous (>75%)	12.33 (4.66–31.58)	<.001 ^a
Peritumoral edema	Yes: no	1.42 (0.62–3.23)	.973
Hydrocephalus	No: yes	2.32 (0.88–6.11)	.089
Midline shift (cm) ^b	1st Quartile: 3rd quartile	4.27 (1.49–12.23)	.027 ^a
Enhancement	Yes: no	1.28 (0.57–2.86)	.555
Necrosis	Yes: no	2.18 (0.61–7.69)	.228
T2* blooming	Yes: no	6.92 (2.04–23.49)	.002 ^a
Cortical infiltration	Yes: no	2.02 (0.67–6.10)	.212
Cyst	No: yes	1.18 (0.48–2.91)	.715
T2 FLAIR mismatch sign ^c	No: yes	22.50 (6.26–∞)	<.001 ^a
Gliomatosis	Yes: no	1.13 (0.18–7.08)	.896
Primary lobe	Frontal: nonfrontal	5.68 (2.08–15.44)	.001 ^a
Age	3rd Quartile: 1st quartile	3.38 (1.71–6.71)	<.001 ^a
Sex	Female: male	1.55 (0.69–3.50)	.283

Mutaciones IDH/ Delección 1p/19q



Mutaciones IDH/ Delección 1p/19q



Batchala et al. AJNR 2019

astrocytoma oligoastrocytoma oligodendroglioma

IDH mutation

IDH-mutant

IDH-wildtype

1p/19q codeletion

TERT promoter, CIC,
and FUBP1 mutations

P53 mutation,
ATRX inactivation

If midline
location,
test for
H3F3A
K27M
mutations

**IDH-mutant,
1p/19q codeleted**

**IDH-mutant,
1p/19q non-codeleted**

IDH-wildtype

Oligodendroglioma, IDH-mutant
and 1p/19q-codeleted (grade II)

Anaplastic oligodendroglioma,
IDH-mutant and 1p/19q-
codeleted (grade III)

Diffuse astrocytoma,
IDH-mutant (grade II)

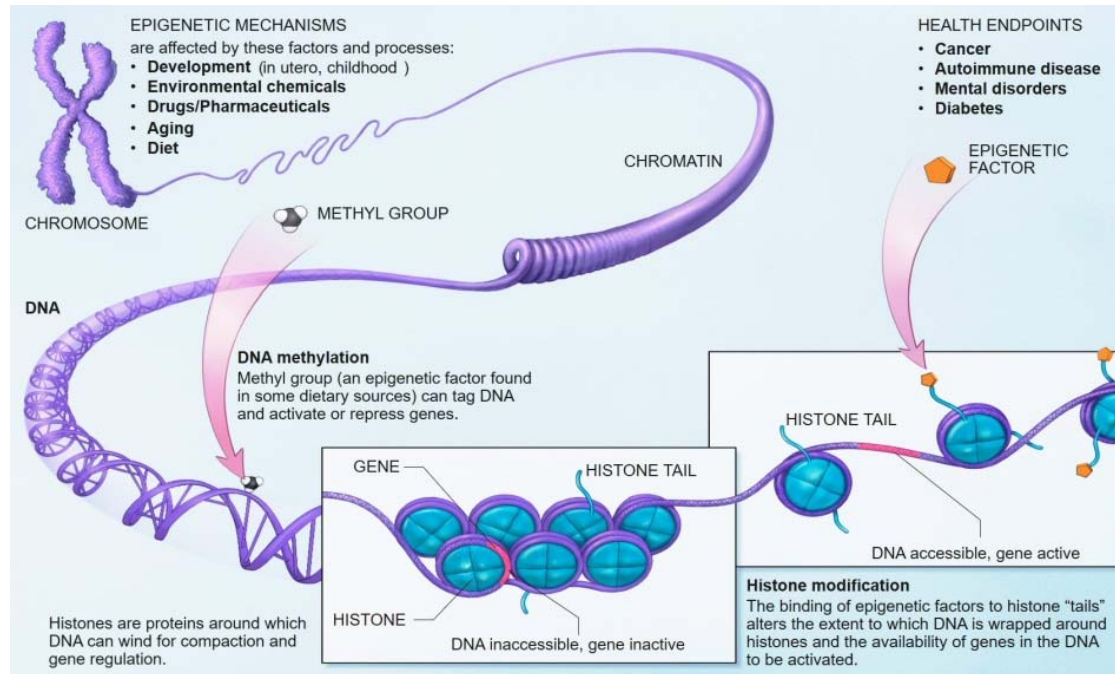
Anaplastic astrocytoma,
IDH-mutant (grade III)

Diffuse astrocytoma,
IDH-wildtype (grade II)

Anaplastic astrocytoma,
IDH-wildtype (grade III)

Diffuse
midline
glioma, H3
K27M-
mutant
(grade IV)

Glioma difuso de línea media H3 K27 mutado



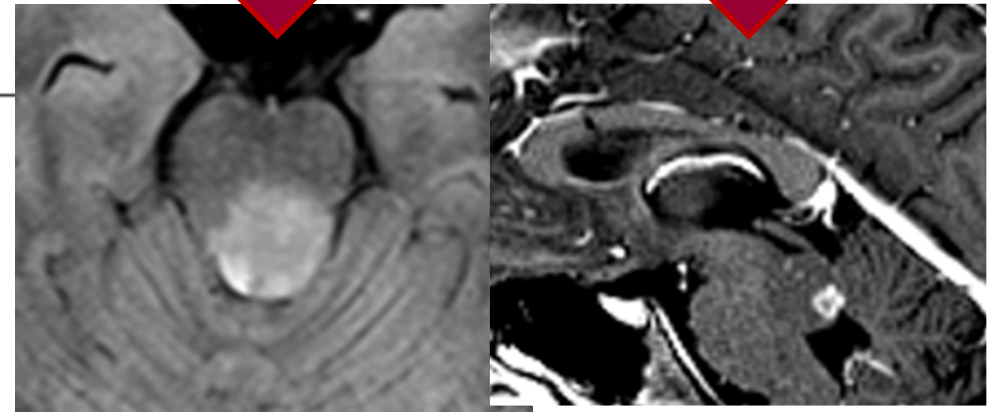
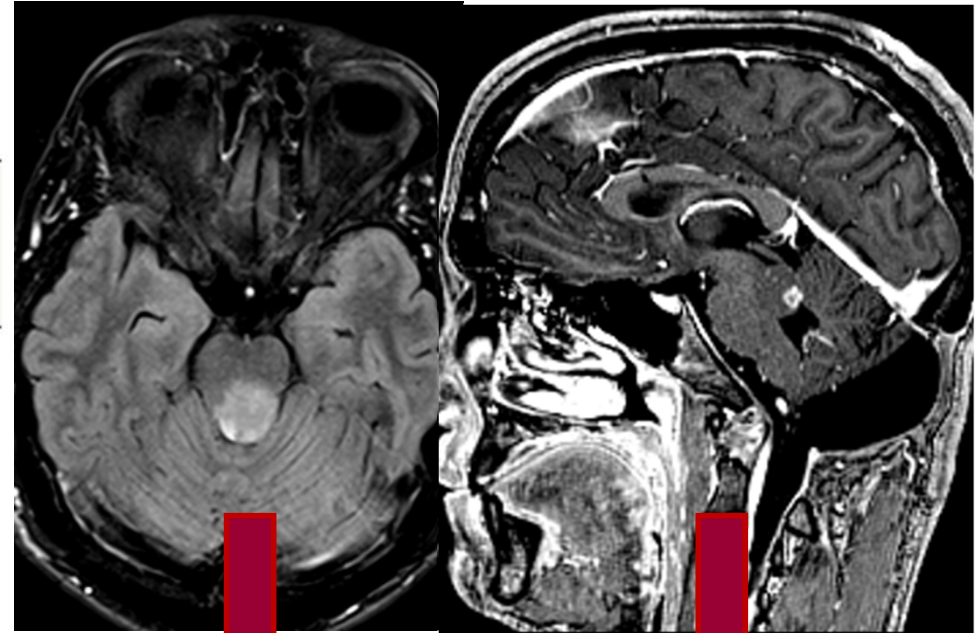
Tálamo
Hipotálamo
Pineal
III v
Cerebelo
Tronco
Médula espinal

Glioma difuso de línea media H3 K27 mutado

Table 2: MRI characteristics^a

	All Patients (n = 33)	Histone H3 K27 Mutant (n = 24)	Histone H3 Wildtype (n = 9)
Multifocality	5	5	0
Contrast enhancement	22	16	6
Cystic component or necrosis	18	15	3
Edema	4	4	0
Infiltrative pattern	27	18	9
Mass effect	32	24	8
Irregular border	27	18	9
CSF-based metastases	7	6	1
Direct cortical invasion	12	9	3

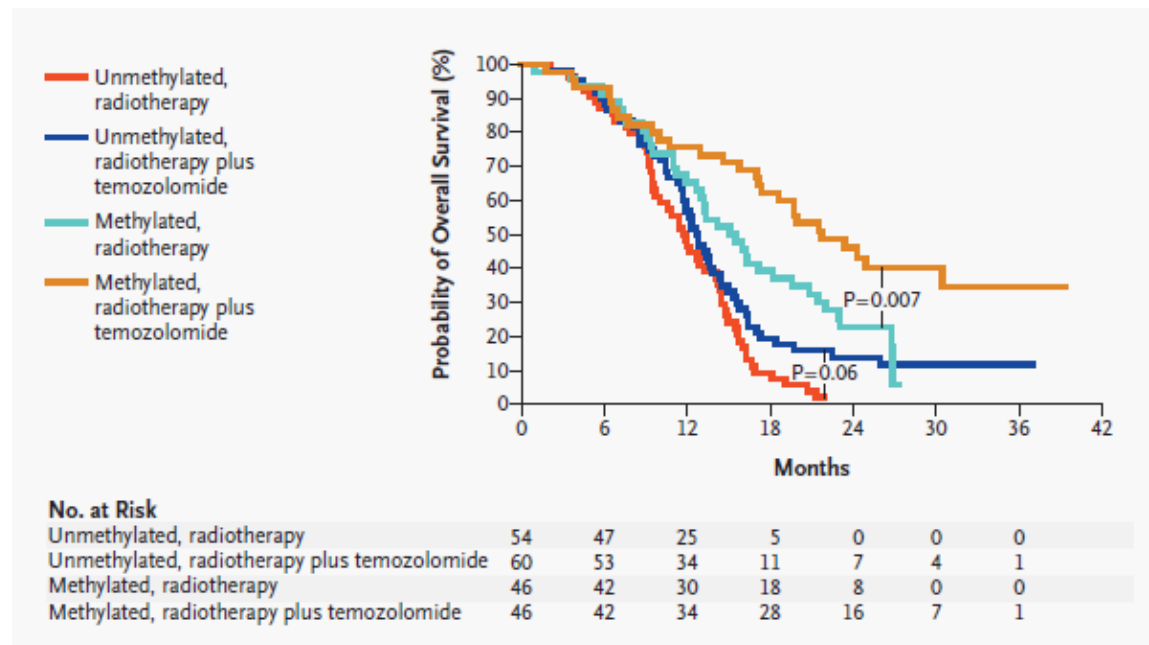
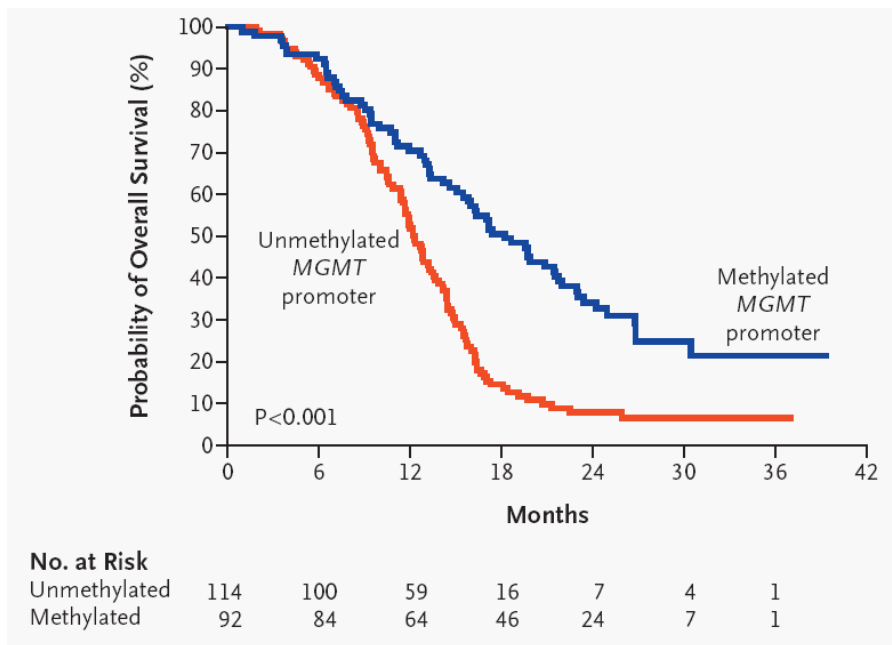
Aboian et al. AJNR2017



Vall d'Hebron

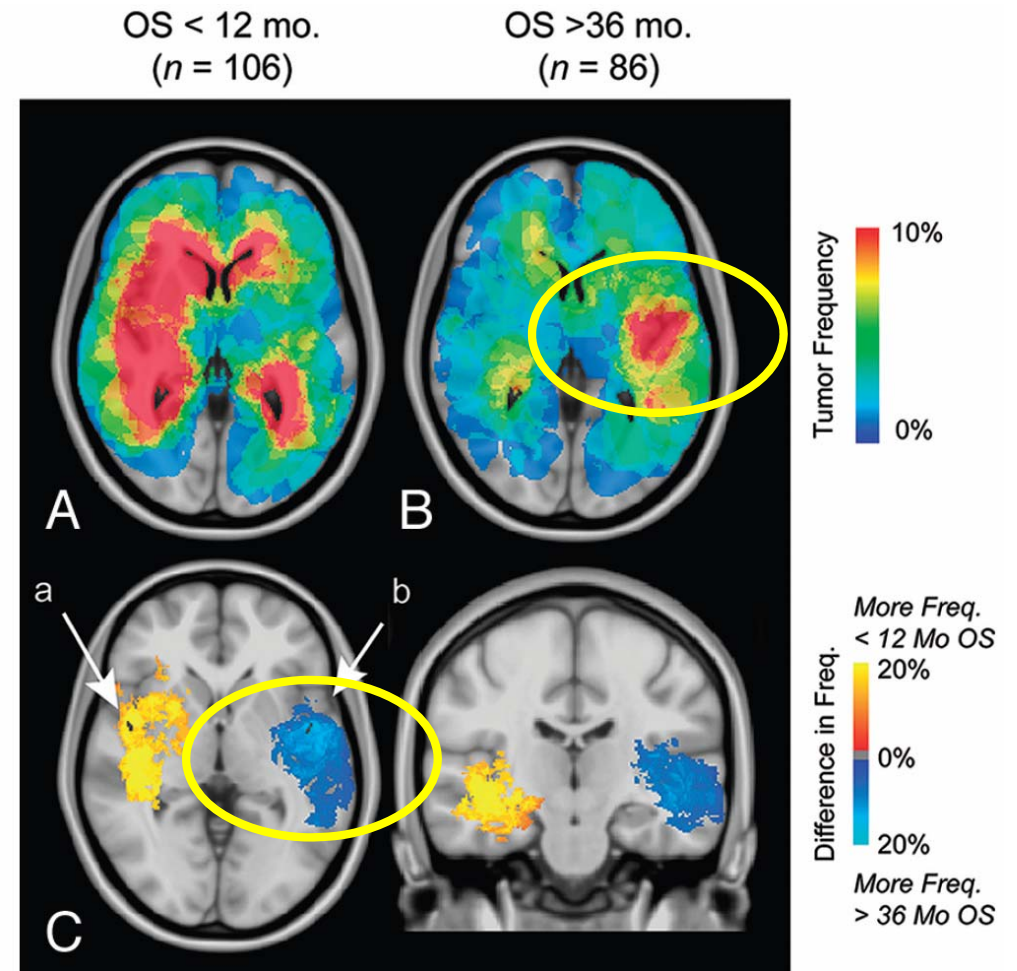
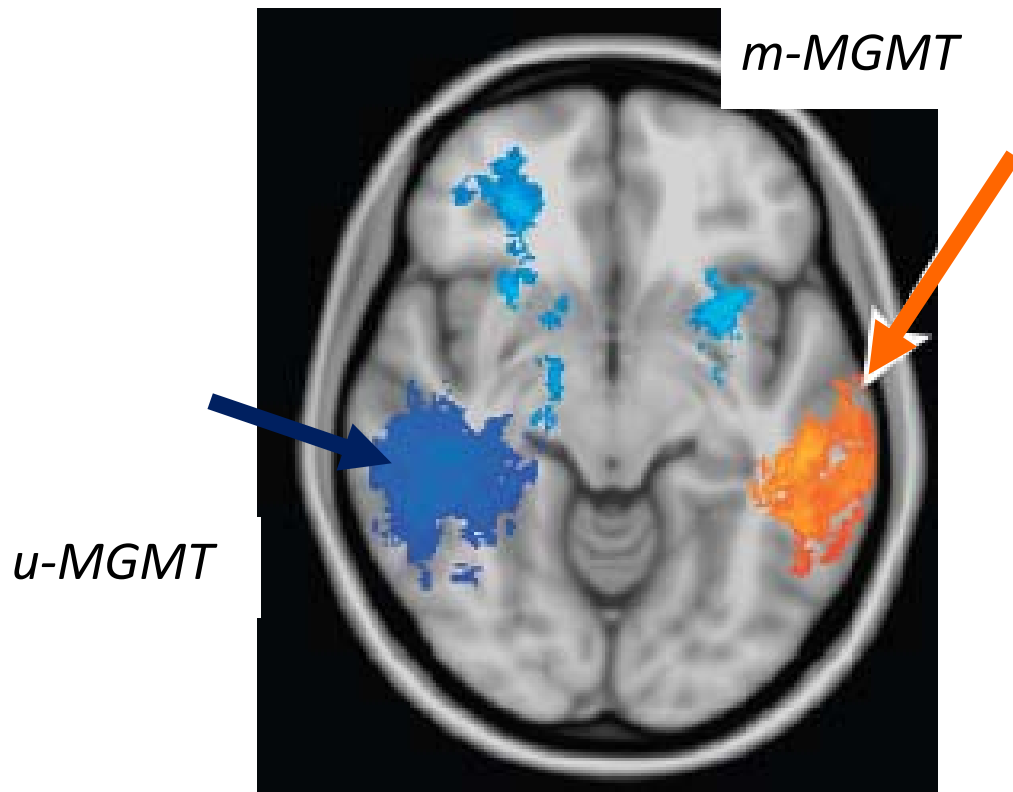
Enzima reparador MGMT

- Repara células tumorales (aumenta su supervivencia)
- Metilación MGMT inactiva su función reparadora (50% de GBMs)
- M-MGMT mayor supervivencia pacientes, mejor respuesta a TMZ, mayor incidencia de PsP
- Pobre correlación entre hallazgos RMc y estado MGMT



Radiogenómica en gliomas alto grado

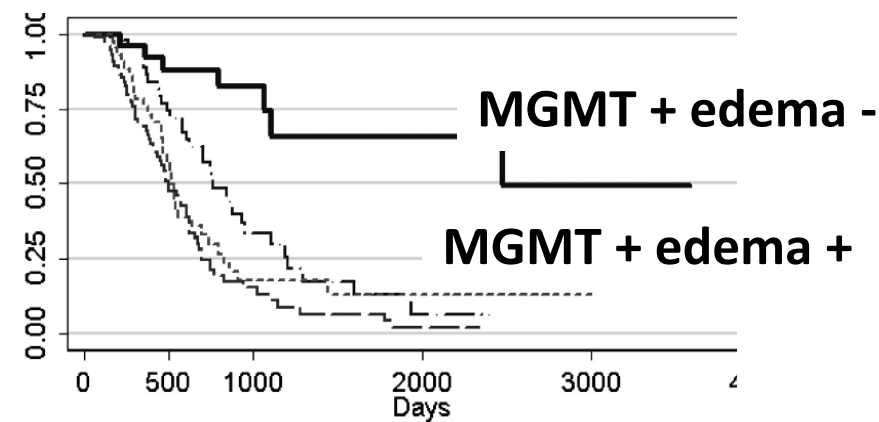
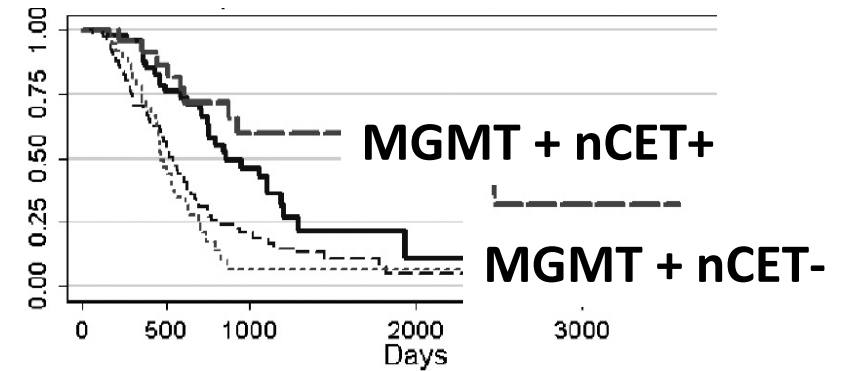
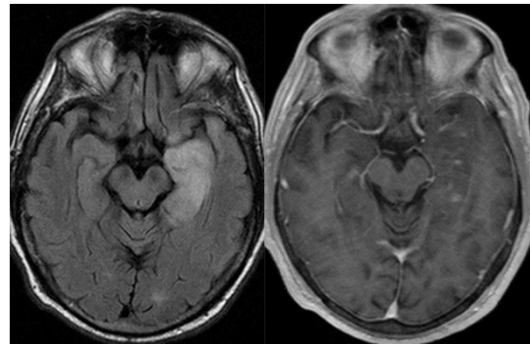
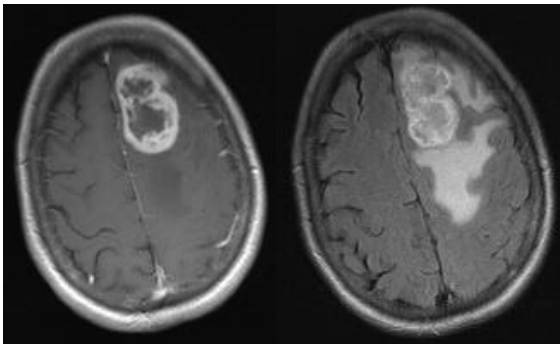
Topografía y supervivencia



Radiogenómica en gliomas alto grado

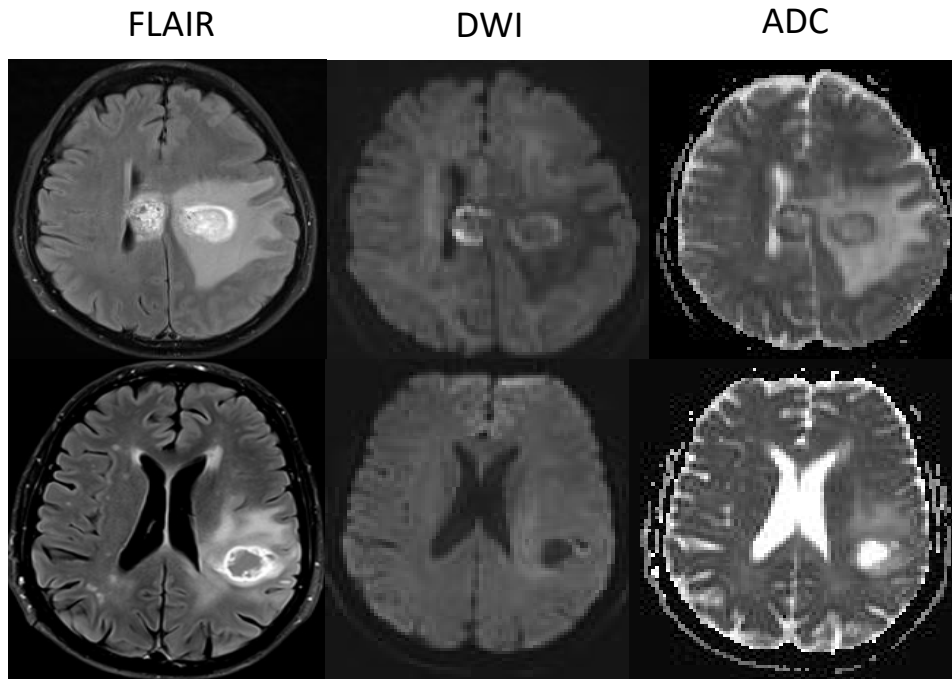
Enzima reparador MGMT

- *Realce en anillo se asocia con MGMT no metilado*
 - *M-MGMT sin edema mayor supervivencia*
 - *M-MGMT con áreas sin realce mayor supervivencia*

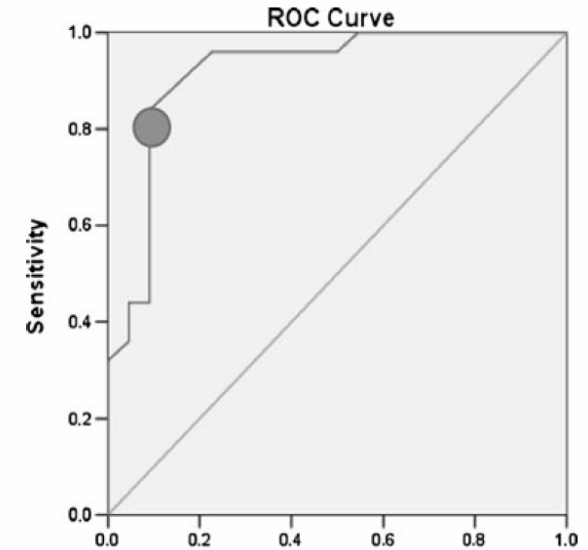


Radiogenómica en gliomas alto grado

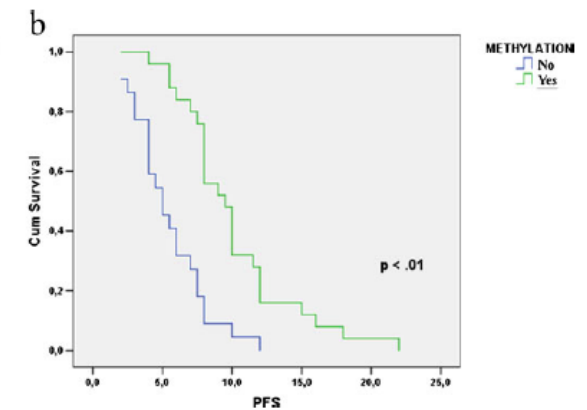
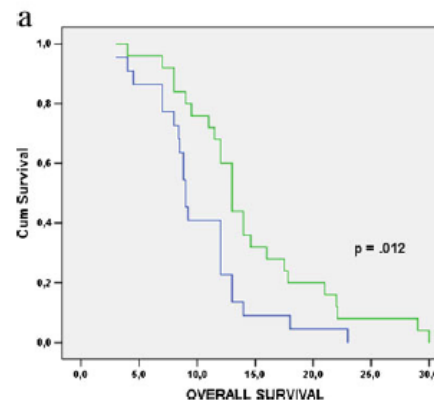
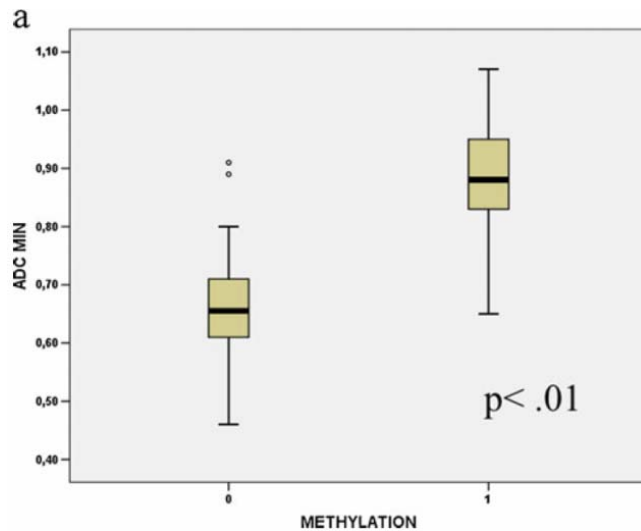
ADC y MGMT



Diferenciación entre gliomas metilados v no-metilados



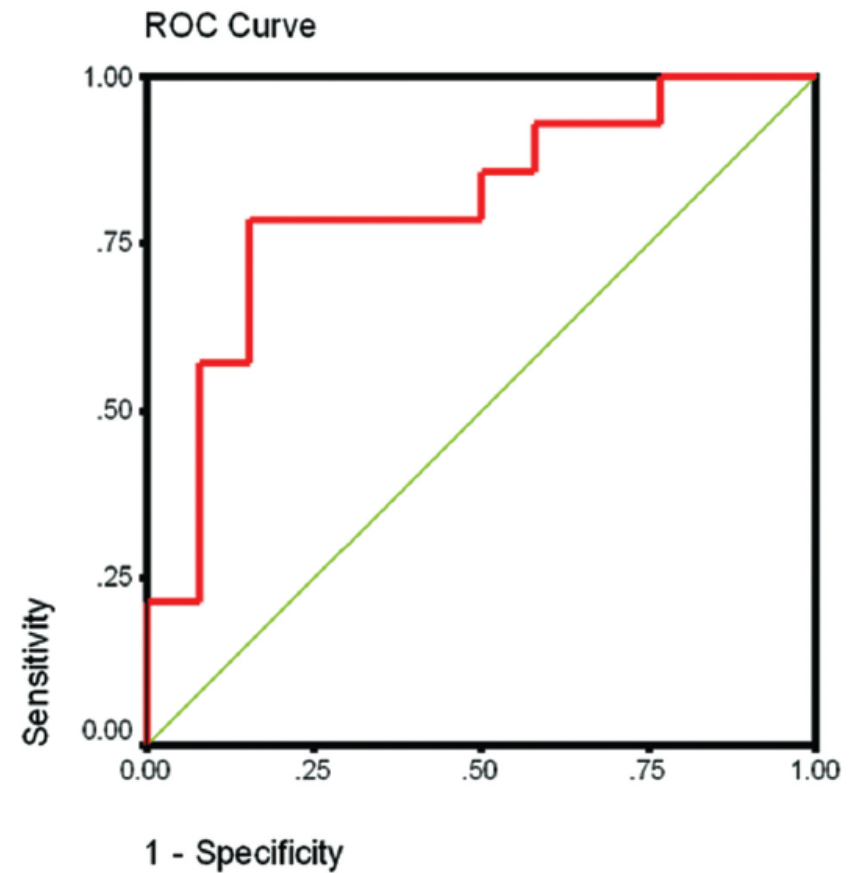
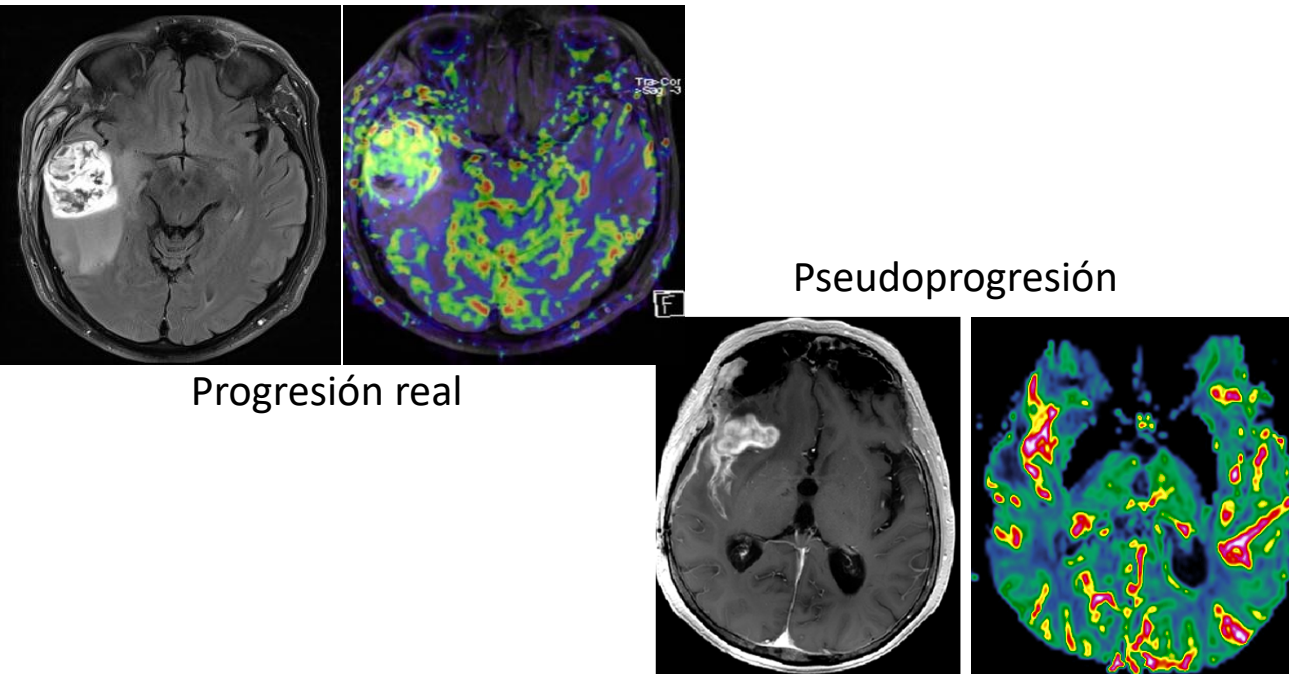
Valor ADC mínimo: $0,80 \times 10^{-3}$ mm^2/s , sensibilidad (84%) y especificidad (91%)



Romano et al. Eur Radiol 2012

Progresión precoz vs. Pseudoprogresión

Valor diagnóstico Perfusión (rCBV)



	No.	rCBV	95% CI	P Value
Unmethylated group	22			
Pseudoprogression	4	0.87	0.10–1.63	.009
Real progression	12	3.25	1.46–5.04	
Methylated group	26			
Pseudoprogression	9	1.56	0.57–2.55	.258
Real progression	7	2.34	1.05–3.61	

rCBV de 1,4 tiene 81,5% sensibilidad y 77,8% especificidad

Conclusiones

Técnicas de RM convencional y avanzada útiles para el diagnóstico y seguimiento de tumores cerebrales

- ❖ *Diagnóstico*
- ❖ *Diagnóstico diferencial*
- ❖ *Gradación*
- ❖ *Planificación terapéutica*
- ❖ *Respuesta-progresión*
- ❖ *Pseudofenómeno: pseudoprogresión / radionecrosis / pseudorespuesta*
- ❖ **Radiogenómica**



- Refinamiento clasificación
- Predicción pronóstica
- Tratamiento individualizado

AGRADECIMIENTOS



Unitat de Recerca Ressonància Magnètica (IDI)

Álex Rovira
Xavier Aymerich
Juli Alonso
Elena Huerga
Juanfra Corral
Manel Alberich



Servicio de Anatomía patológica

Elena Martínez-Sáez

Servicio de Neurocirugía

Fran Martínez-Ricarte

Servicio de Oncología Radioterápica

Xavier Maldonado

Servicio de Oncología Médica

María Vieito