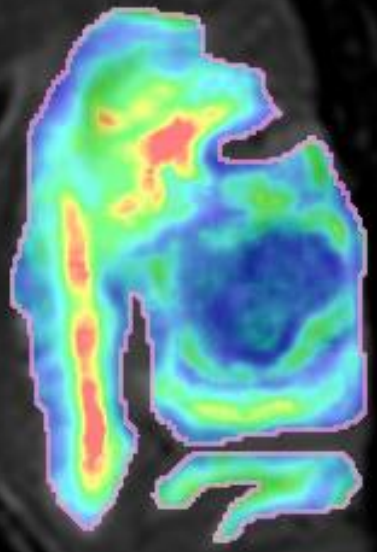
Radiomique des Gliomes

Dissection des tumeurs par l'imagerie
Avenir en clinique ?



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Pr. Vincent DOUSSET[1,2], Pr. Thomas TOURDIAS[1,2]

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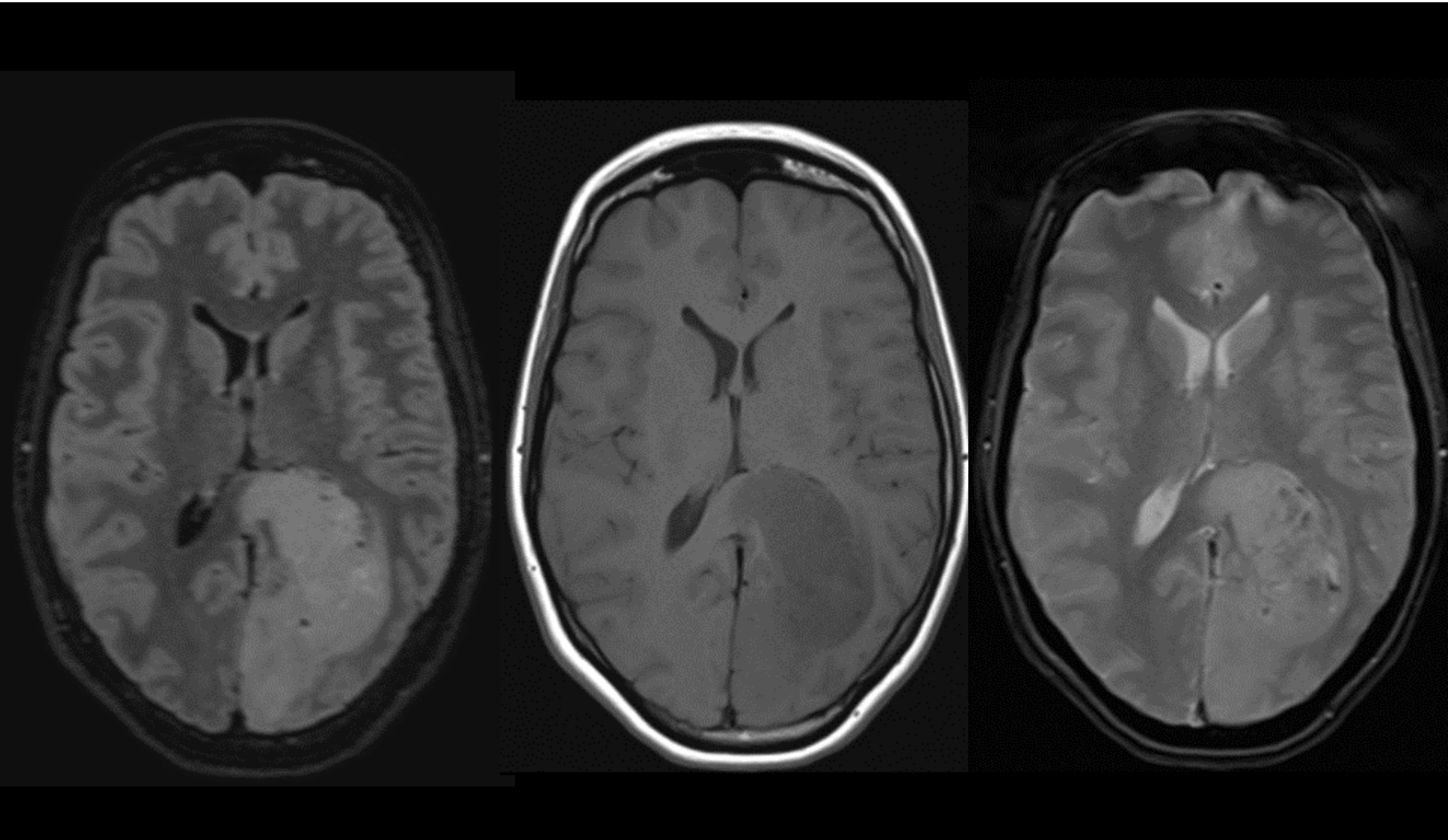
Vendredi 12 Avril 2019

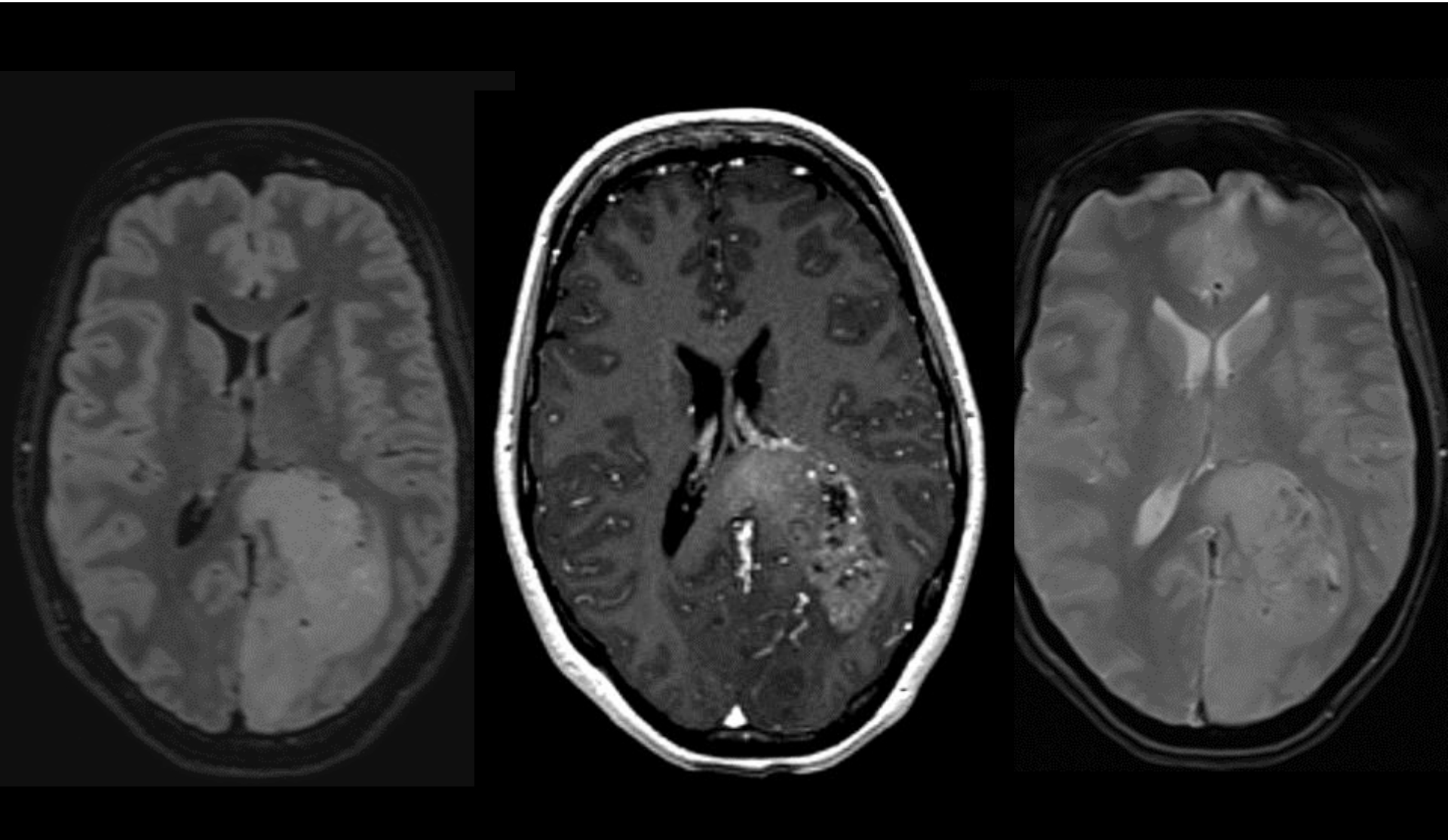
Sommaire

- Contextualisation & Définitions
- Recherche et applications en Neuro-Oncologie
- “Worklow” : Limites et solutions
- Synthèse

Imagerie Actuelle des Gliomes…



Imagerie Actuelle des Gliomes…



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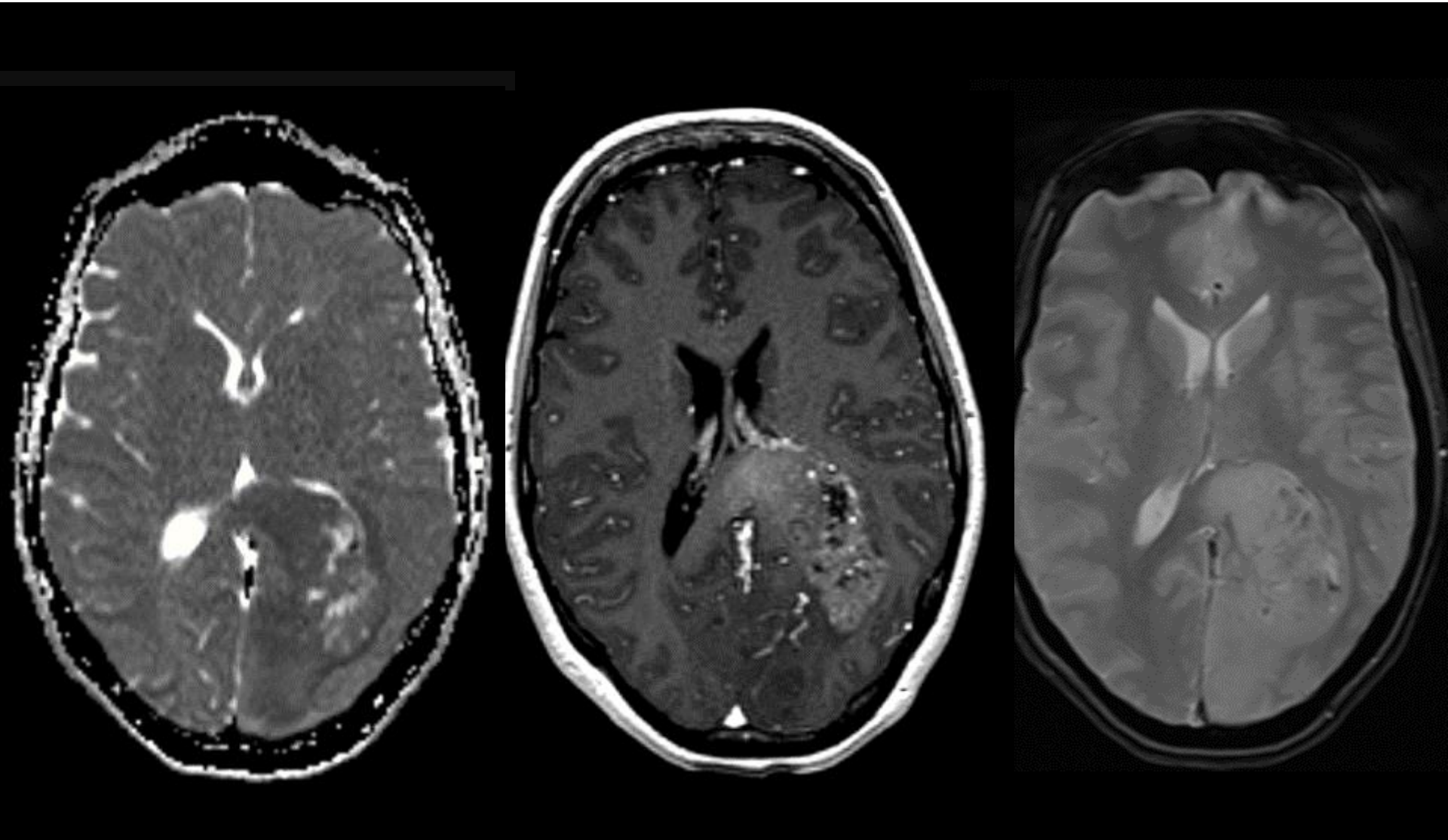

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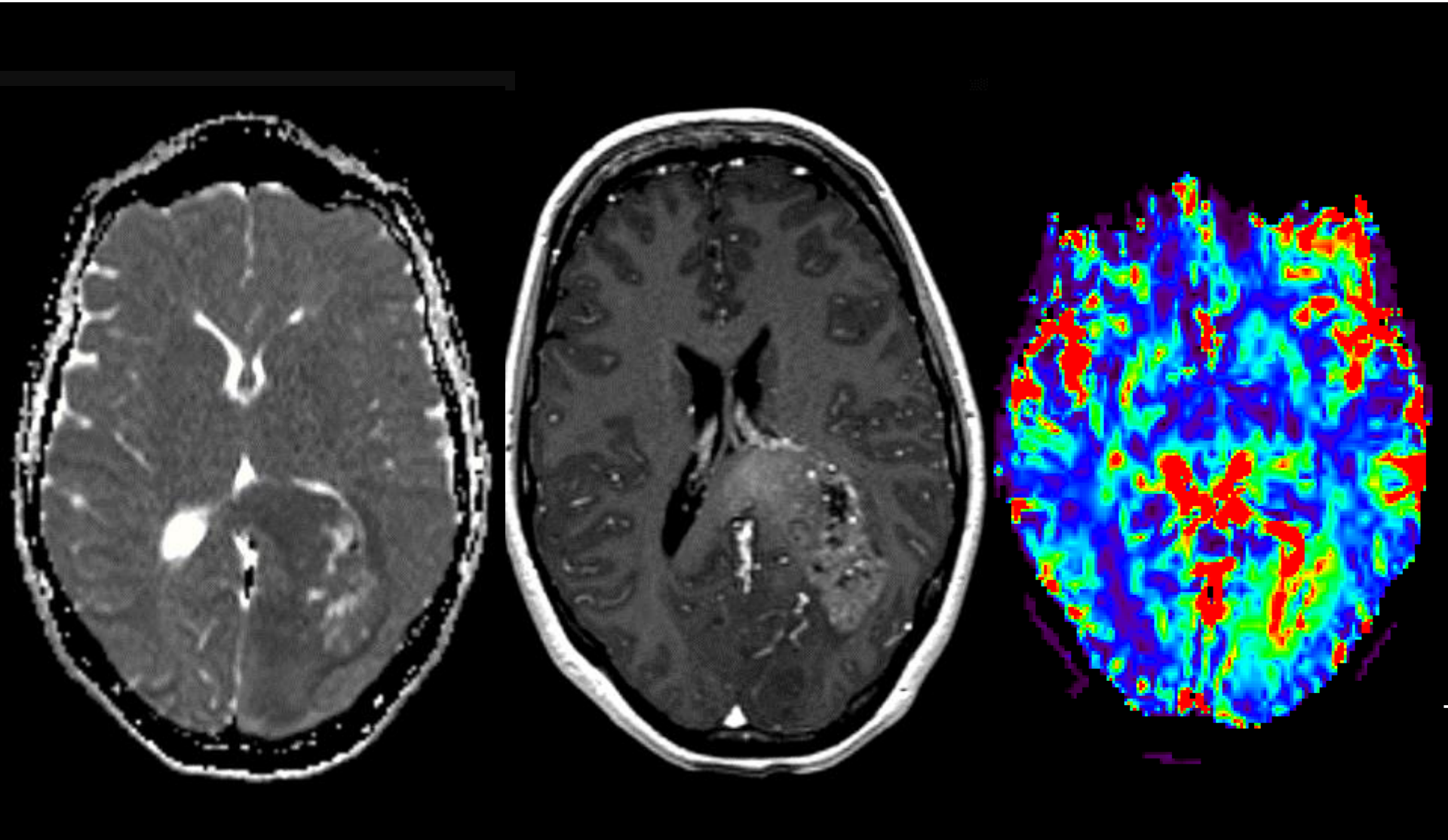

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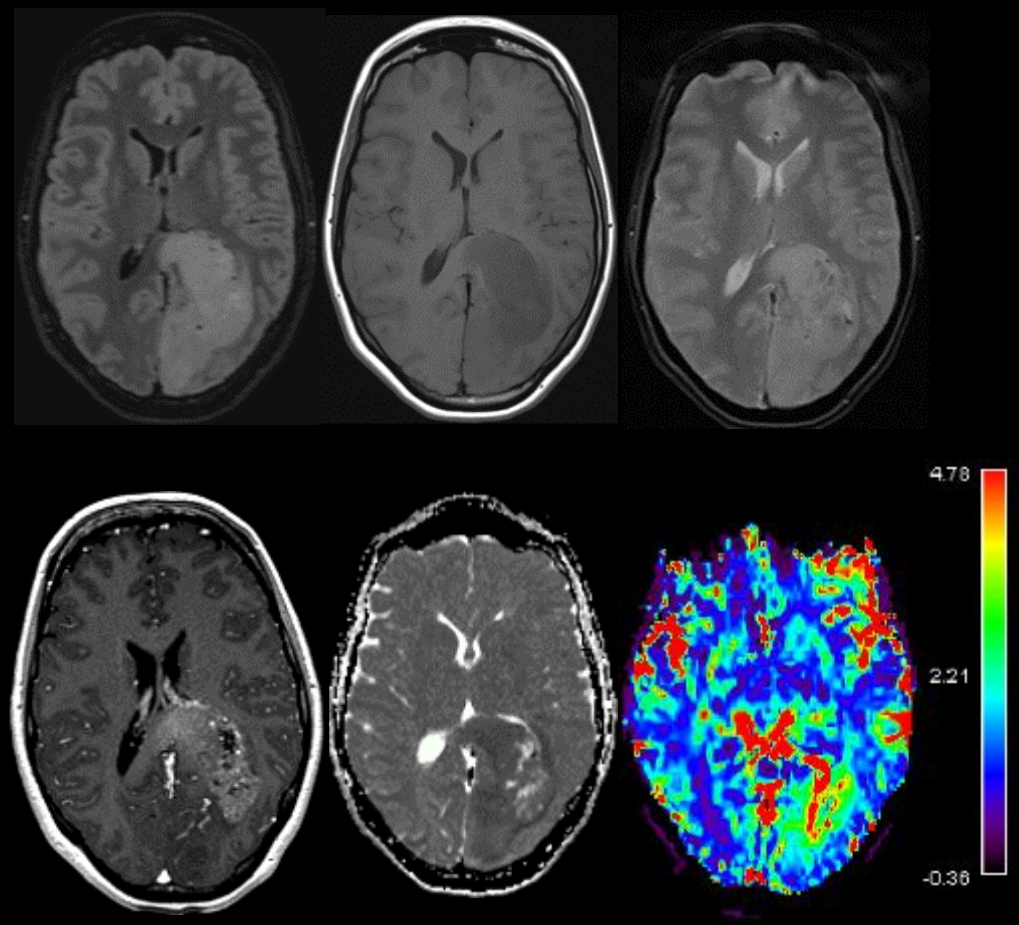

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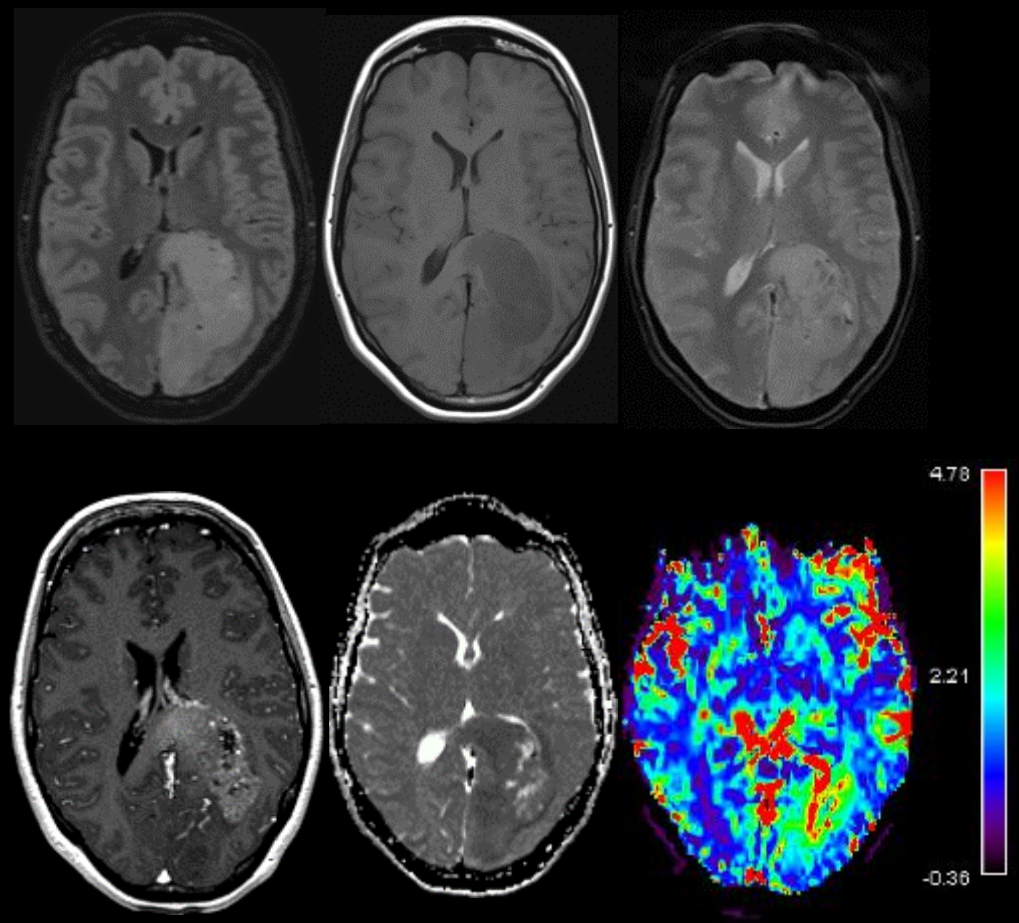
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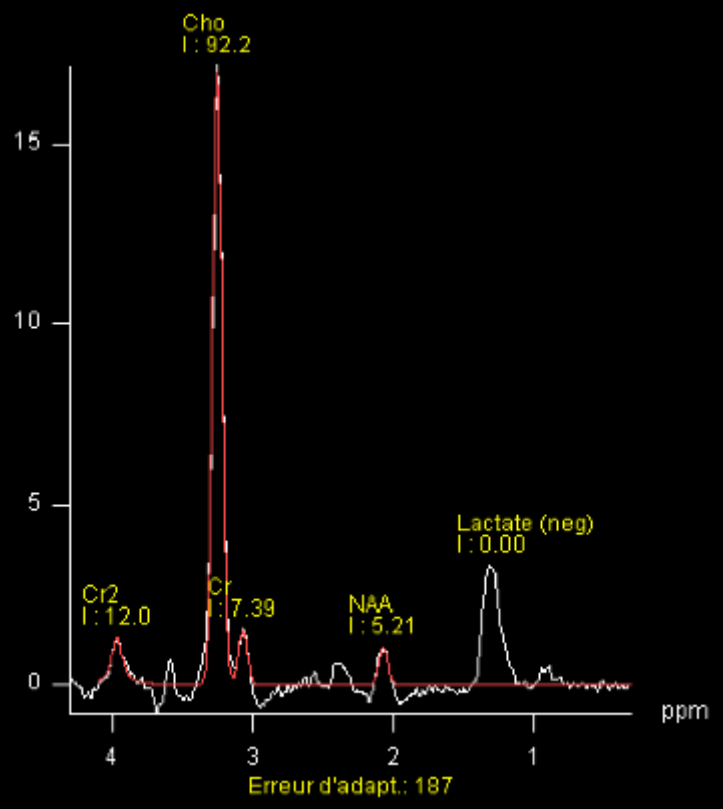
2.21
-0.36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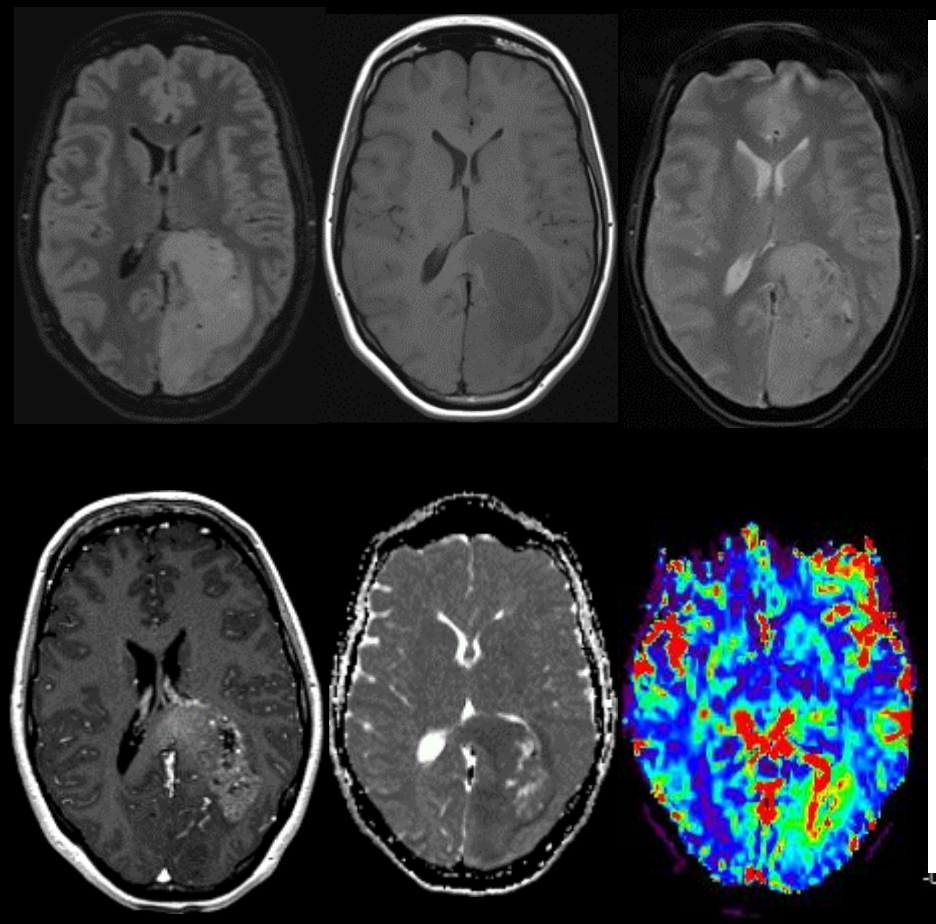
I : 92.2
15
10
5
0
Lactate (neg)
I : 0.00
Cr2
I : 12.0
Cr
I : 7.39
NAA
I : 5.21
ppm
4
3
2
1
Erreur d'adapt.: 187

Aujourd’hui …



Résultat :

Lésion unique intra axiale bien limitée de contenu hétérogène cortico sous corticale développée aux dépens du lobe occipital gauche et se prolongeant jusqu’au contact du lobe pariétal et franchissant la ligne médiane par le splénium du corps calleux.

Cette lésion refoule les sillons corticaux adjacents ainsi que la corne occipitale du ventricule latéral gauche.

Cette lésion apparaît spontanément en hyposignal T1 en majorité avec quelques hypersignaux T1 et hyposignaux T2 en faveur de discrets remaniements hémorragiques au sein de celle-ci.

Elle se rehausse de façon hétérogène après injection de produit de contraste avec quelques portions nécrotiques.

Sur les séquences de perfusion, il est visualisé une néo angiogénèse avec un rapport tumeur sur parenchyme sain estimé à 3.

Sur les séquences de diffusion, la lésion apparaît majoritairement en restriction de diffusion.

Sur l’analyse de la spectroscopie, on visualise un pic important de choline avec une inversion du rapport créatinine/choline et une diminution du NAA. Elles paraissent également augmentées au sein de la lésion.

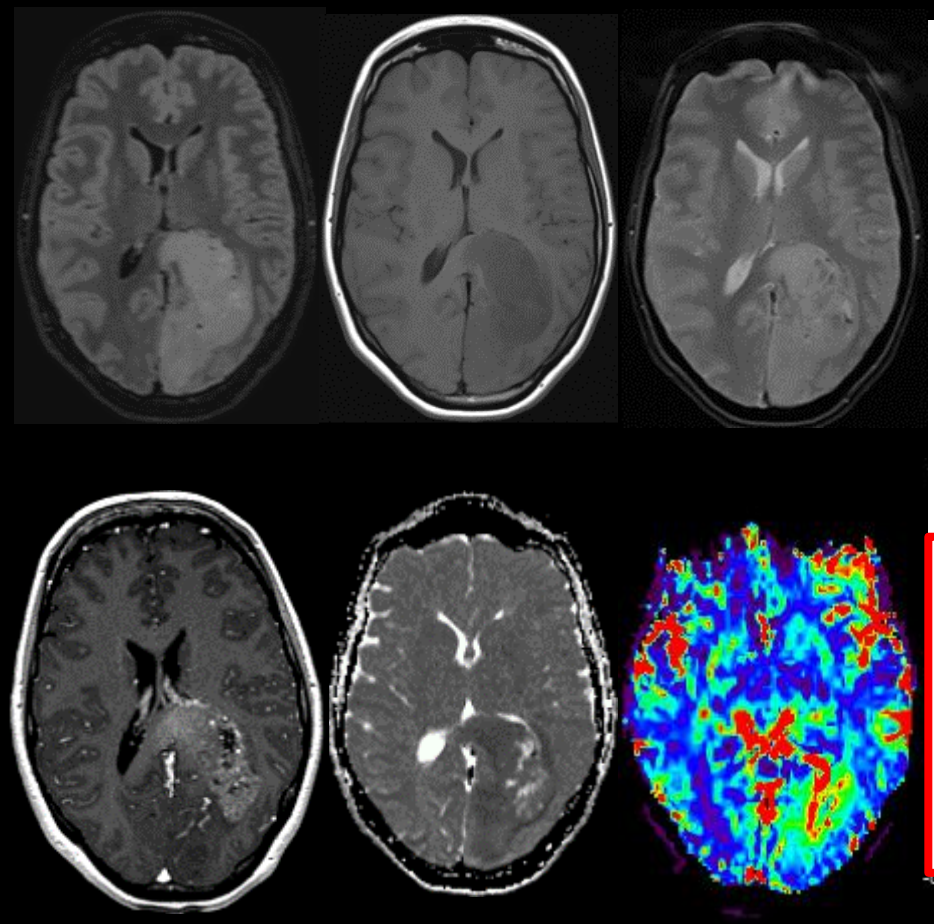
On peut donc évoquer deux hypothèses :

- une tumeur de la ligne gliale, avec pour principaux arguments la néo angiogénèse, le caractère hétérogène et l’analyse de la spectroscopie.
- une pathologie lymphomateuse, avec pour principaux arguments la restriction de diffusion, et en défaveur de cette hypothèse, une néo angiogénèse, le caractère hétérogène et les remaniements hémorragiques.

Conclusion :

Lésion unique pariéto occipitale gauche prenant le contraste, plutôt d’allure gliale de haut grade, franchissant la ligne médiane par le splénium du corps calleux.

Aujourd’hui …



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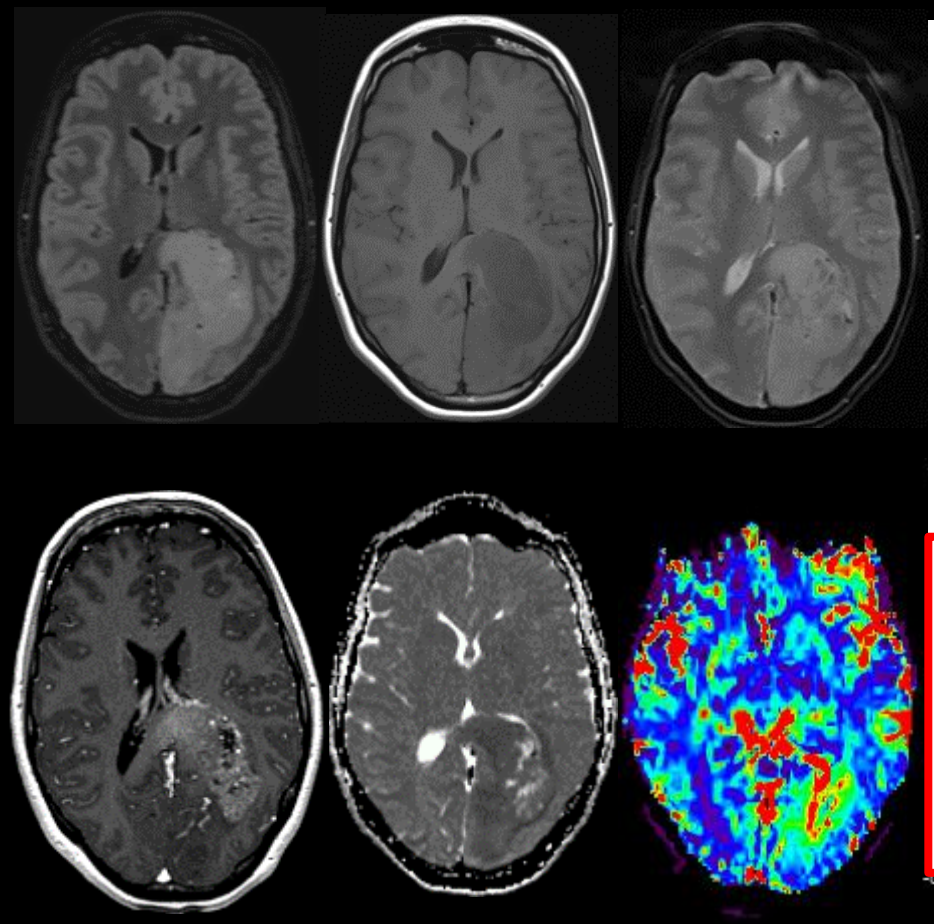

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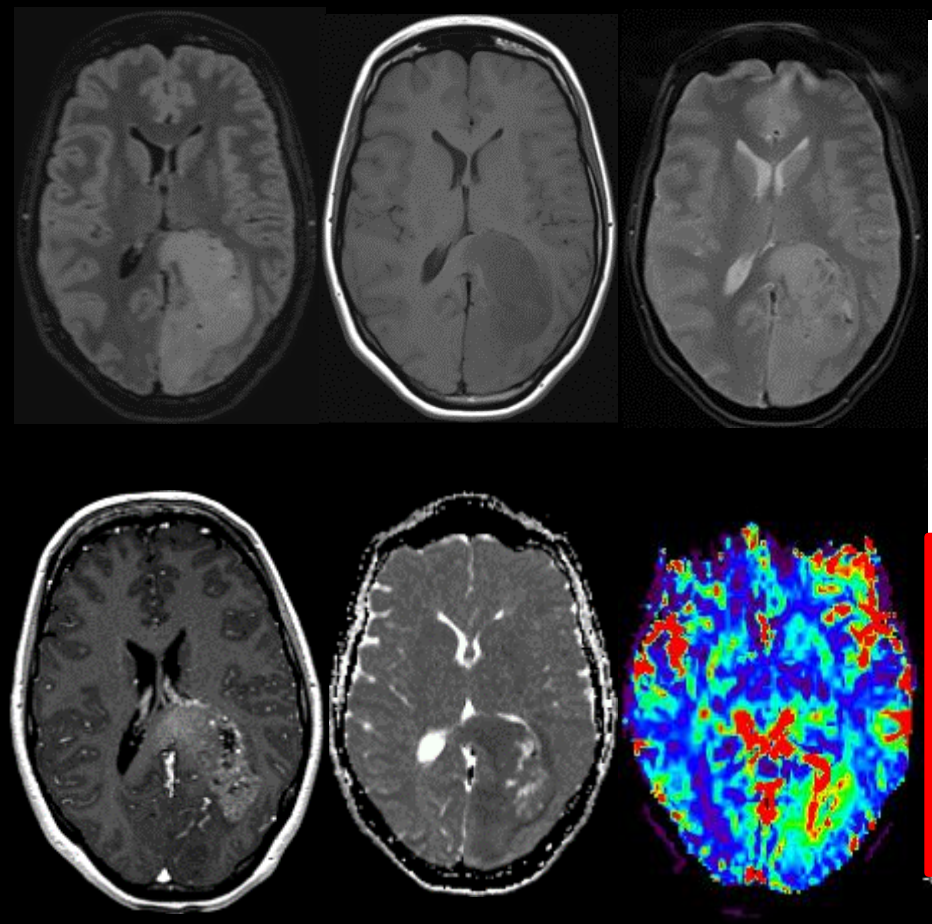


Résultat :

Lésion unique intra axiale bien limitée de contenu hétérogène cortico sous corticale

Probabilité GBM : %
Grade

Radiomic Risk
Profil IDH
Profil mMGMT / EGFRvIII …

Réponse AVASTIN®, ITK…

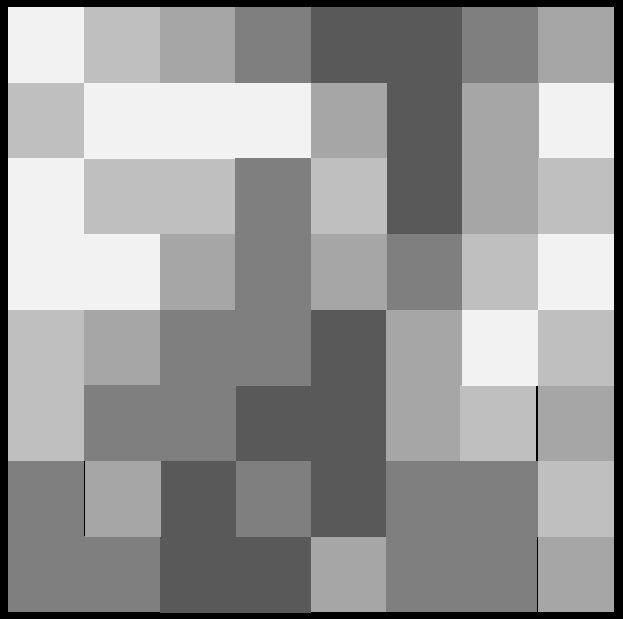
Lésion unique pariéto occipitale gauche prenant le contraste, plutot d'allure gliale de haut grade, franchissant la ligne médiane par le splénium du corps calleux.

Généralités

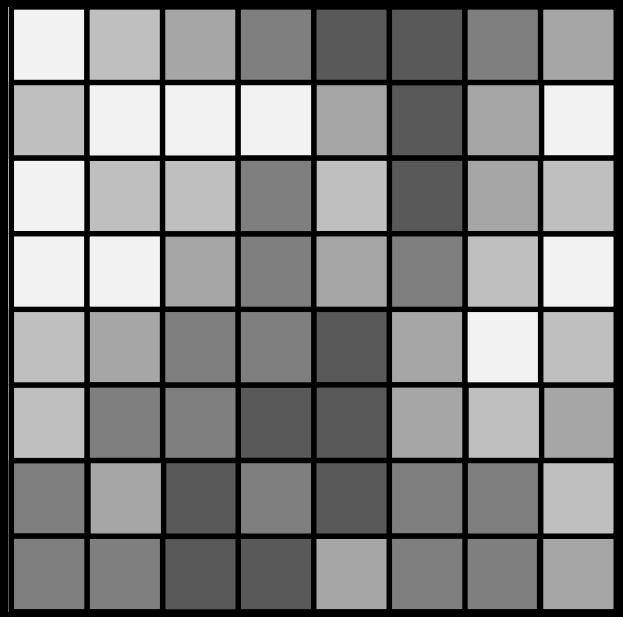
-Omics

- Big Data
  1. Extraction grande quantité de données
  2. Traitement de l’information émission hypothèses
- Substratum physiopathologique ?
- Biomarqueur

Radiomics Features

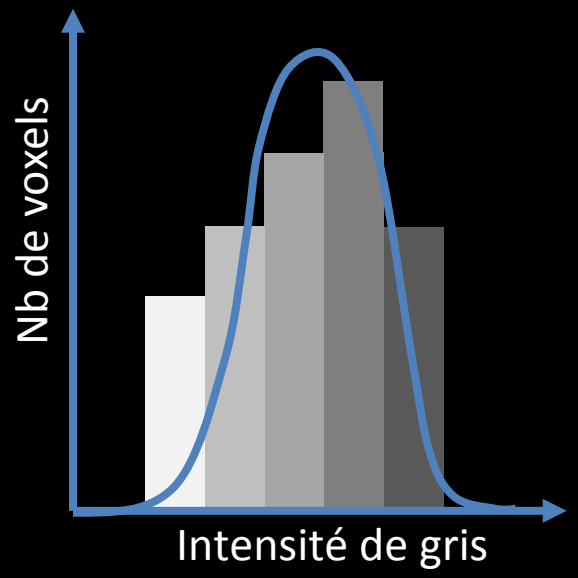


Radiomics Features



Radiomics Features

1er Ordre



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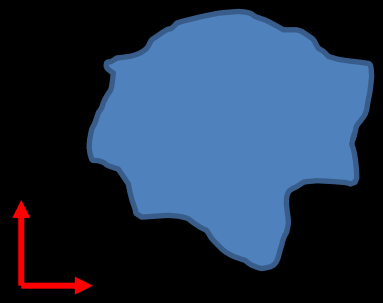

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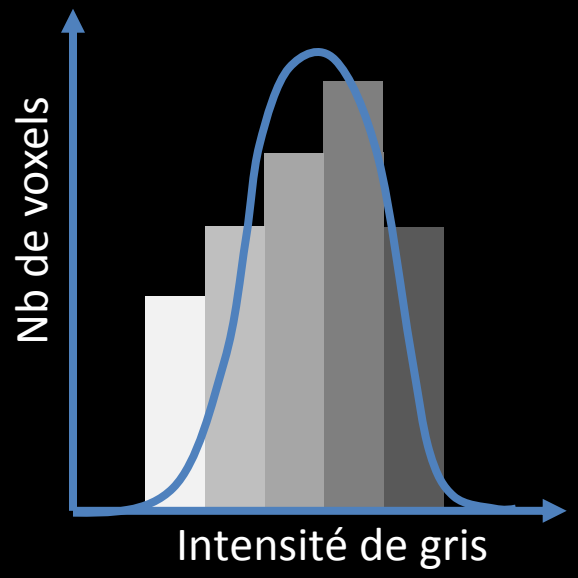

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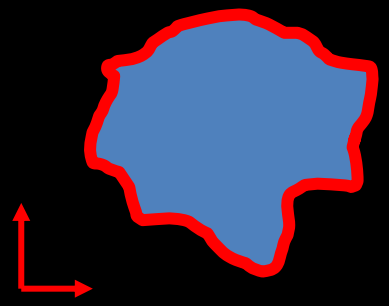

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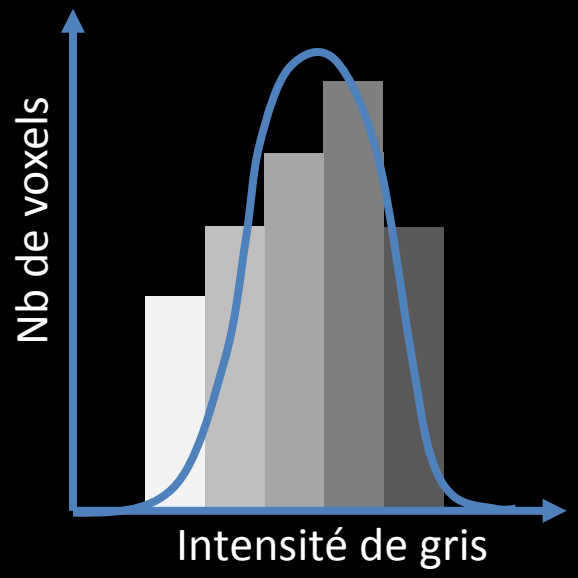

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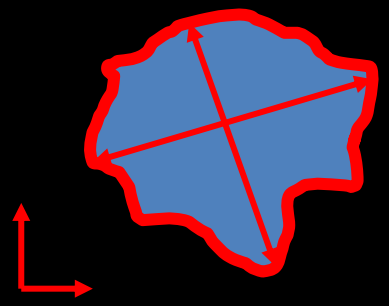

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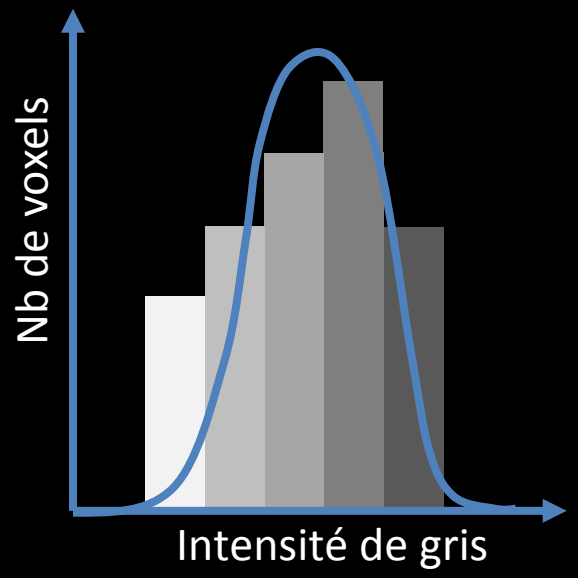

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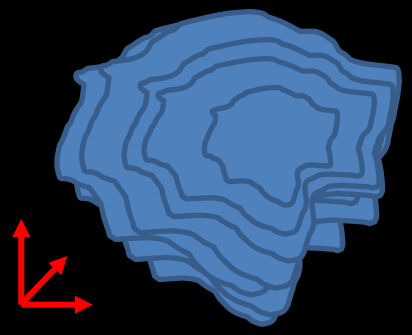

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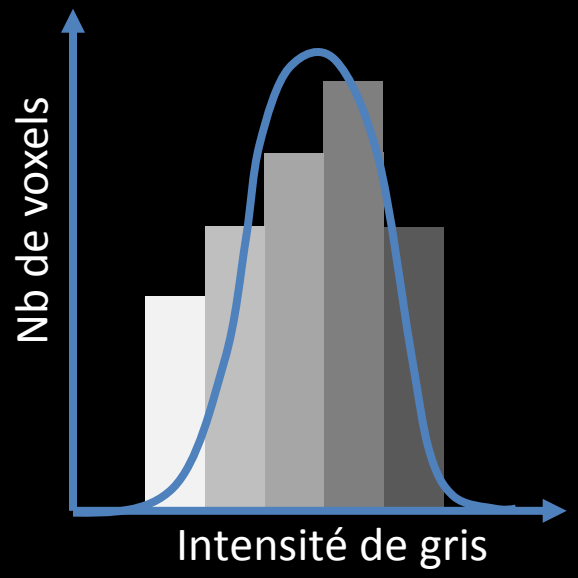

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2e Ordre

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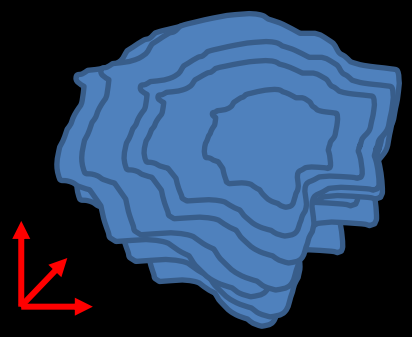

Radiomics Features

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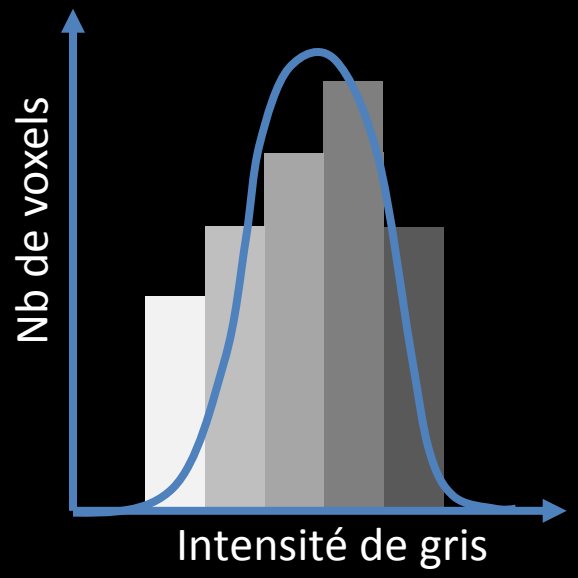

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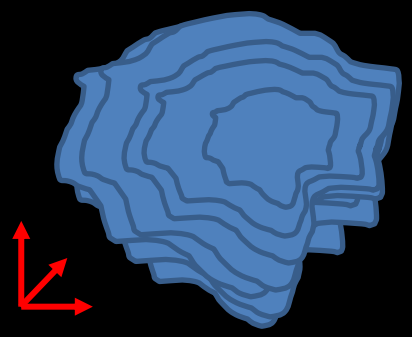

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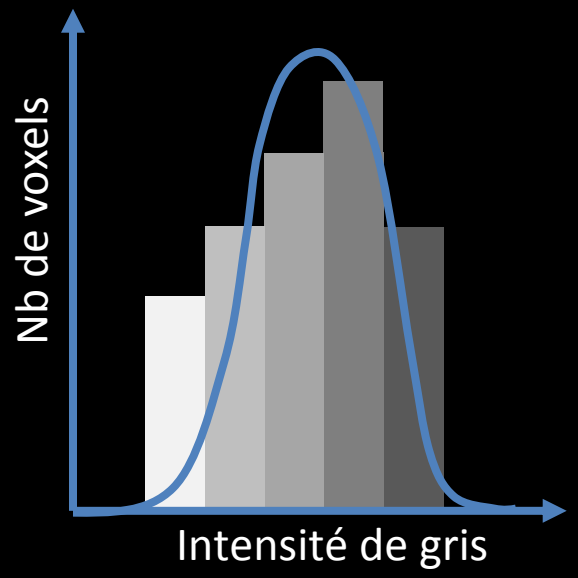

2e Ordre

= TEXTURE

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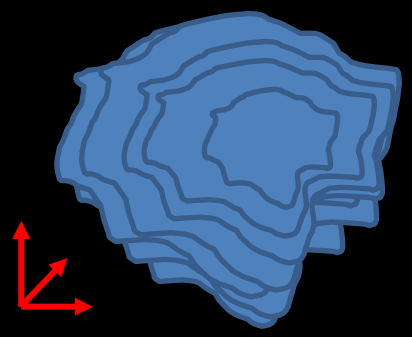
GLCM



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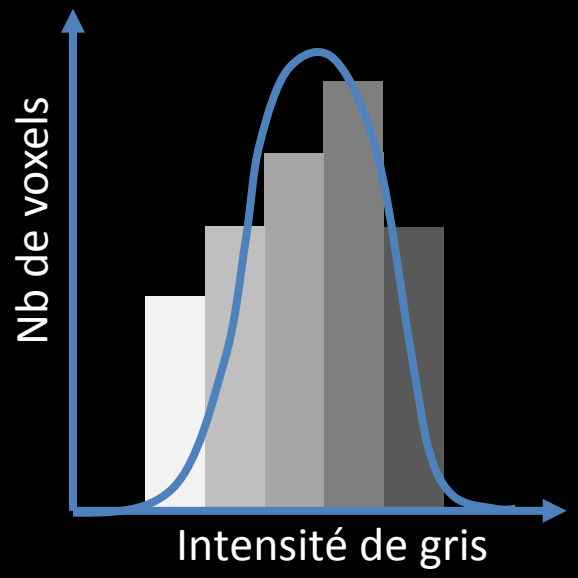

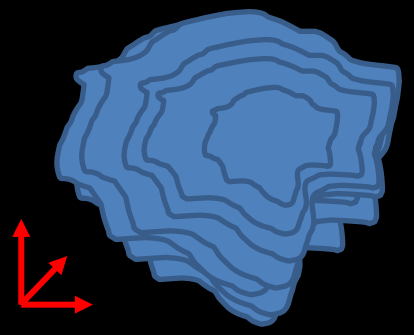

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= TEXTURE

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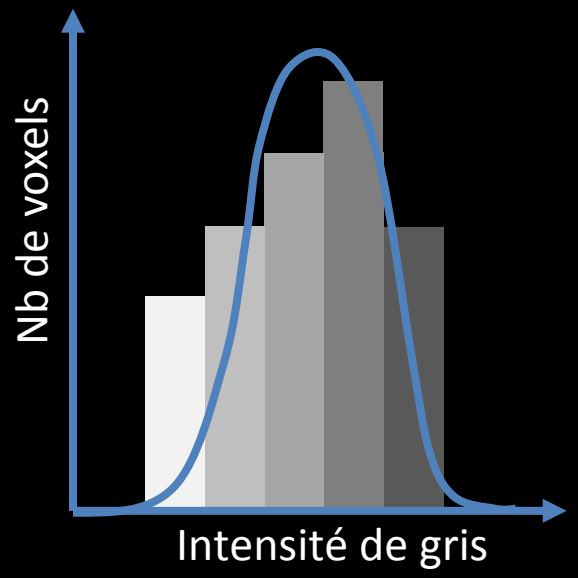
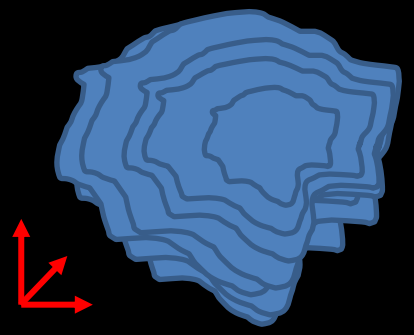
GLCM
GLSZM

Radiomics Features

1er Ordre





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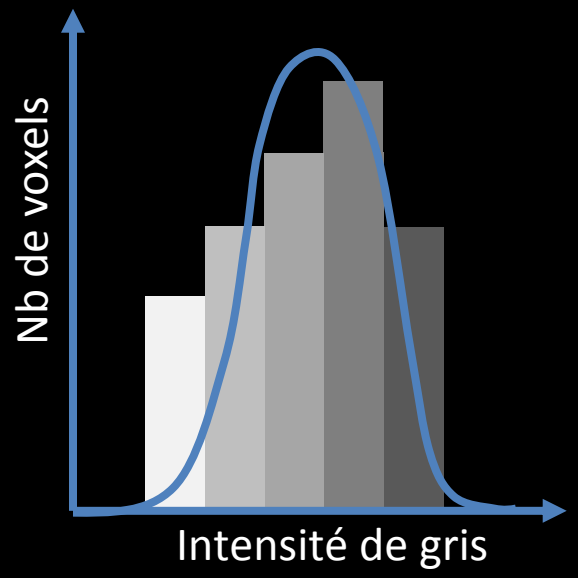
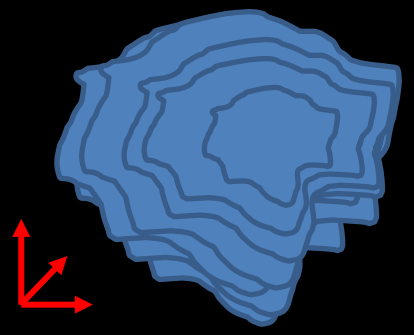
GLCM
GLSZM
GLRLM

Radiomics Features

1er Ordre





2e Ordre

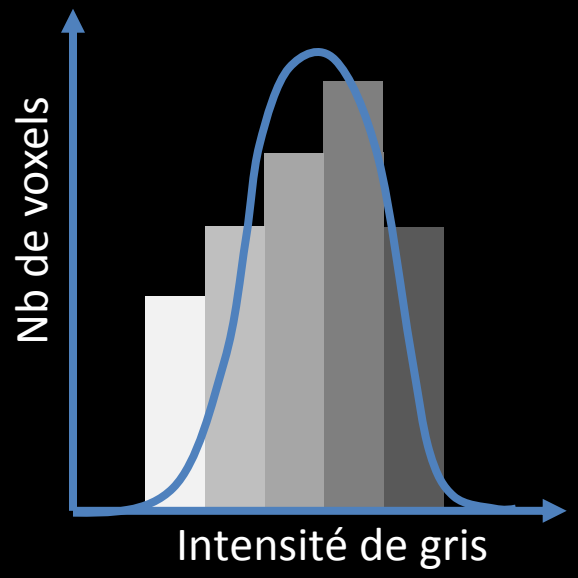
= TEXTURE

1	2	3	4	5	5	4	3
2	1	1	1	3	5	3	1
1	2	2	4	2	5	3	2
1	1	3	4	3	4	2	1
2	3	4	4	5	3	1	2
2	4	4	5	5	3	2	3
4	3	5	4	5	4	4	2
4	4	5	5	3	4	4	3

GLCM
GLSZM
GLRLM
NGTDM

Radiomics Features

1er Ordre

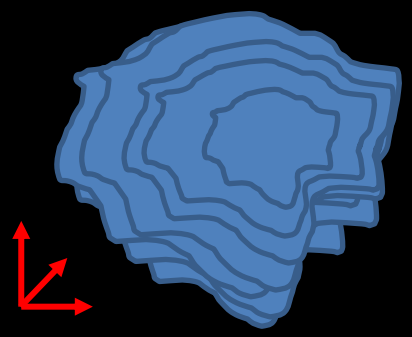


1	2	3	4	5	5	4	3
2	1	1	1	3	5	3	1
1	2	2	4	2	5	3	2
1	1	3	4	3	4	2	1
2	3	4	4	5	3	1	2
2	4	4	5	5	3	2	3
4	3	5	4	5	4	4	2
4	4	5	5	3	4	4	3

2e Ordre

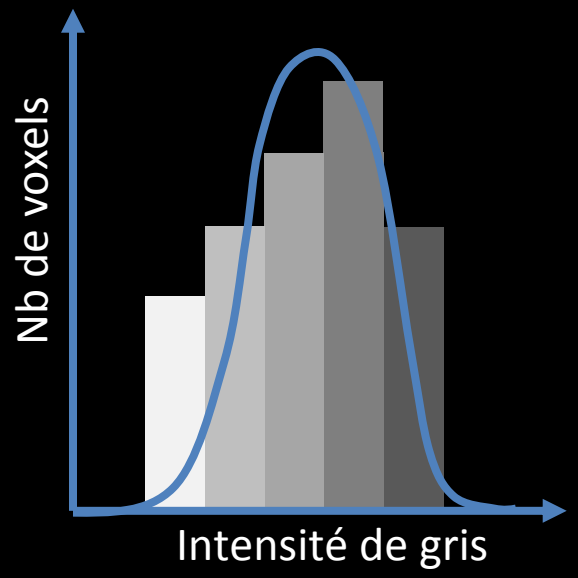
= TEXTURE

GLCM
GLSZM
GLRLM
NGTDM
GLDM



Radiomics Features

1er Ordre

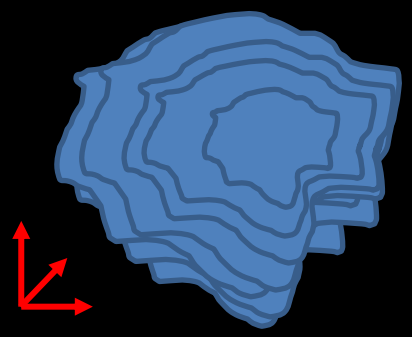


2e Ordre

= TEXTURE

1	2	3	4	5	5	4	3
2	1	1	1	3	5	3	1
1	2	2	4	2	5	3	2
1	1	3	4	3	4	2	1
2	3	4	4	5	3	1	2
2	4	4	5	5	3	2	3
4	3	5	4	5	4	4	2
4	4	5	5	3	4	4	3

GLCM
GLSZM
GLRLM
NGTDM
GLDM



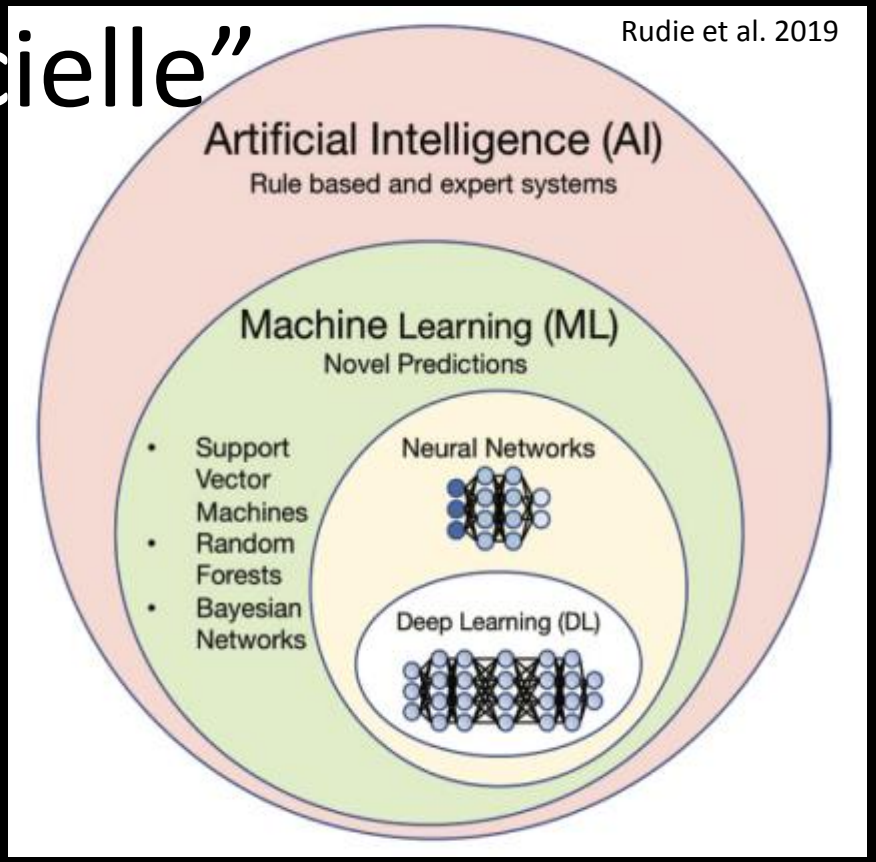
Ordre Supérieur

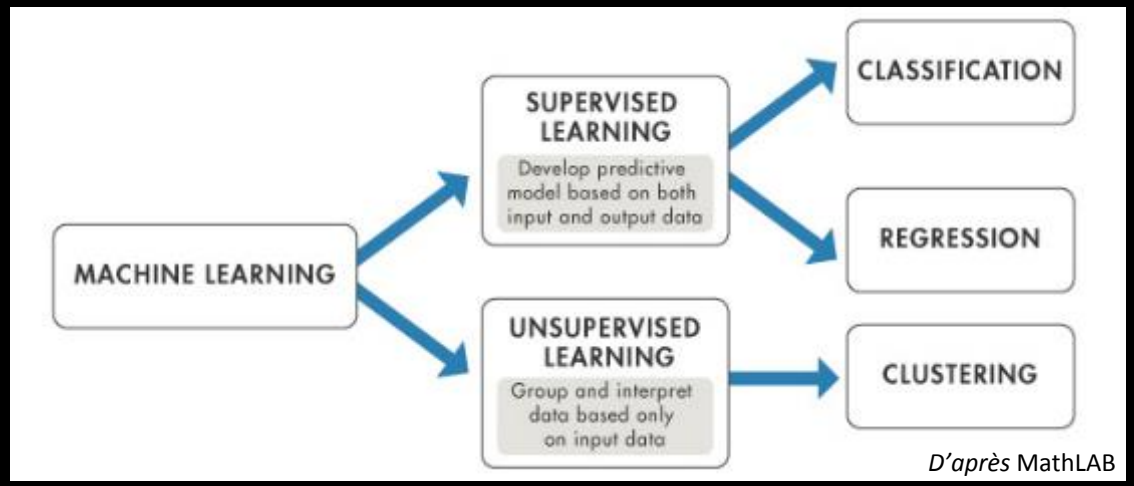
“Intelligence Artificielle”

Intelligence « Faible »

Machine Learning

- *Ground truth label*
- Supervisés vs Non supervisés
- Algorithmes de classification ++
- *Training* vs *Validation* sets



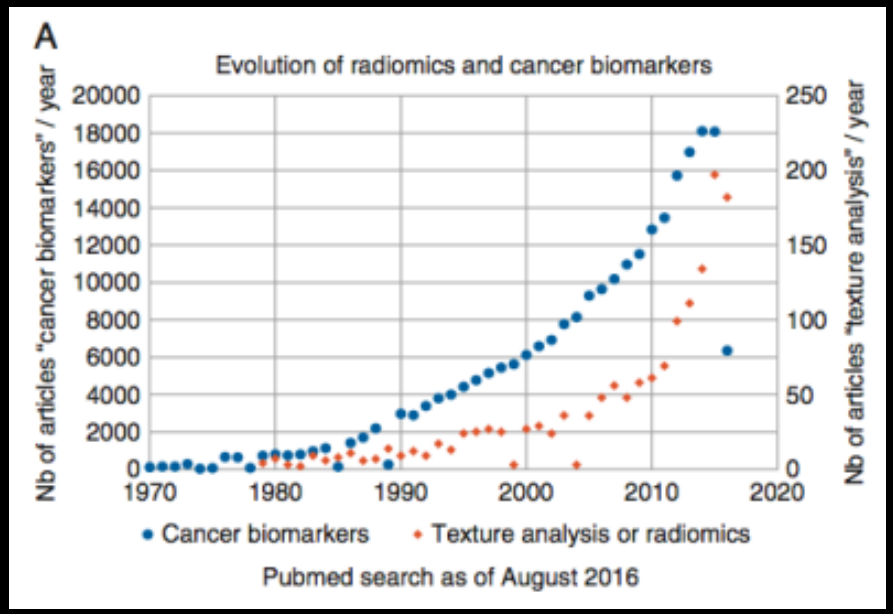


Sommaire

- Contextualisation & Définitions
- Recherche et applications en Neuro-Oncologie
- “Worklow” : Limites et solutions
- Synthèse

“Etat de l’art” en Neuro-Oncologie

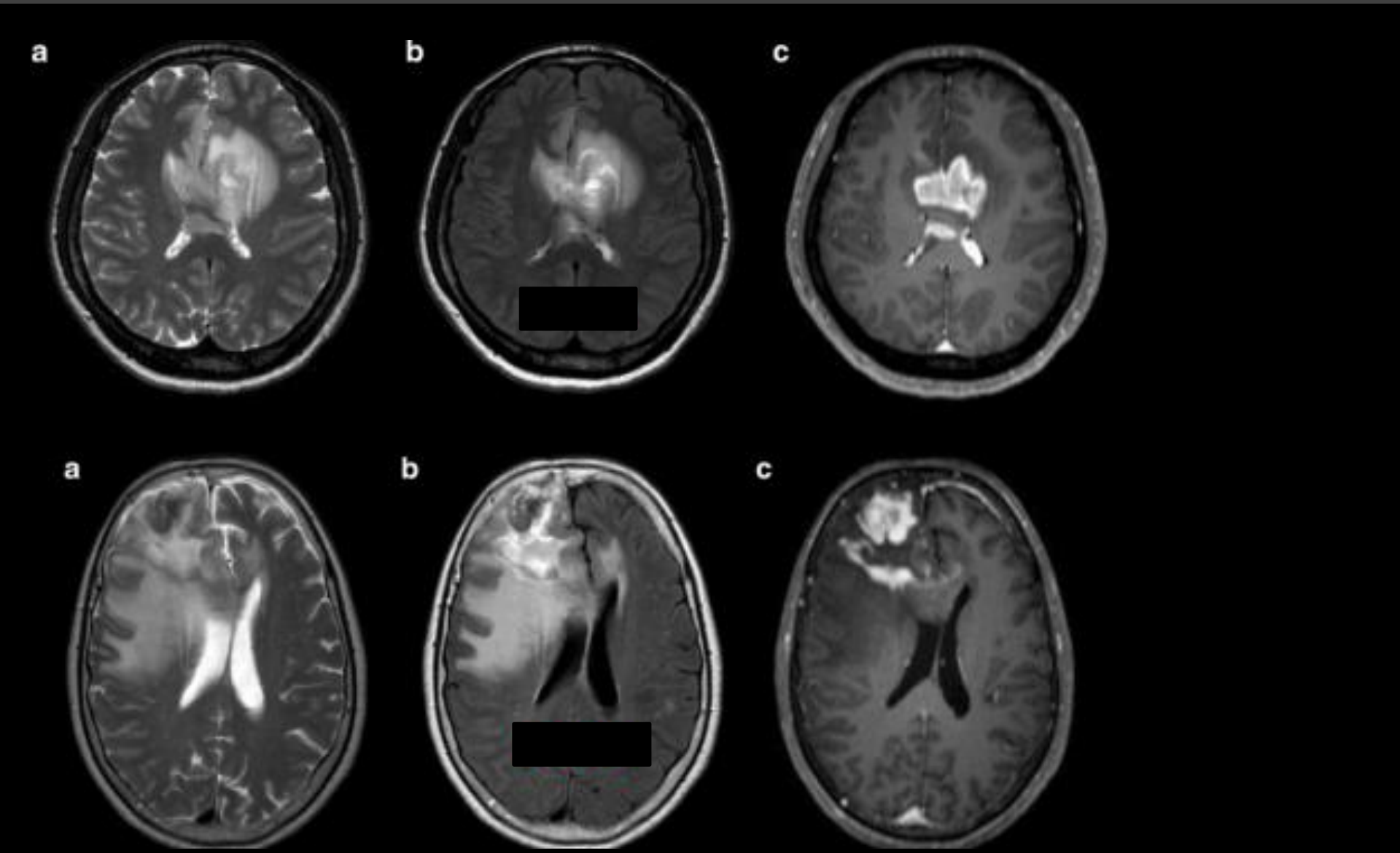
- Intérêt Diagnostique
- Intérêt Pronostique
- Plannification Thérapeutique



Limkin et al. 2017

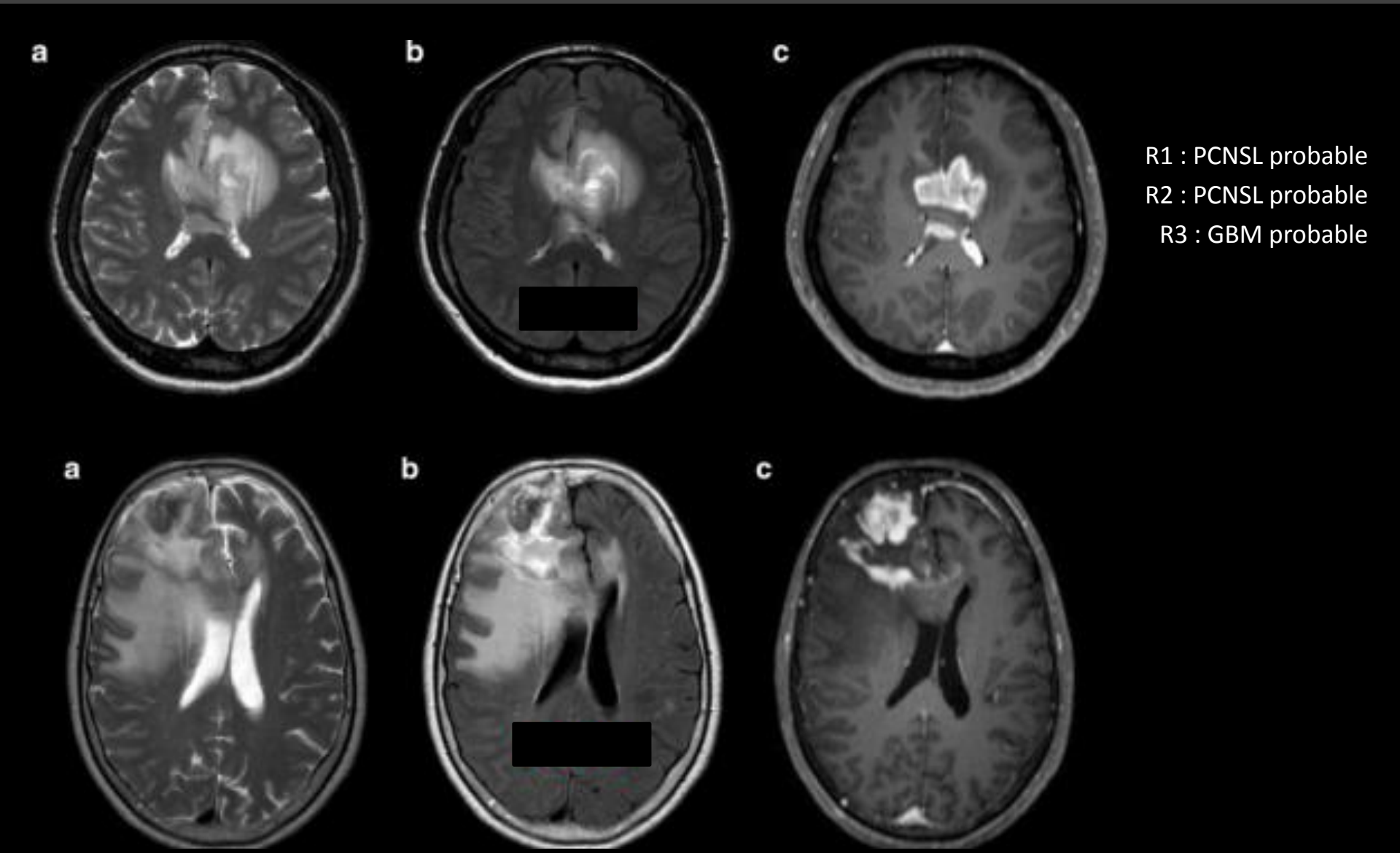
Diagnostic initial

Suh et al. *ESR* 2018



Diagnostic initial

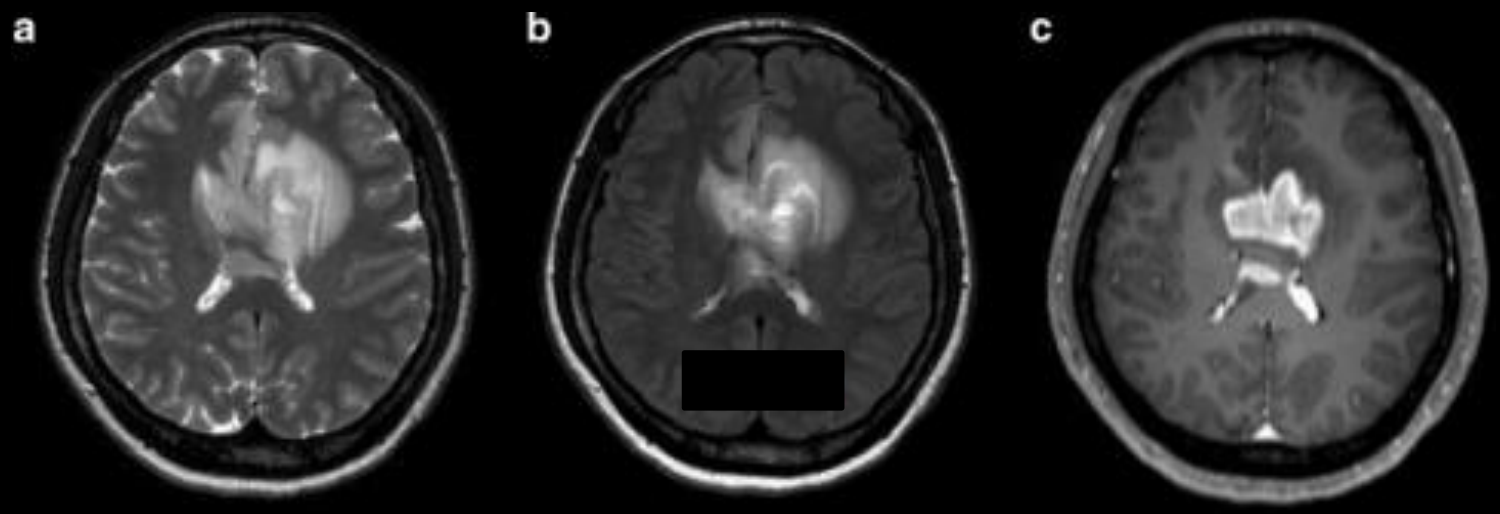
Suh et al. *ESR* 2018



R1 : PCNSL probable
R2 : PCNSL probable
R3 : GBM probable

Diagnostic initial

Suh et al. *ESR* 2018



R1 : PCNSL probable
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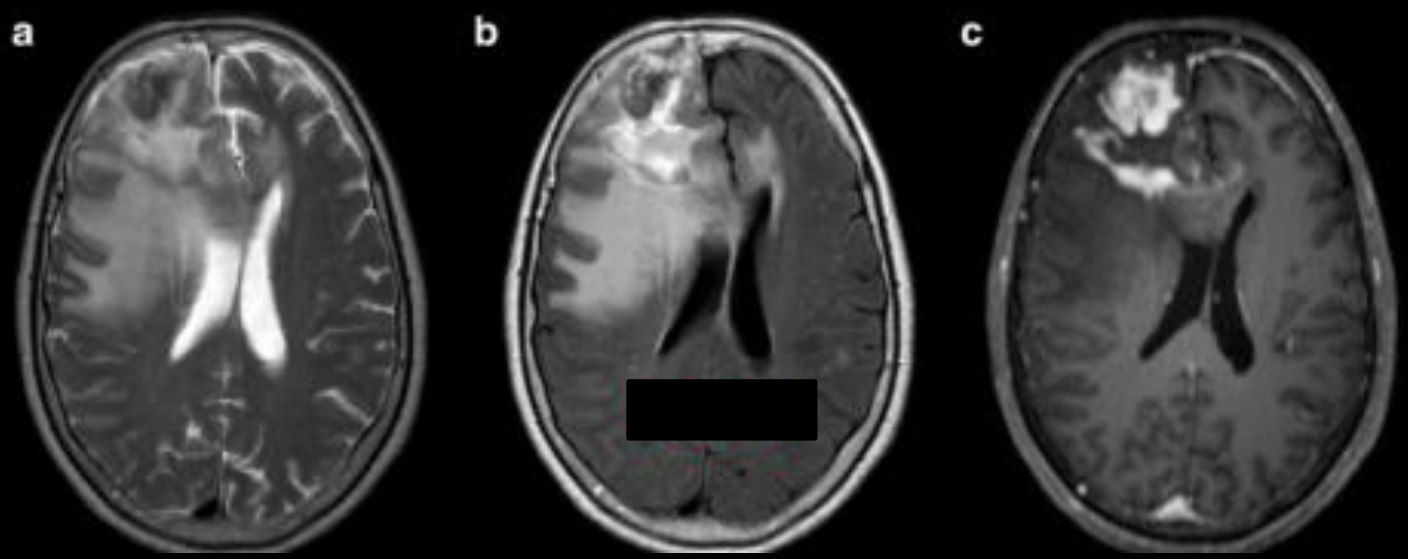

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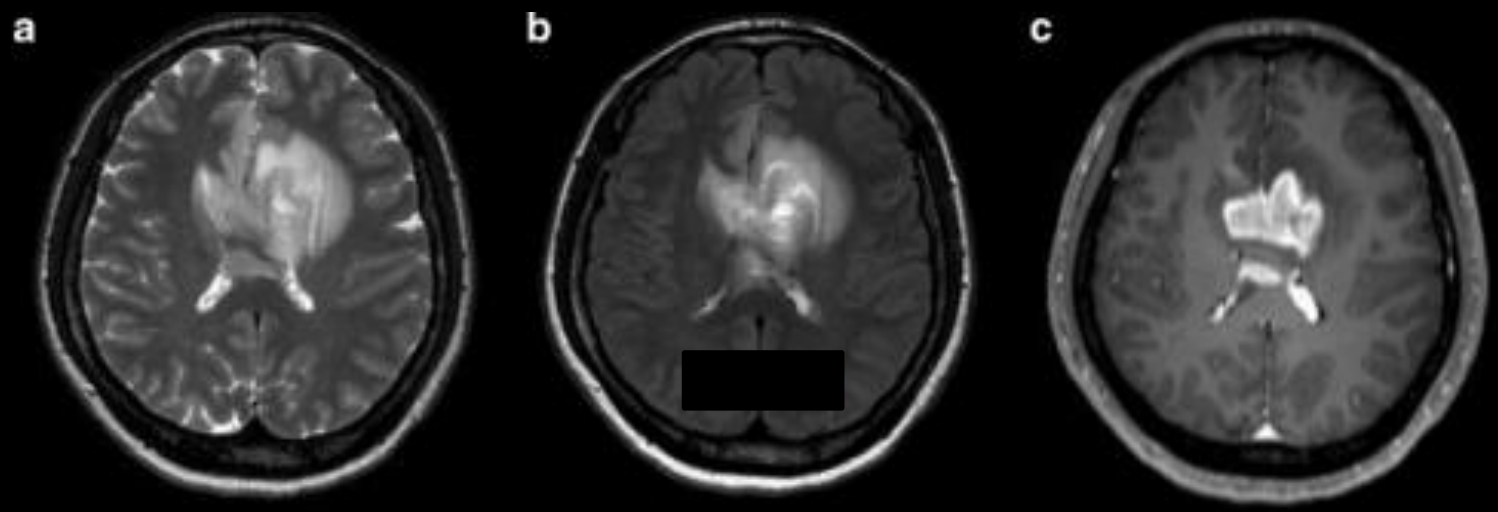
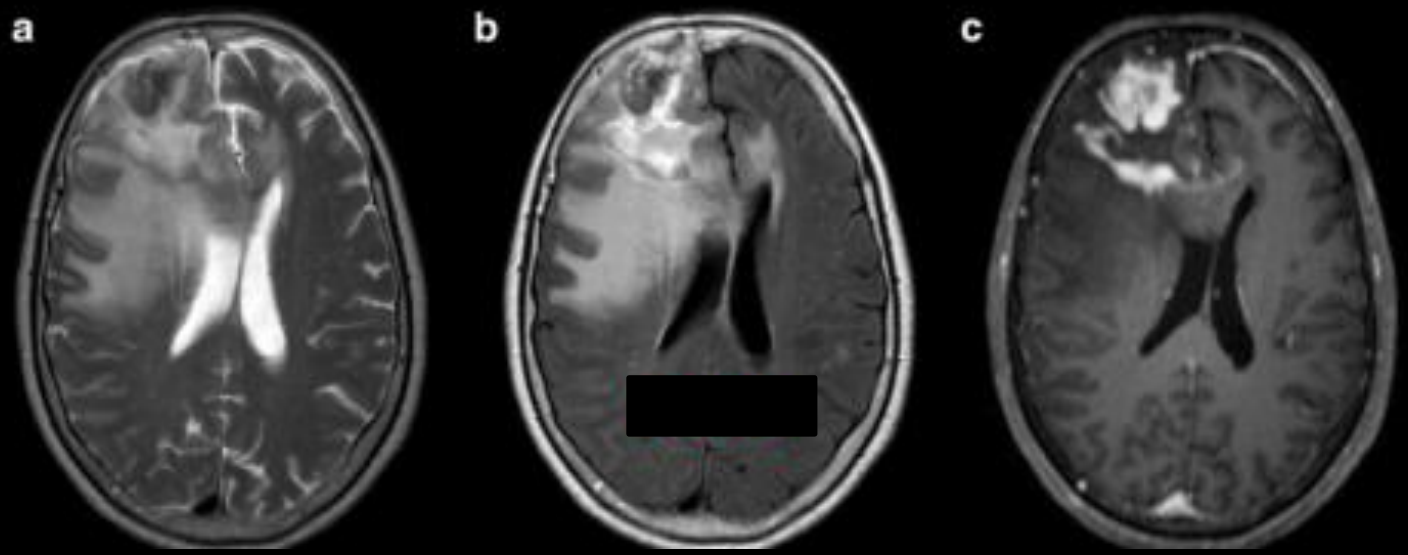
Diagnostic initial

Suh et al. *ESR* 2018



R1 : PCNSL probable
R2 : PCNSL probable
R3 : GBM probable

Machine Learning : GBM probable



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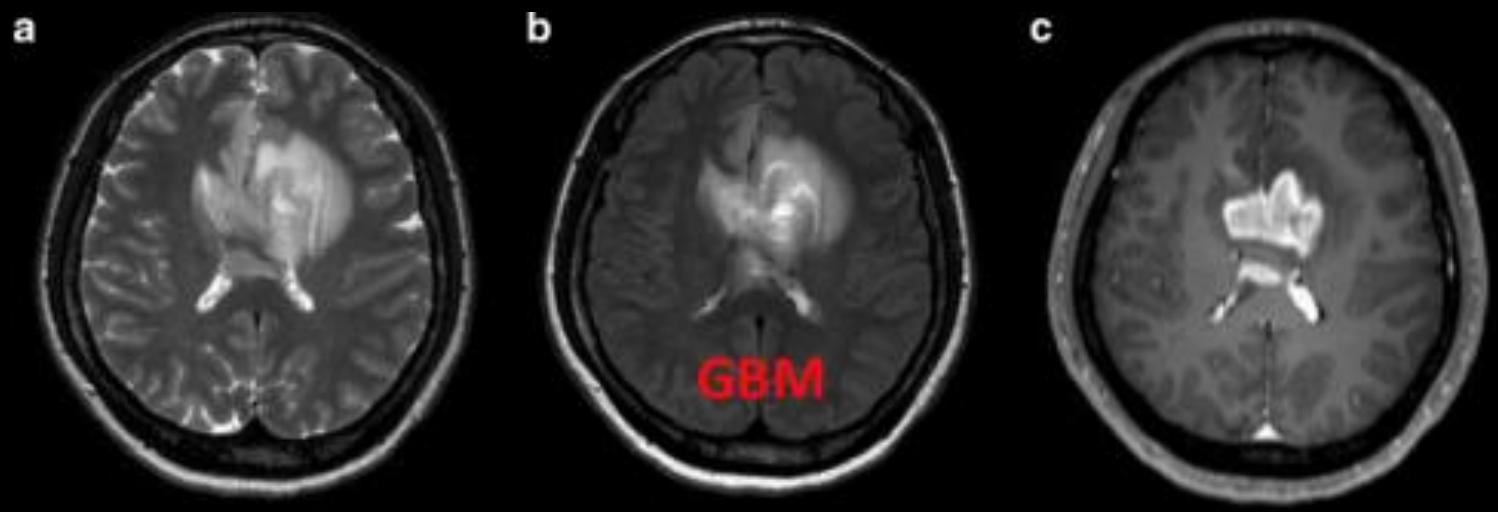
R2 : GBM
R3 : GBM probable

Machine Learning : PCNSL probable

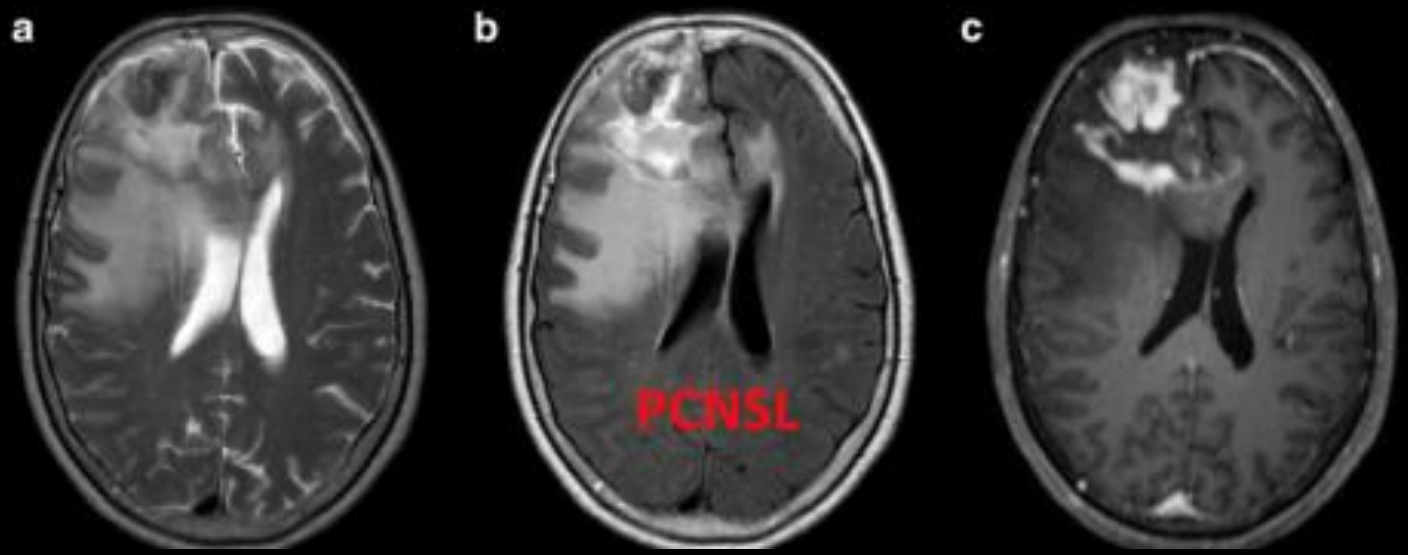
Diagnostic initial

Suh et al. *ESR* 2018



R1 : PCNSL probable
R2 : PCNSL probable
R3 : GBM probable

Machine Learning : GBM probable



R1 : GBM probable
R2 : GBM
R3 : GBM probable

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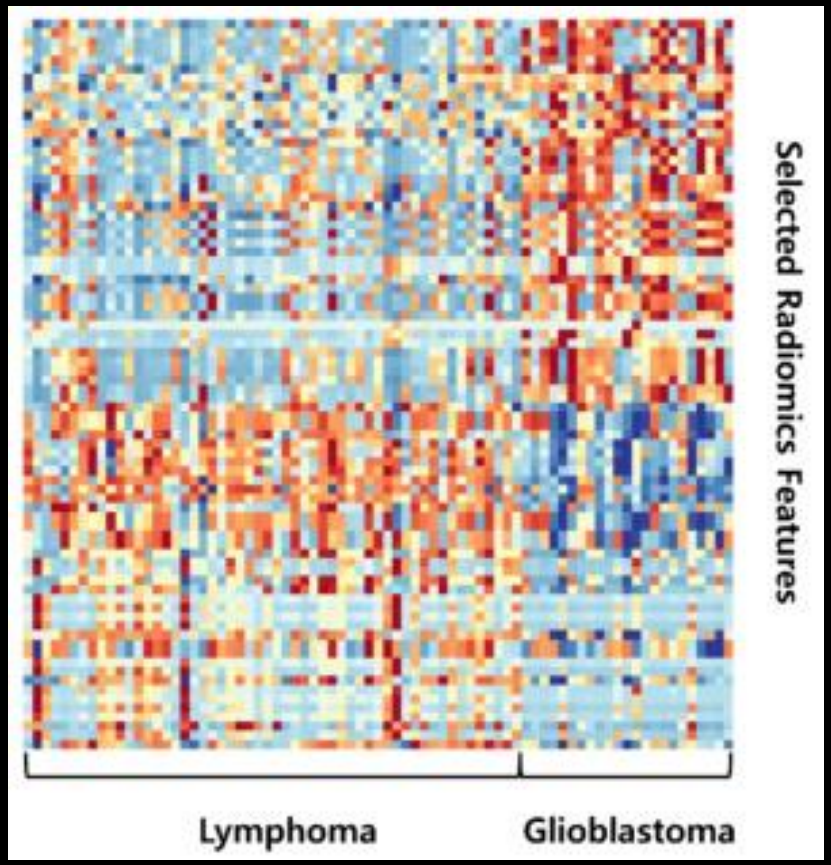
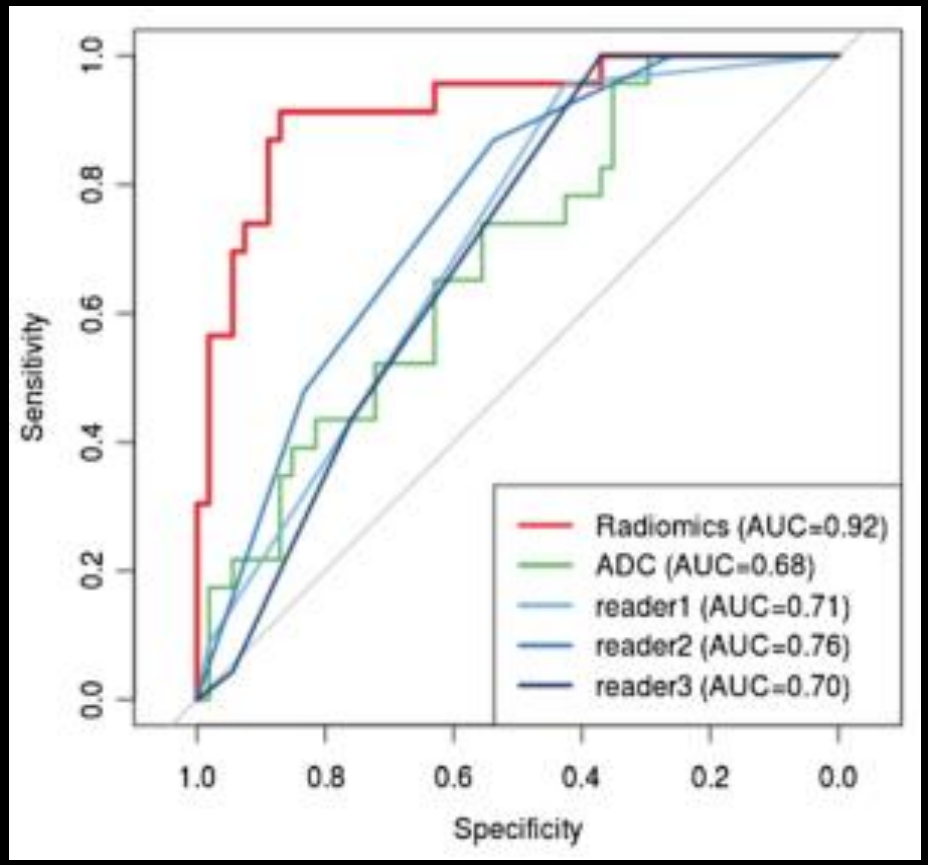
Diagnostic initial

Suh et al. *ESR* 2018
Kagawa et al. *EJR* 2018





Diagnostic initial

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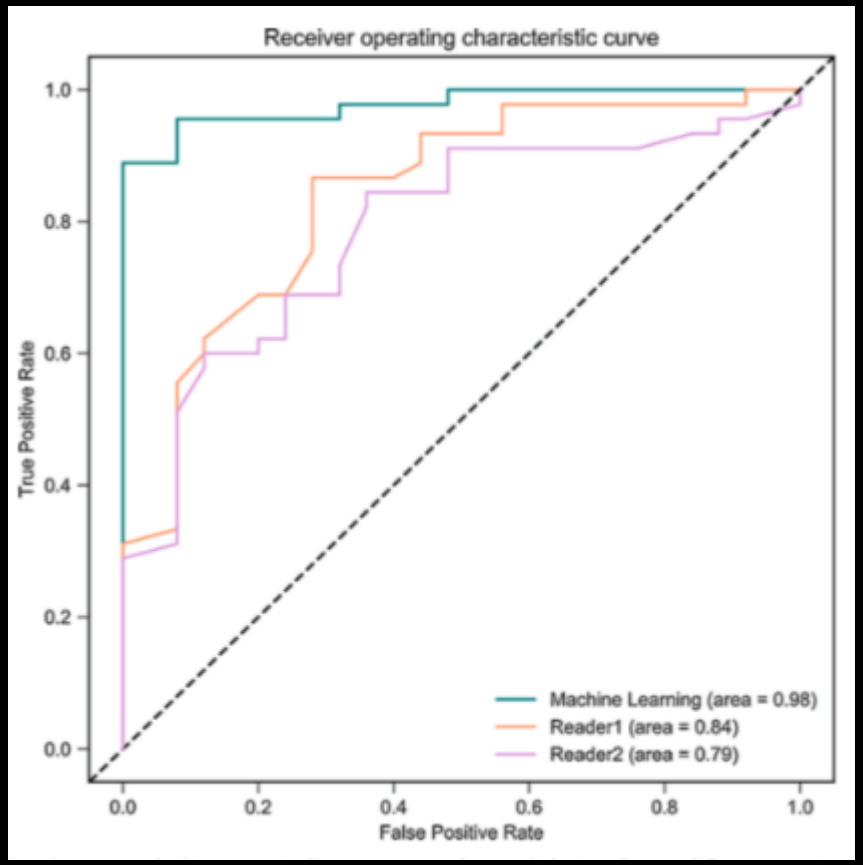
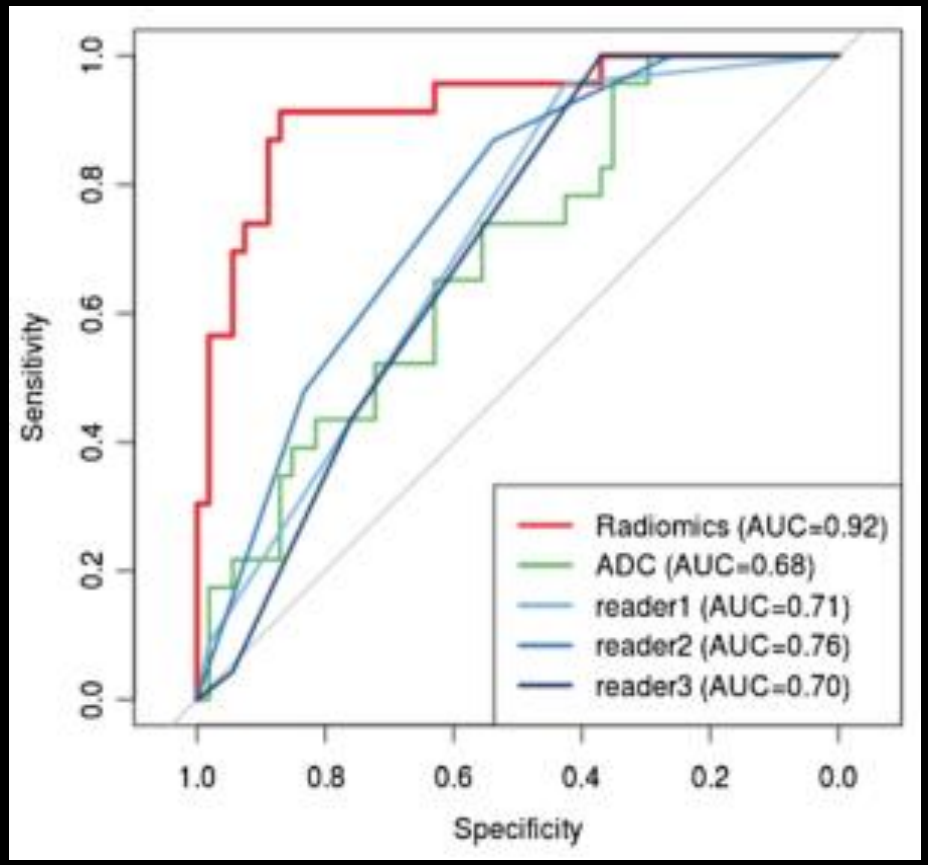
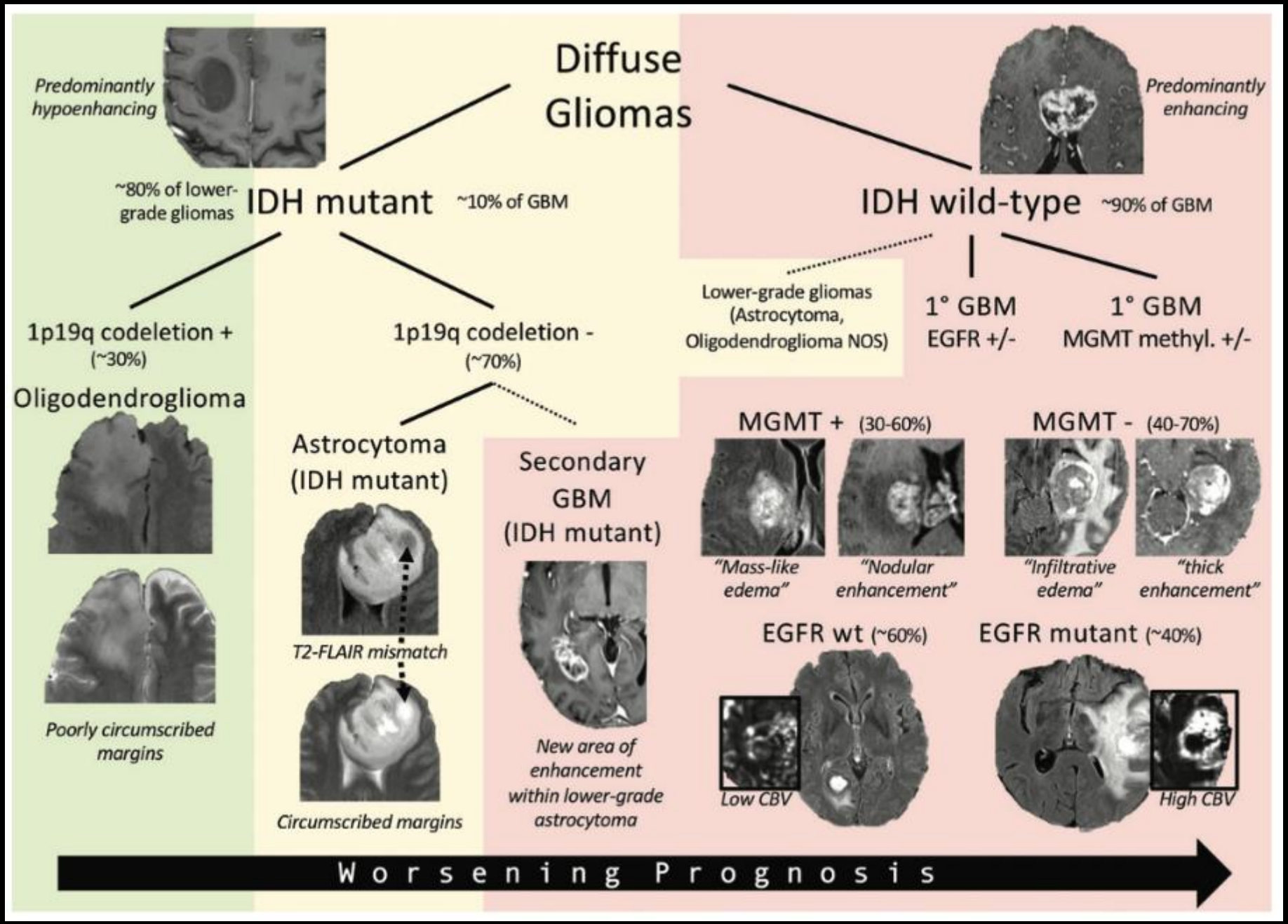




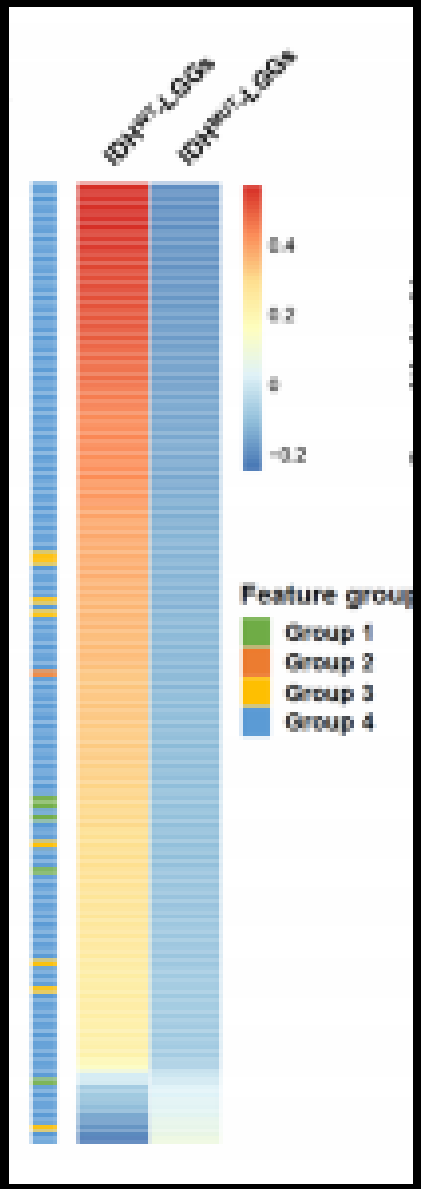

Diffuse Gliomas
Predominantly hypoenhancing
~80% of lower-grade gliomas
IDH mutant
~10% of GBM
Predominantly enhancing
IDH wild-type
~90% of GBM
1p19q codeletion +
(~30%)
Oligodendroglioma
Poorly circumscribed margins
1p19q codeletion -
(~70%)
Astrocytoma (IDH mutant)
T2-FLAIR mismatch
Circumscribed margins
Secondary GBM (IDH mutant)
New area of enhancement within lower-grade astrocytoma
Lower-grade gliomas (Astrocytoma, Oligodendroglioma NOS)
1° GBM
EGFR +/-
1° GBM
MGMT methyl. +/-
MGMT + (30-60%)
"Mass-like edema"
"Nodular enhancement"
MGMT - (40-70%)
"Infiltrative edema"
"thick enhancement"
EGFR wt (~60%)
Low CBV
EGFR mutant (~40%)
High CBV
Worsening Prognosis

“Etat de l’art” en Neuro-Oncologie

- Intérêt Diagnostique
- Intérêt Pronostique
  - Corrélations Radiogénomiques
  - Signatures Pronostiques indépendantes
- Plannification Thérapeutique

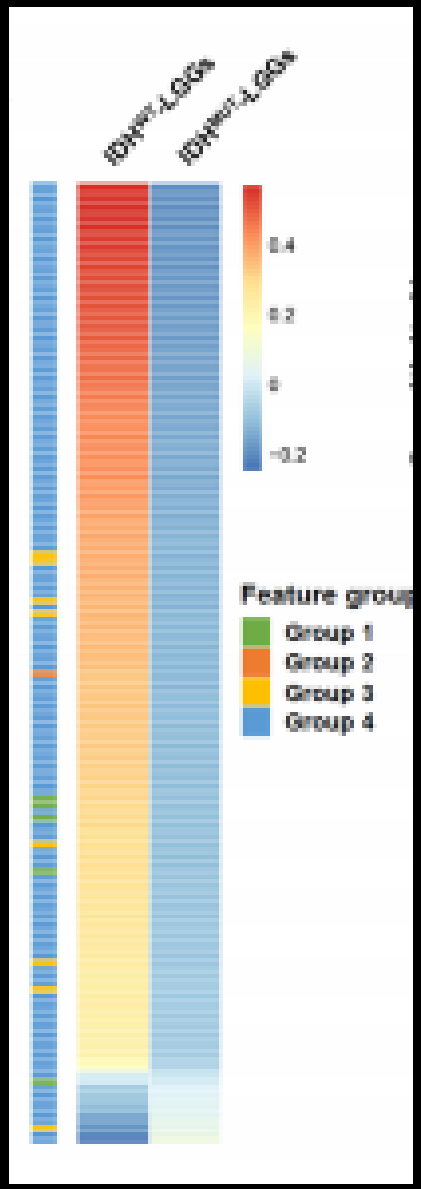
Radiogénomique

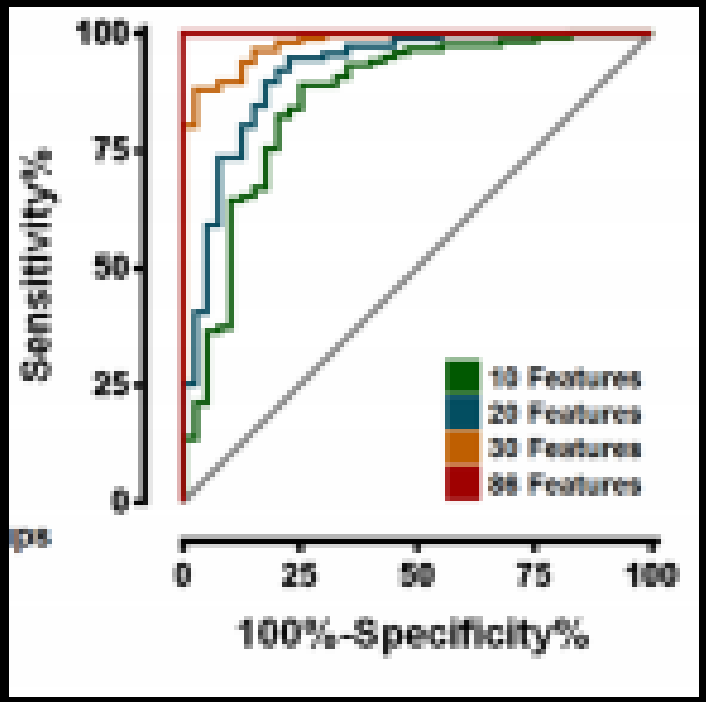
Liu et al. *AGING* 2019



Radiogénomique

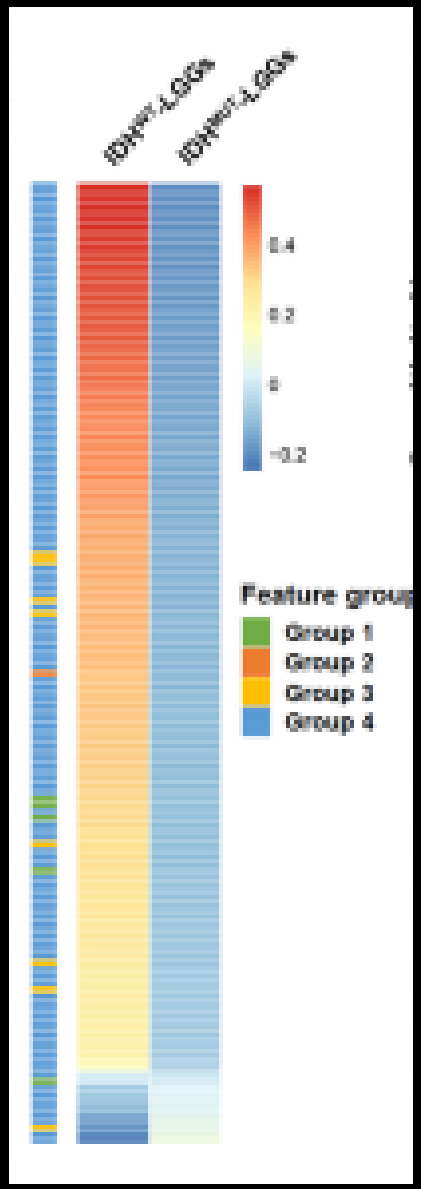
Liu et al. *AGING* 2019

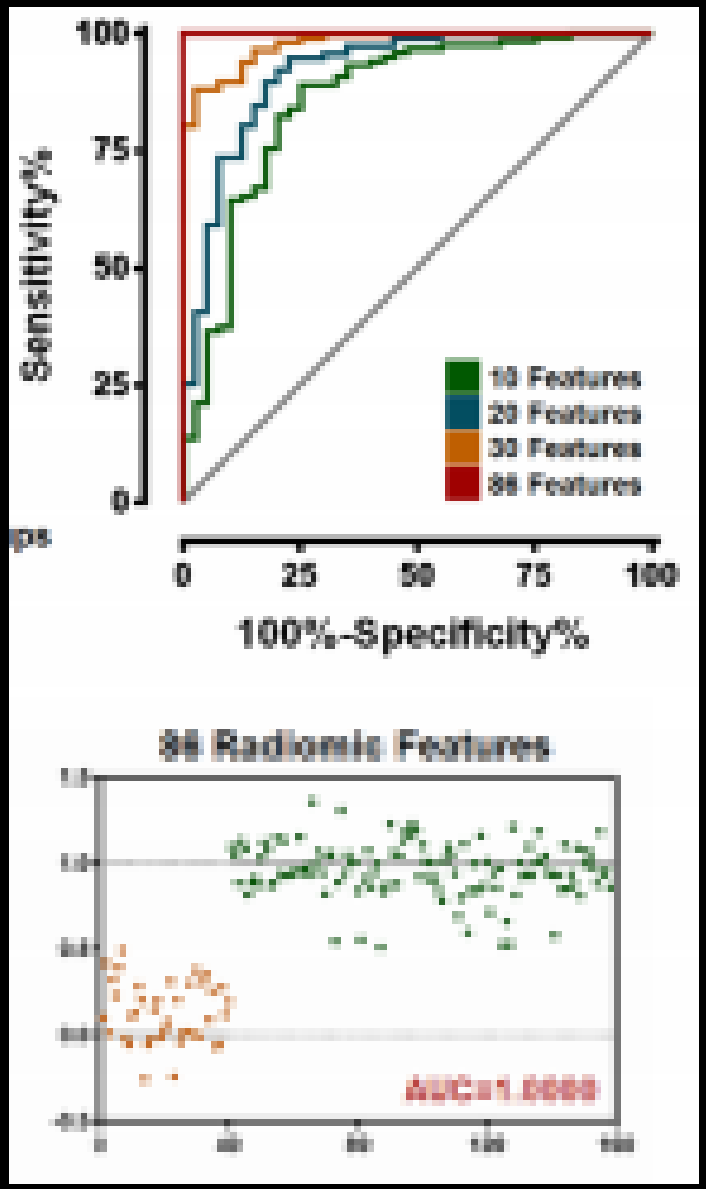




Radiogénomique

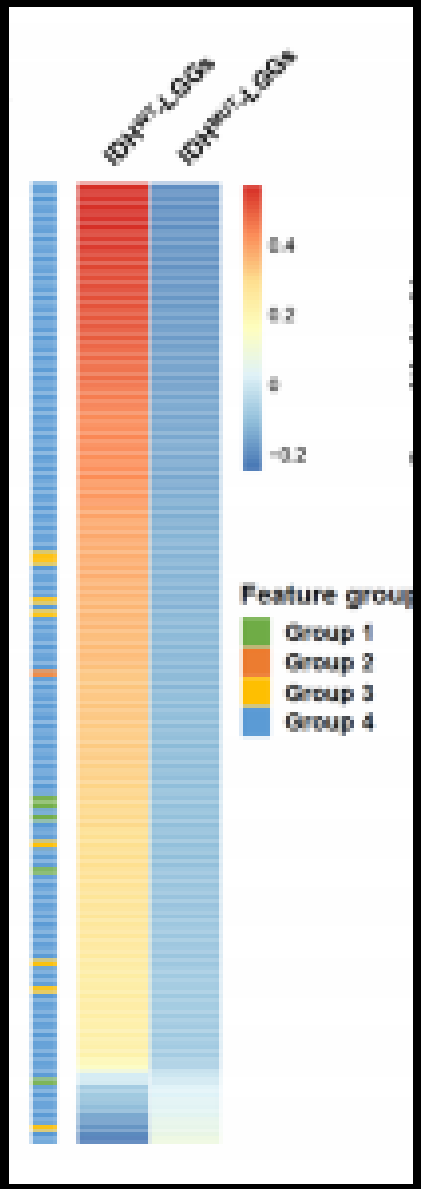
Liu et al. *AGING* 2019

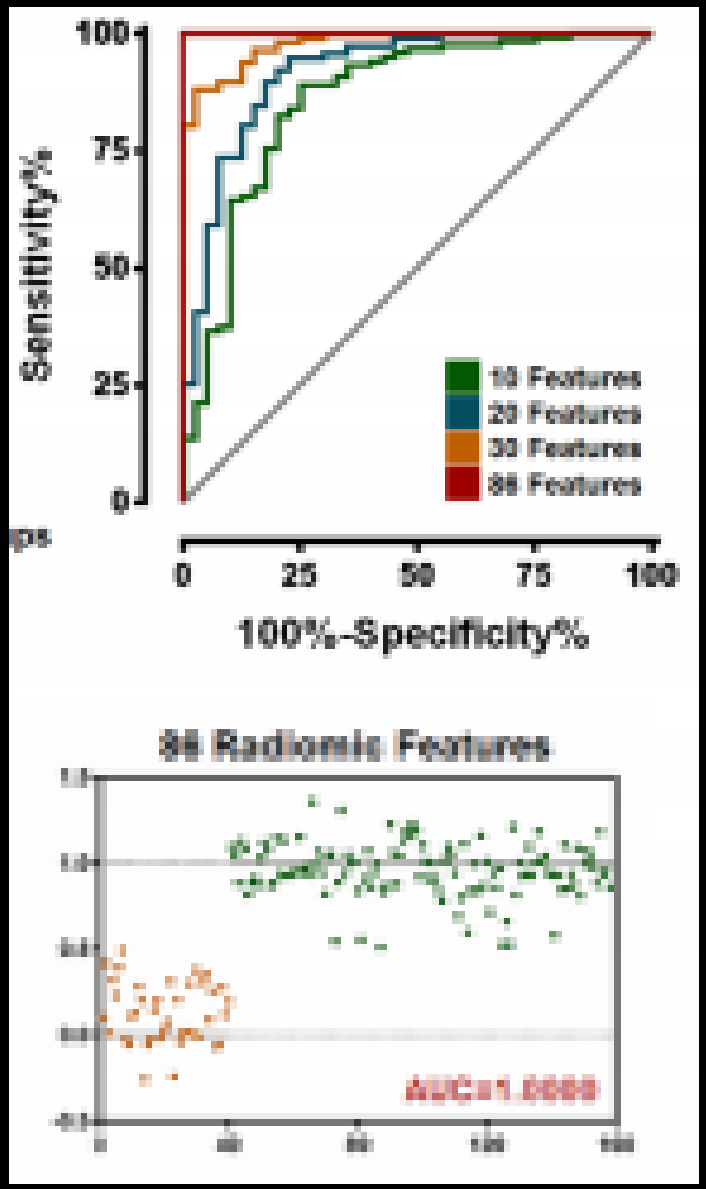


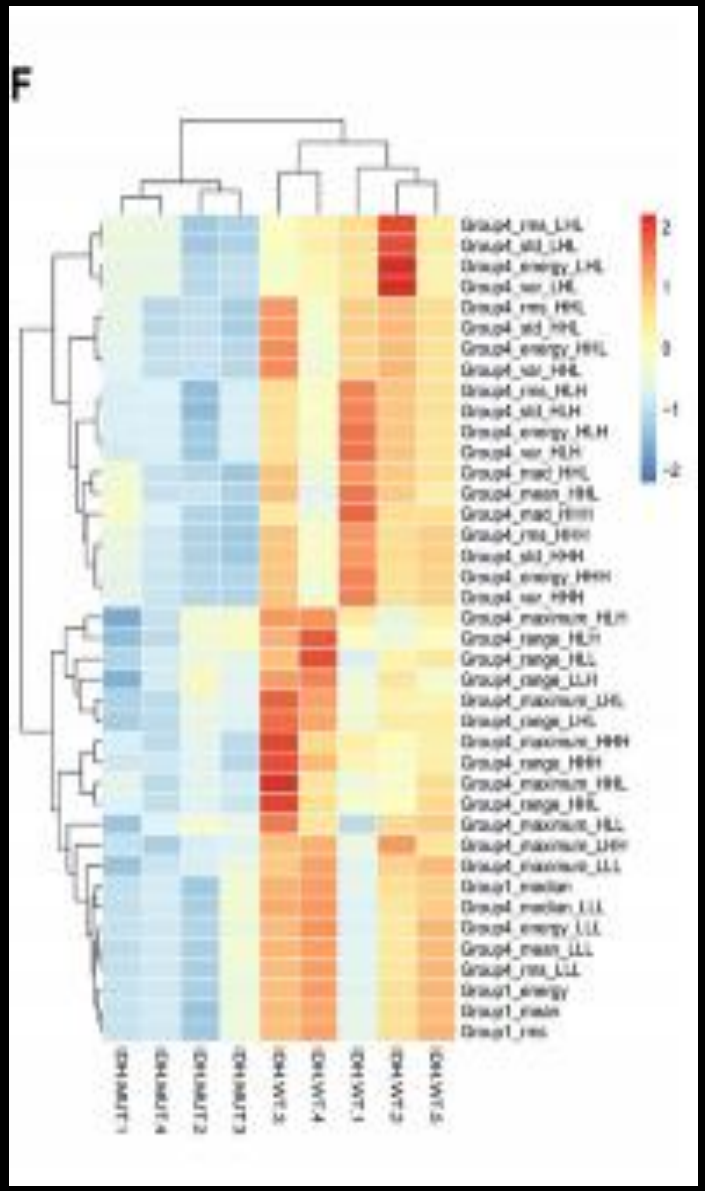


Radiogénomique

Liu et al. *AGING* 2019

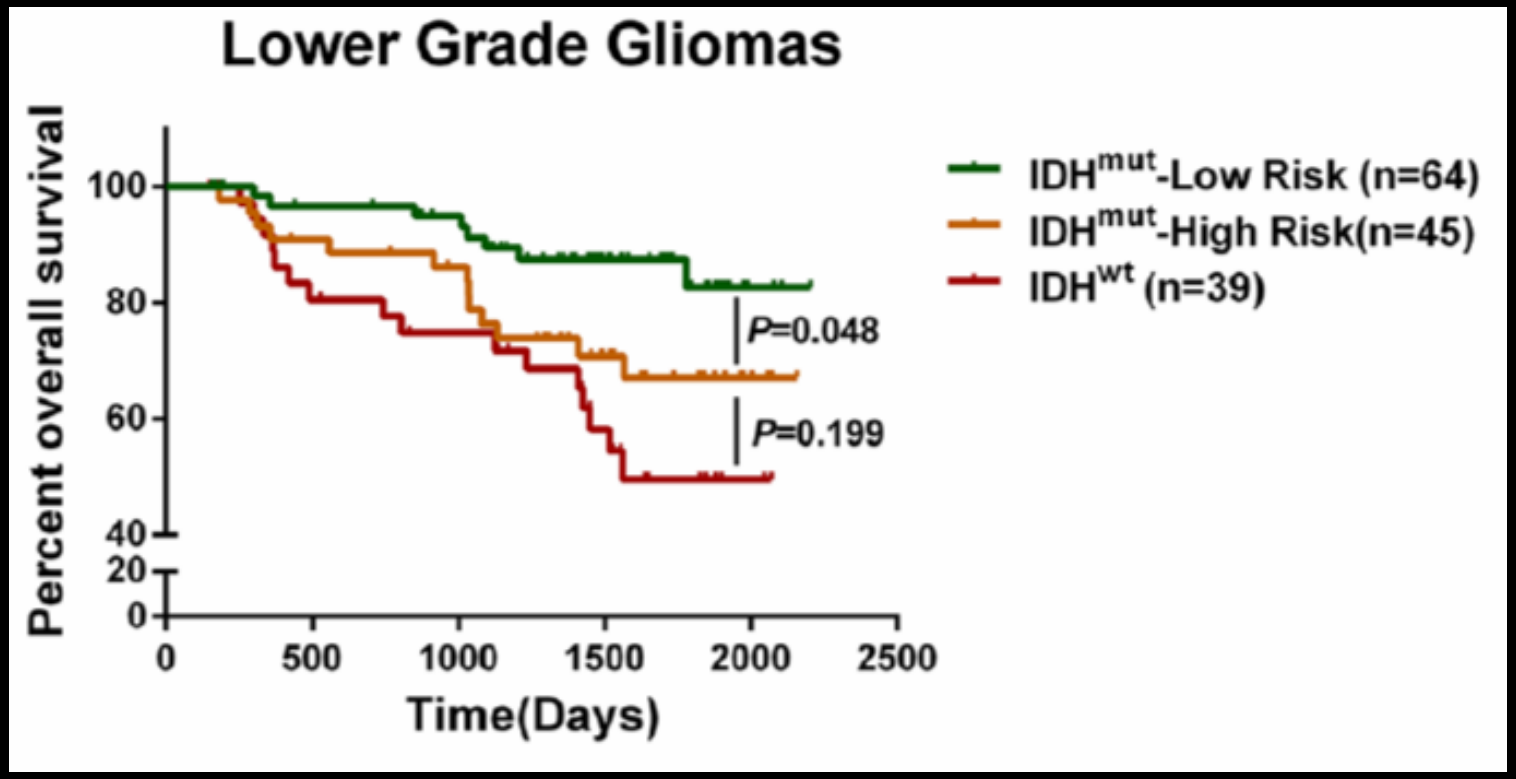






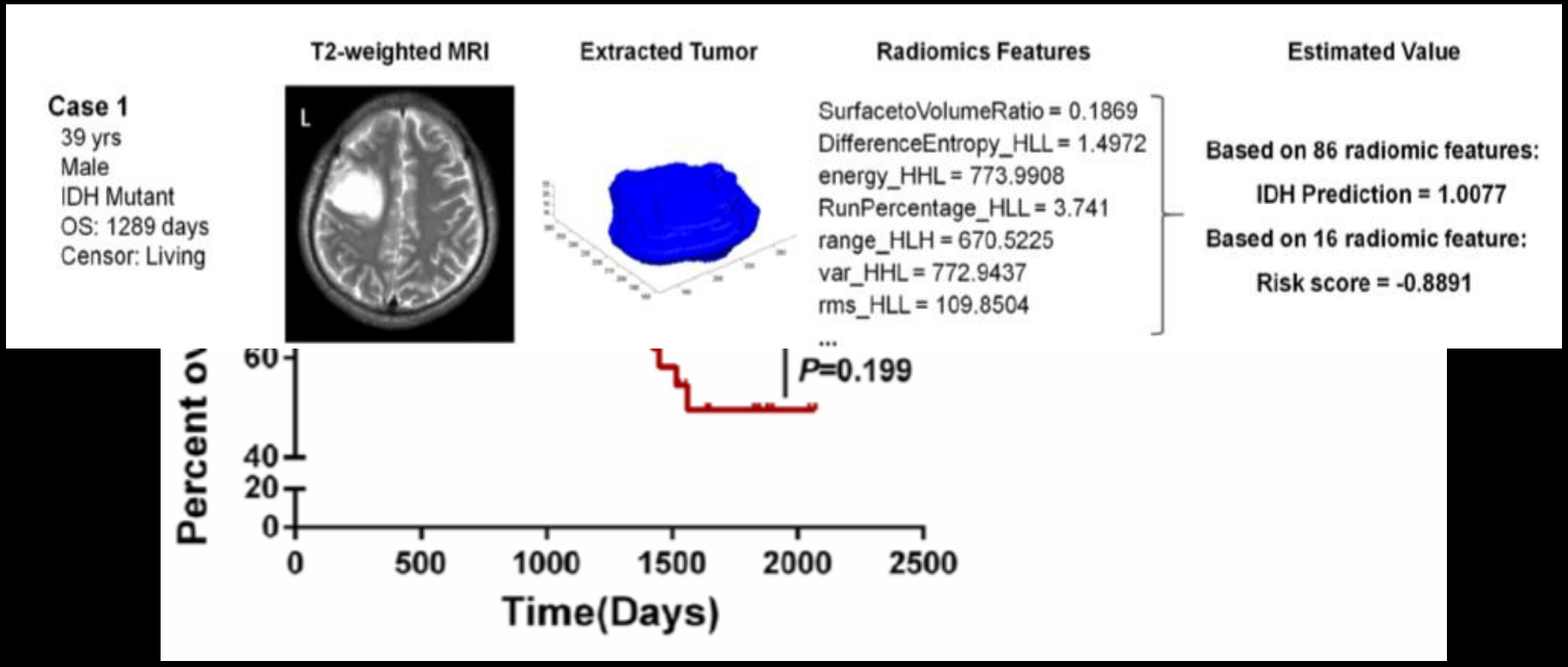
Radiogénomique

Liu et al. *AGING* 2019



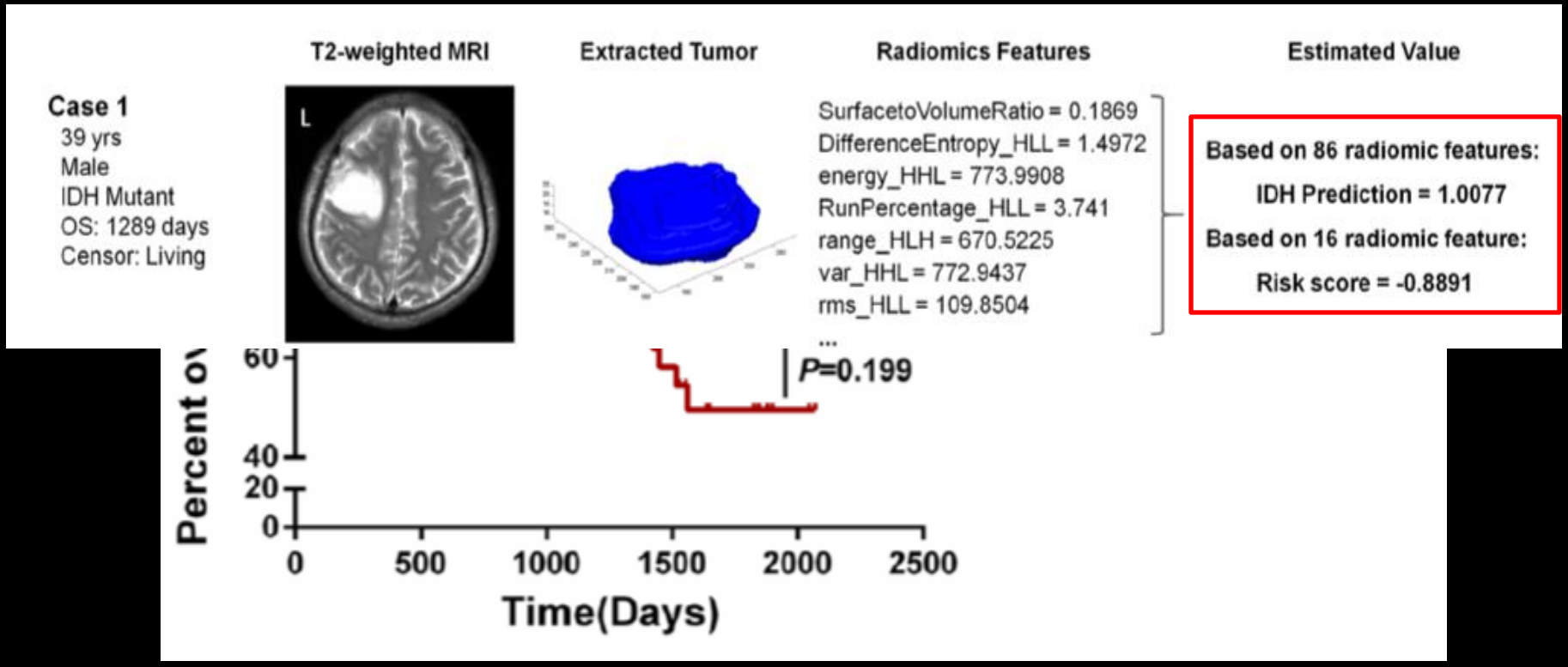
Radiogénomique

Liu et al. *AGING* 2019



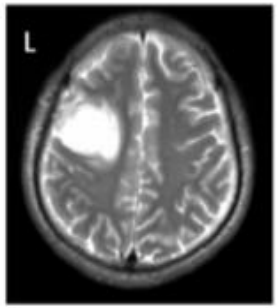
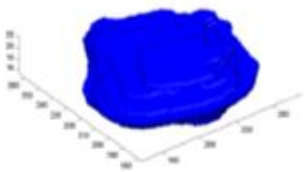
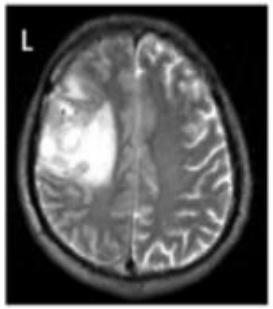
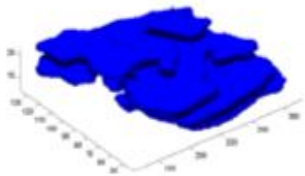
Radiogénomique

Liu et al. *AGING* 2019



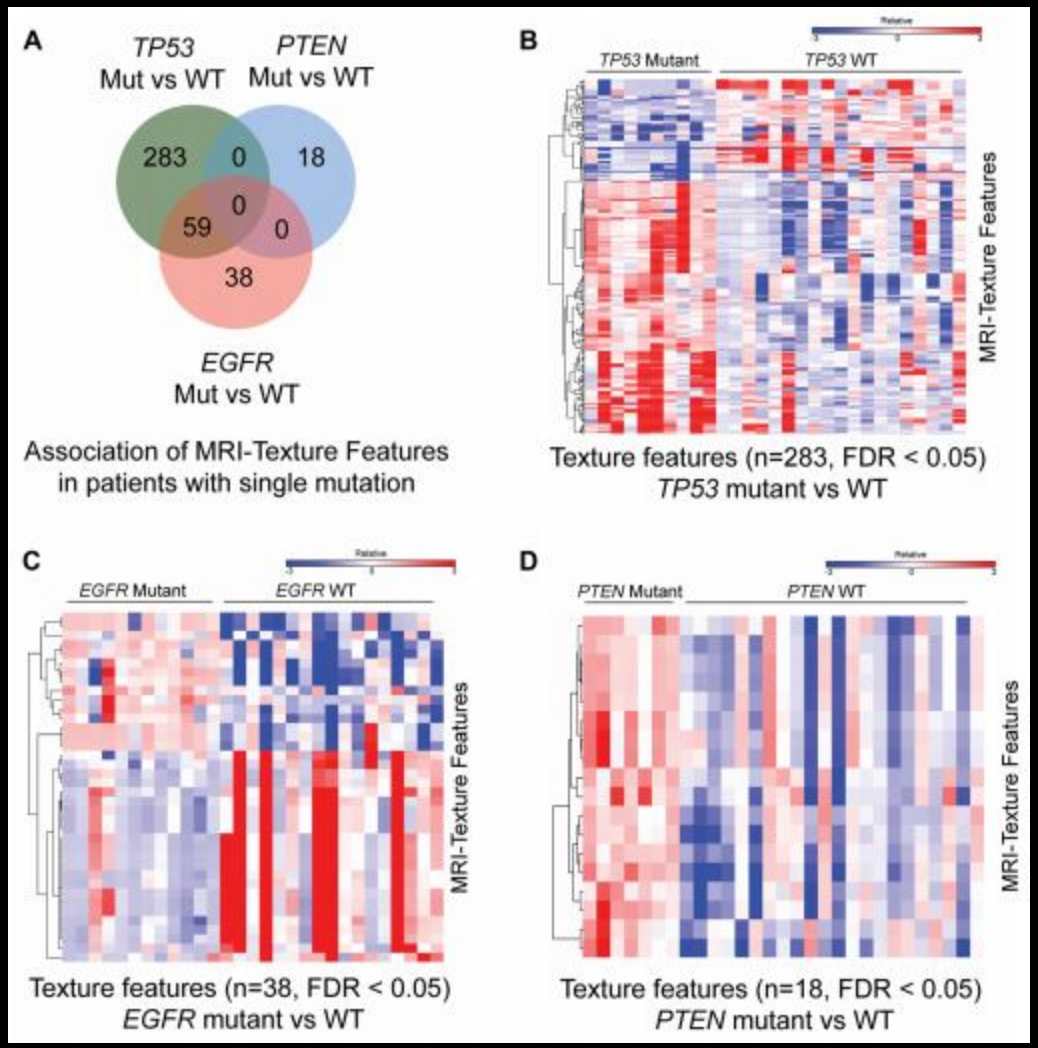
Radiogénomique

Liu et al. *AGING* 2019

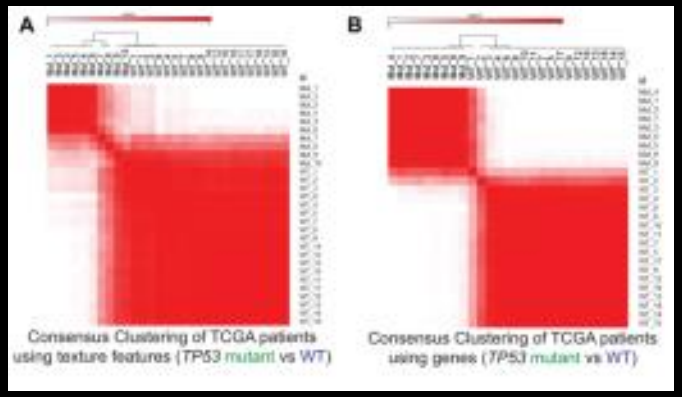
	T2-weighted MRI	Extracted Tumor	Radiomics Features	Estimated Value
Case 1 39 yrs Male IDH Mutant OS: 1289 days Censor: Living			SurfacetoVolumeRatio = 0.1869 DifferenceEntropy_HLL = 1.4972 energy_HHL = 773.9908 RunPercentage_HLL = 3.741 range_HLH = 670.5225 var_HHL = 772.9437 rms_HLL = 109.8504 ...	**Based on 86 radiomic features:** **IDH Prediction = 1.0077** **Based on 16 radiomic feature:** **Risk score = -0.8891**
Case 2 46 yrs Male IDH Wildtype OS: 1121 days Censor: Dead			SurfacetoVolumeRatio =0.4516 DifferenceEntropy_HLL = 2.1369 energy_HHL = 5664.8545 RunPercentage_HLL = 9.3052 range_HLH = 785.578 var_HHL = 5631.1454 rms_HLL = 326.7327 ...	**Based on 86 radiomic features:** **IDH Prediction = -0.0575** **Based on 16 radiomic feature:** **Risk score = 11.3116**

Radiogénomique

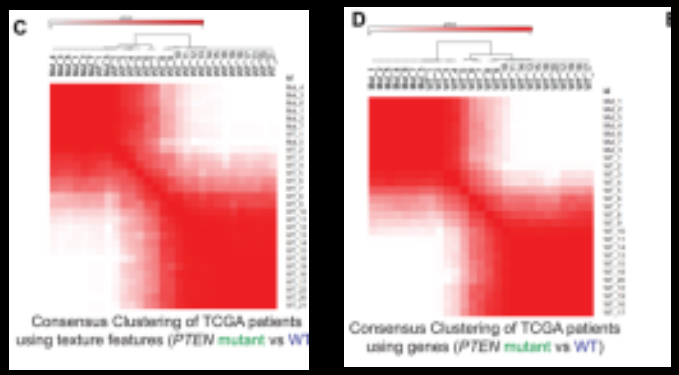
Zinn et al. *Clinical Neurosurgery* 2017



Statut TP53



Statut EGFR



Radiopsy ?

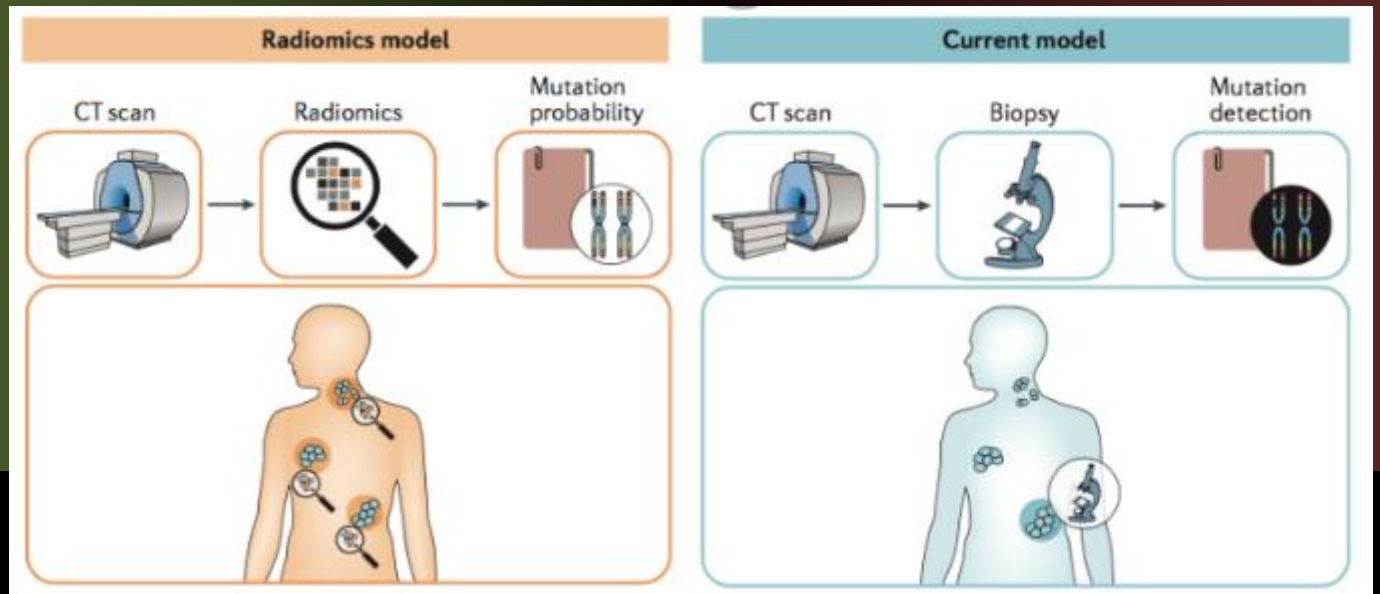
Zinn et al. 2017
Lambin et al. 2017

Sample errors

Non representative

Contraintes techniques, spatiales

Morbidity



Radiopsy ?

Zinn et al. 2017
Lambin et al. 2017

Whole tumor heterogeneity
- In space
- Over time

Non invasive : iterative

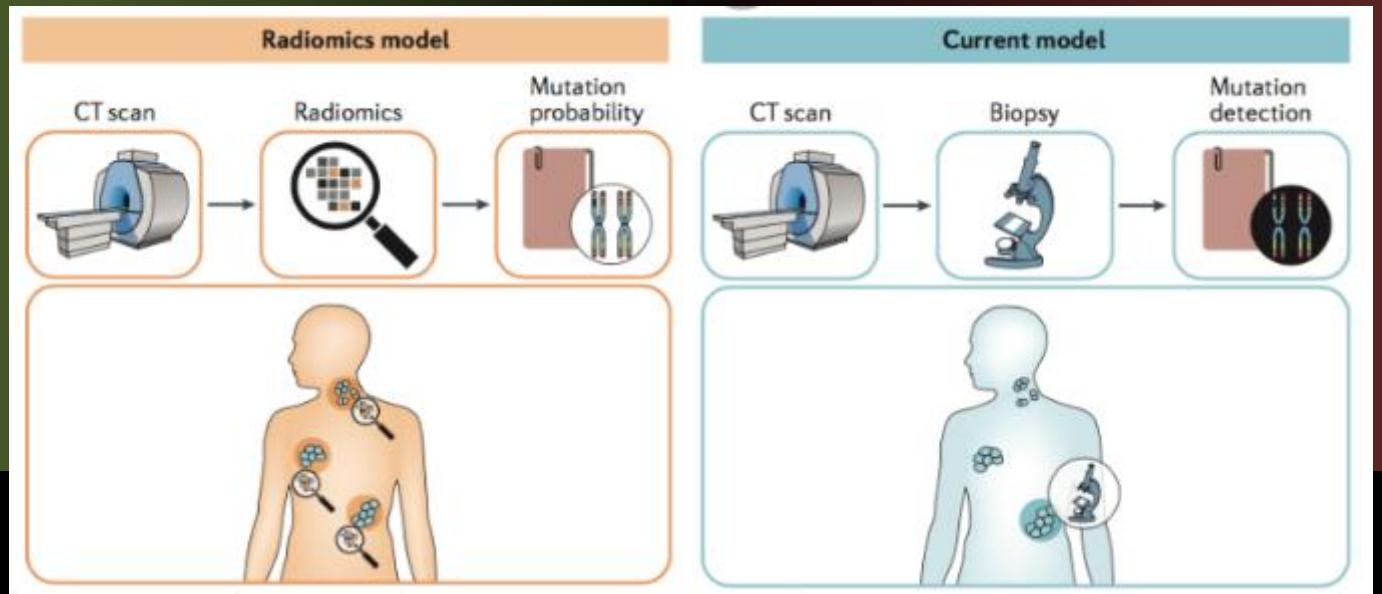
Low cost

Sample errors

Non representative

Contraintes techniques, spatiales

Morbidity



“Etat de l’art” en Neuro-Oncologie

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- Intérêt Pronostique
  - Corrélations Radiogénomiques
  - Signatures Pronostiques indépendantes
- Plannification Thérapeutique

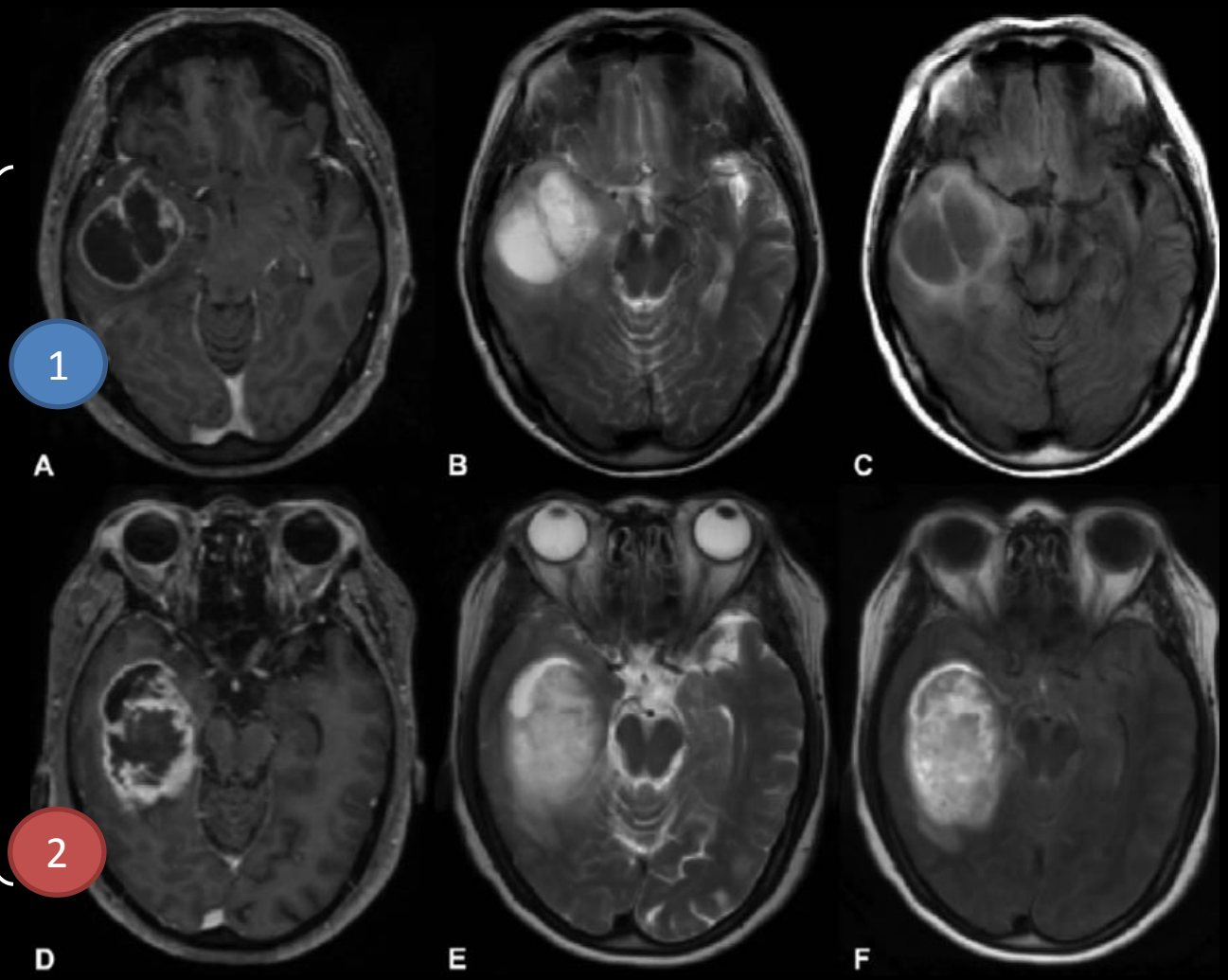
Signature Pronostique

Bae et al. *Radiology* 2018

70 yo W
KPS 70
Subtotal resection
Adj radioTTT

Wild-t IDH
Unmeth MGMT

Radiologie conventionnelle ?



Signature Pronostique

Bae et al. *Radiology* 2018

70 yo W
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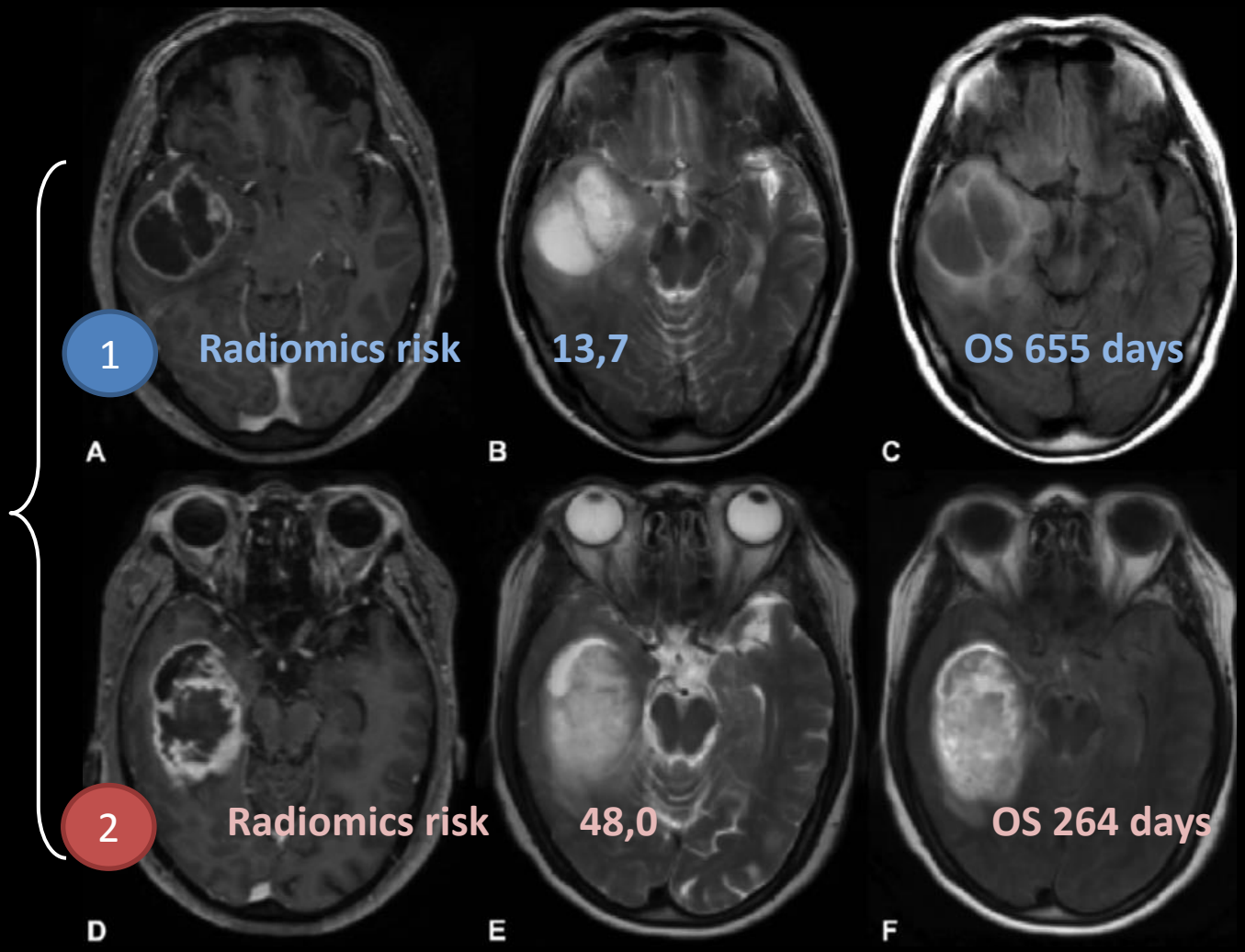
Adj radioTTT

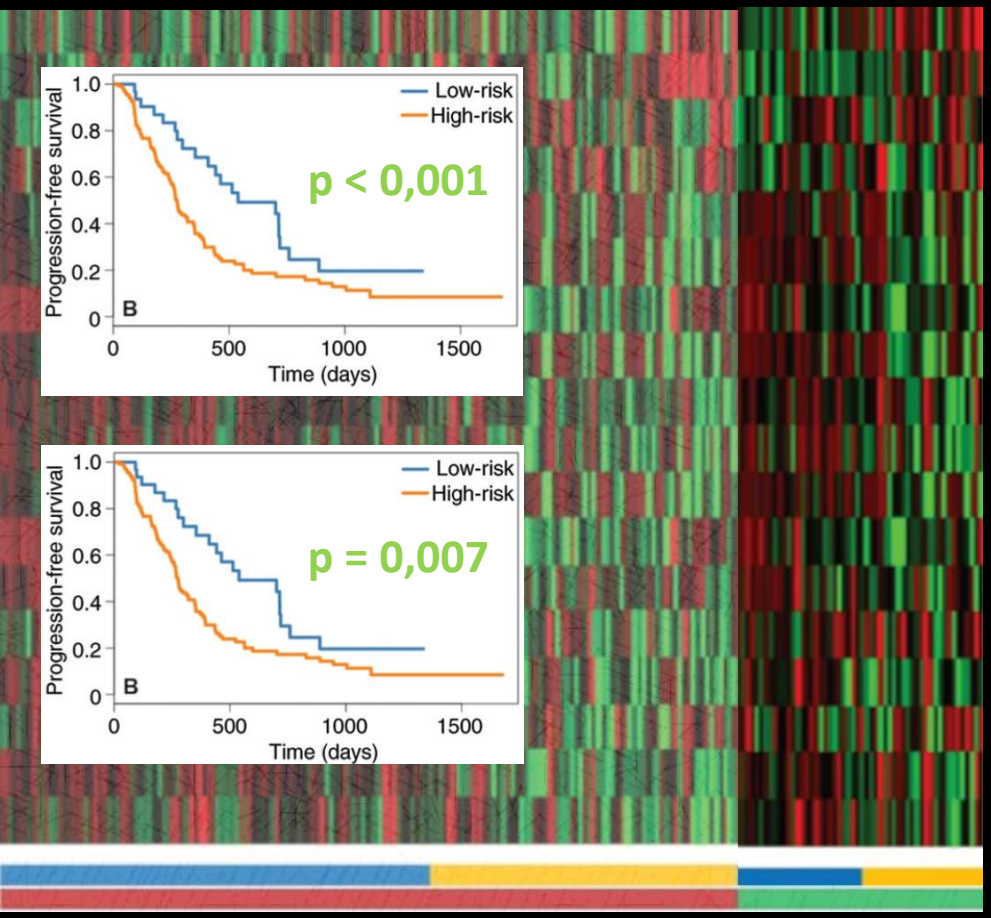
Wild-t IDH
Unmeth MGMT

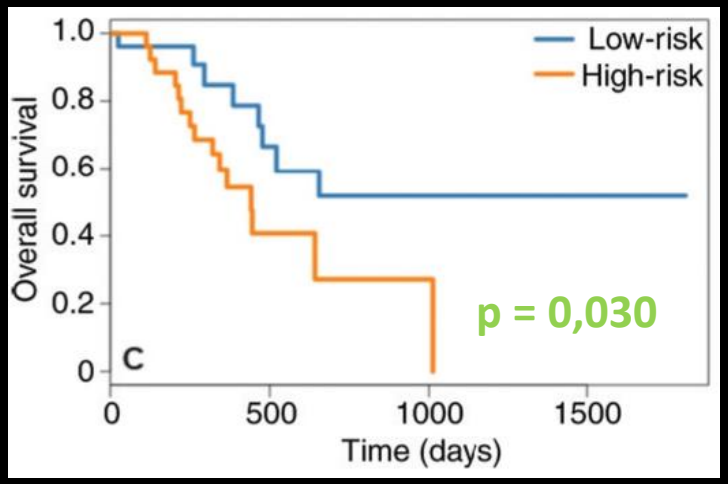


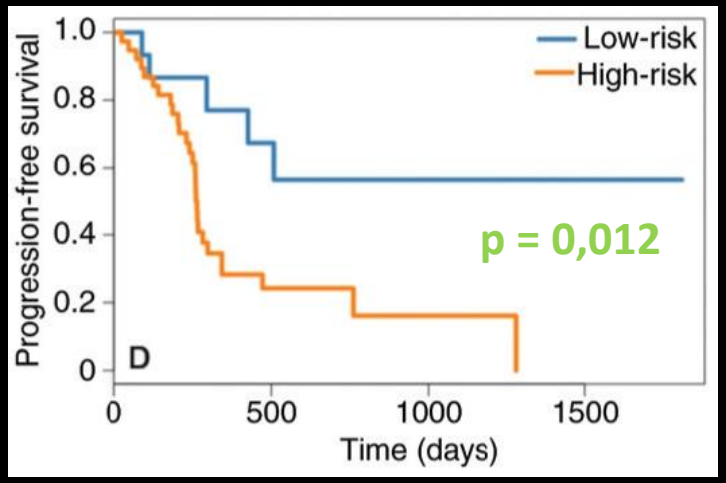
Signature Pronostique

Bae et al. *Radiology* 2018
Kickingereder et al. *Radiology* 2016

LR gp HR gp

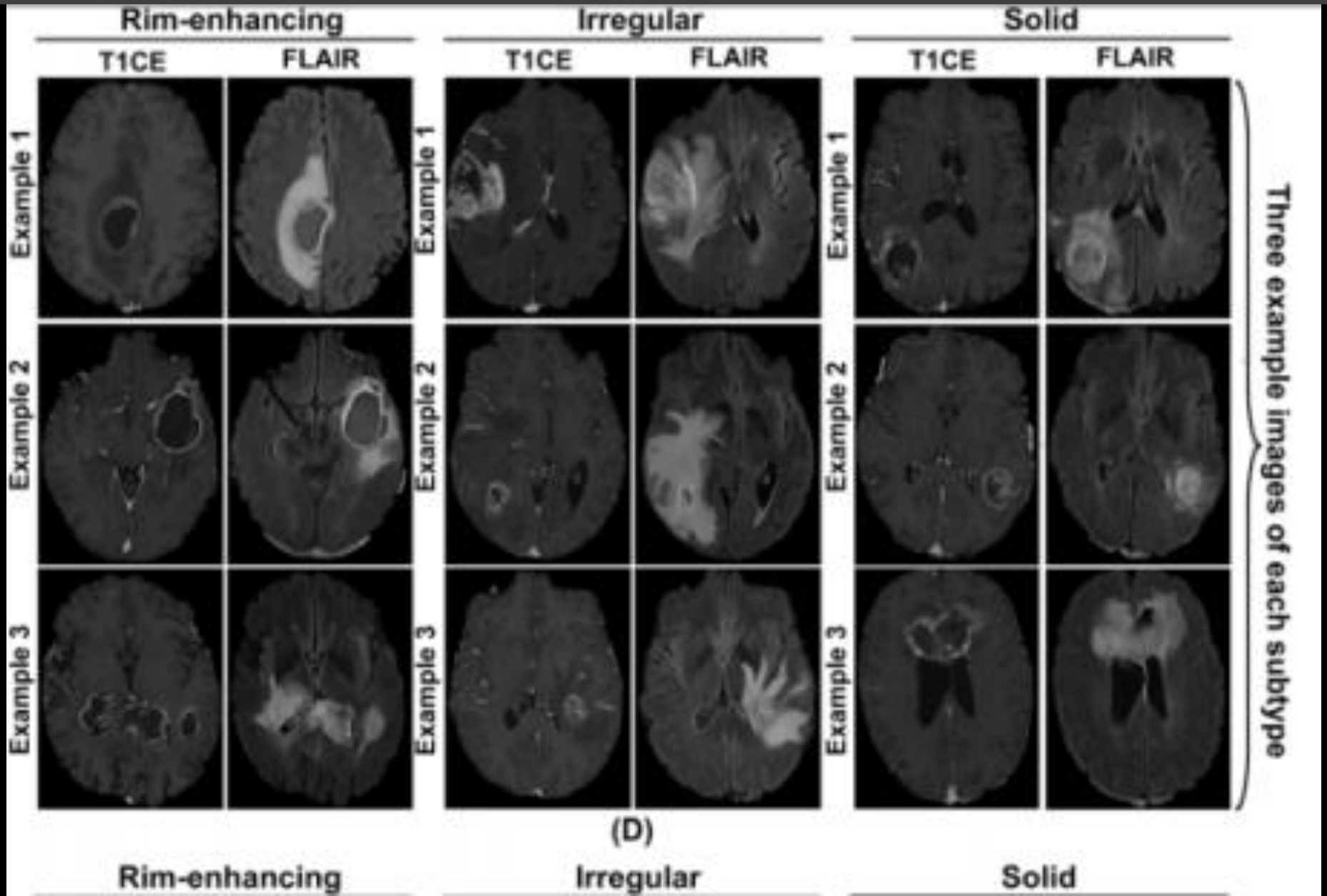






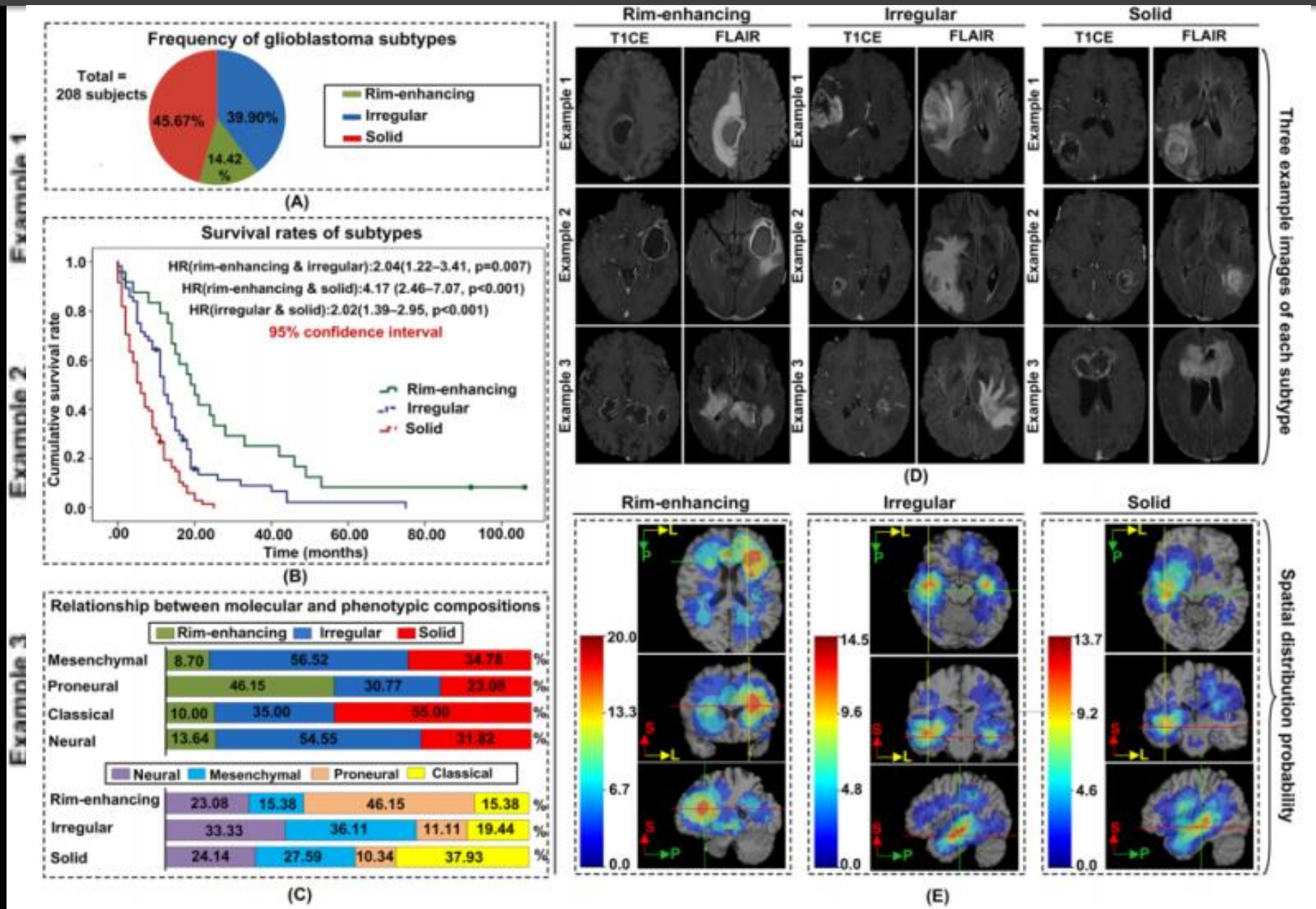
Approche pronostique Globale

Rathore et al., *Nature* 2018



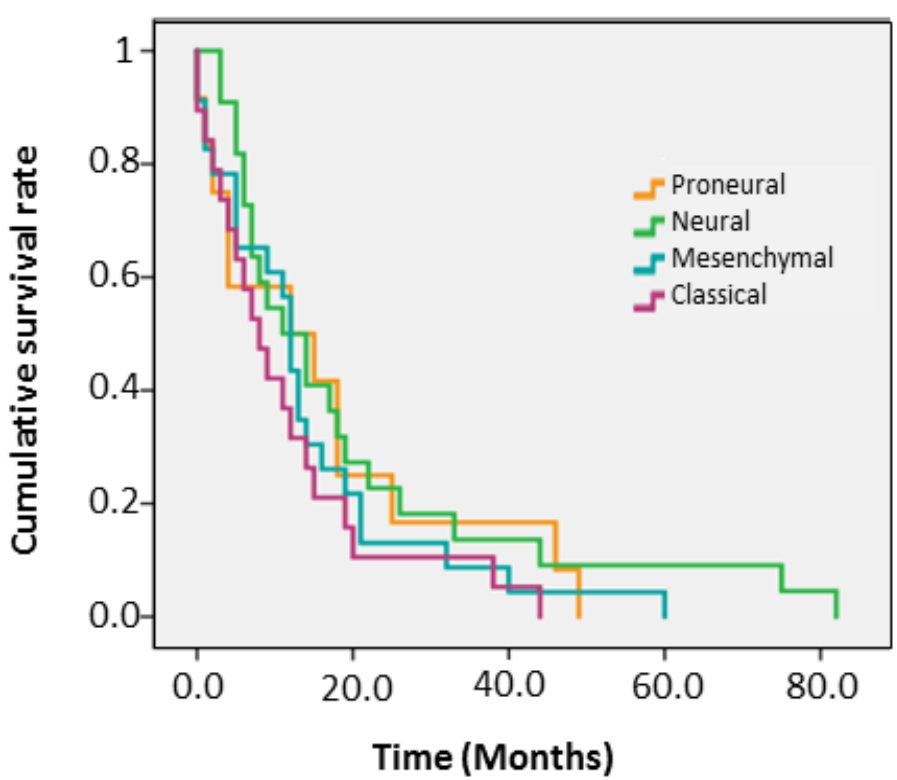
Approche pronostique Globale

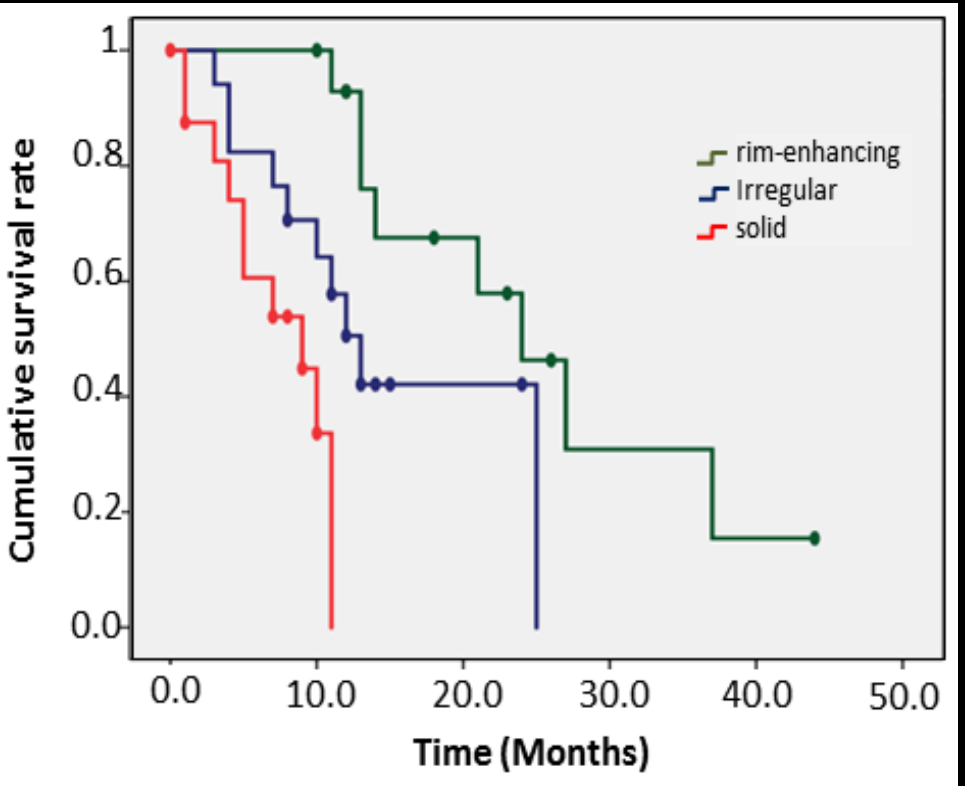
Rathore et al., *Nature* 2018



Approche pronostique Globale

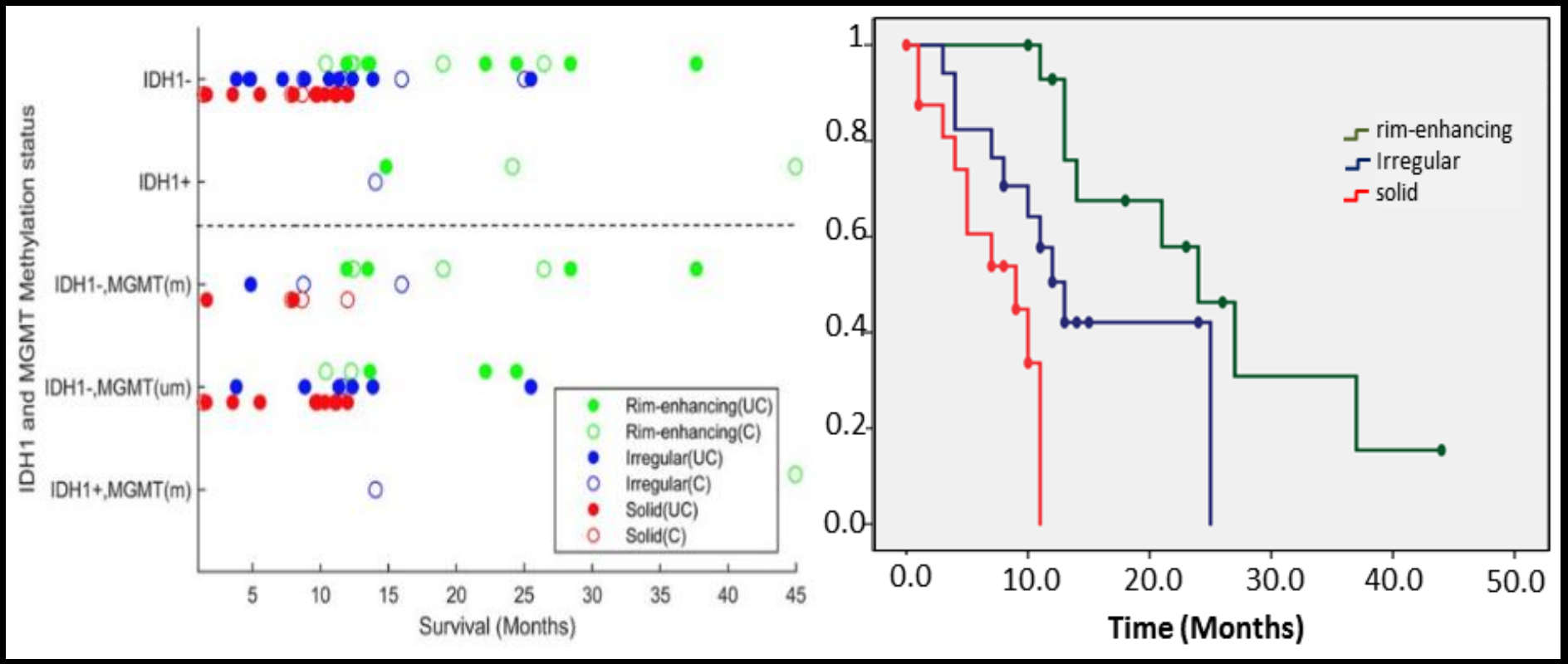
Rathore et al., *Nature* 2018





Approche pronostique Globale

Rathore et al., *Nature* 2018



“Etat de l’art” en Neuro-Oncologie

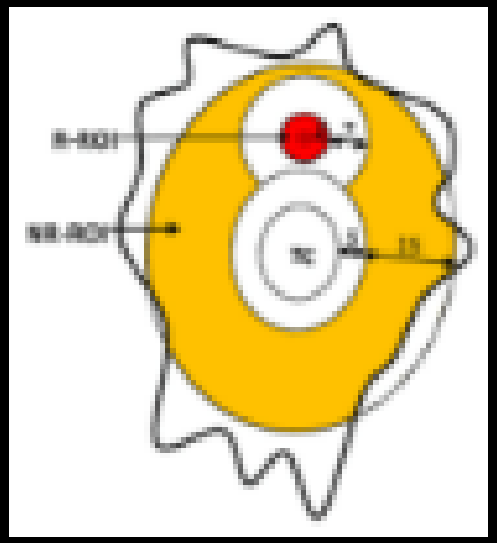
- Intérêt Diagnostique
- Intérêt Pronostique
  - Corrélations Radiogénomiques
  - Signatures Pronostiques indépendantes
- Plannification Thérapeutique

Environnement péri-tumoral

Plannification Thérapeutique

Akbari et al. 2016

Rathore et al. 2017



Environnement péri-tumoral

Plannification Thérapeutique

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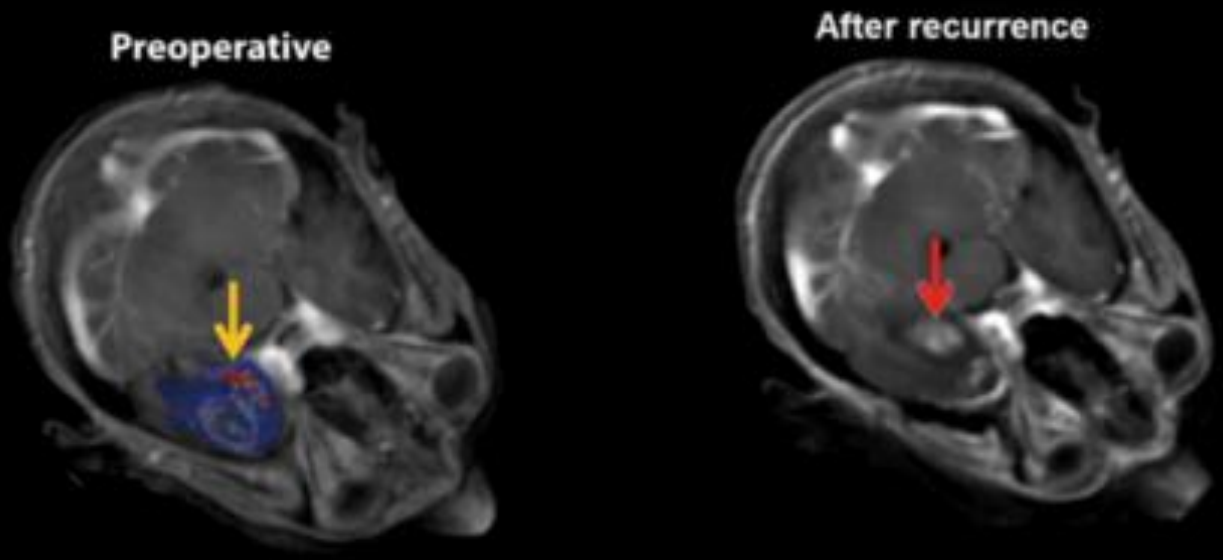
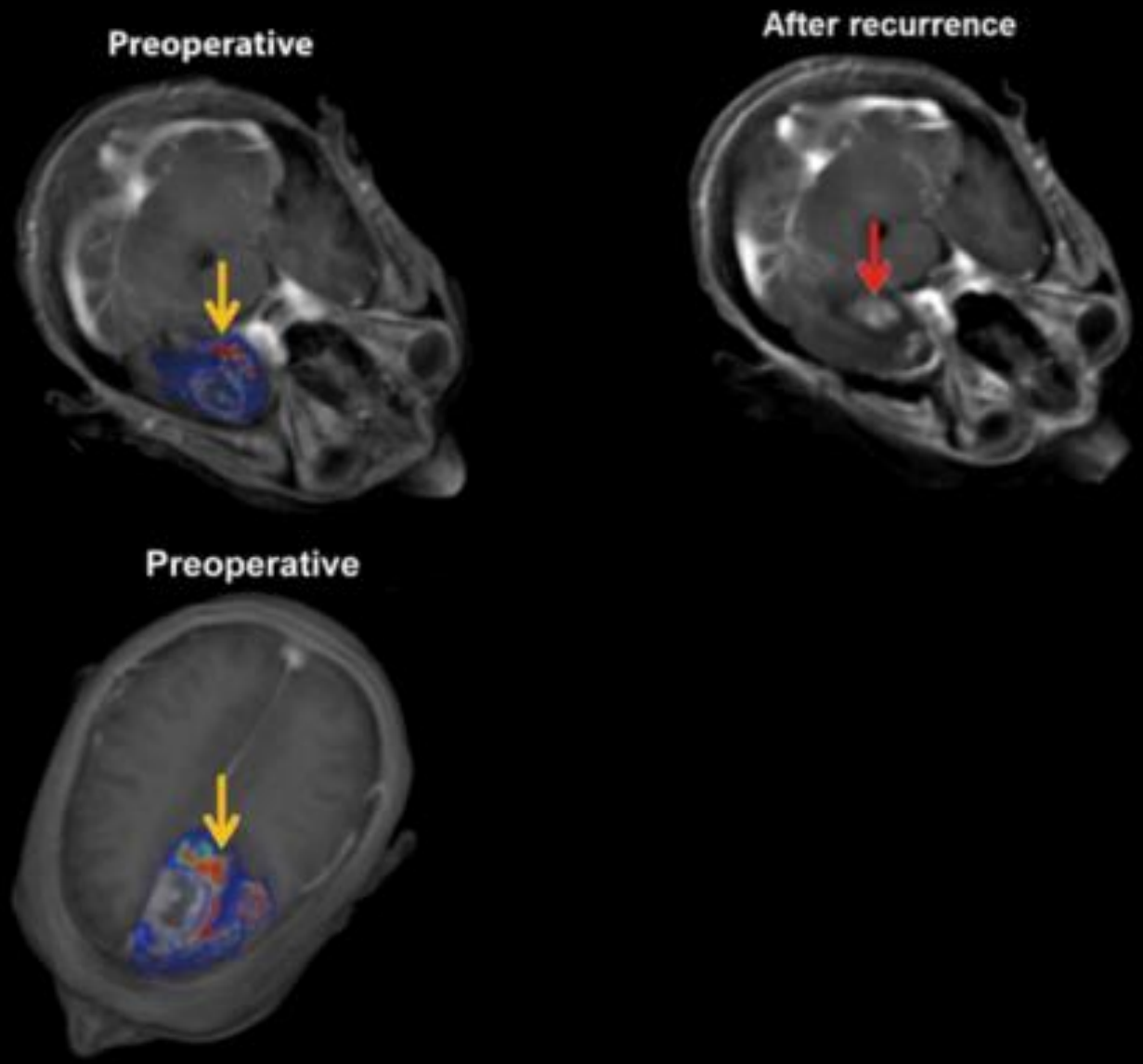


Discovery Set

Environnement péri-tumoral

Plannification Thérapeutique

Akbari et al. 2016
Rathore et al. 2017



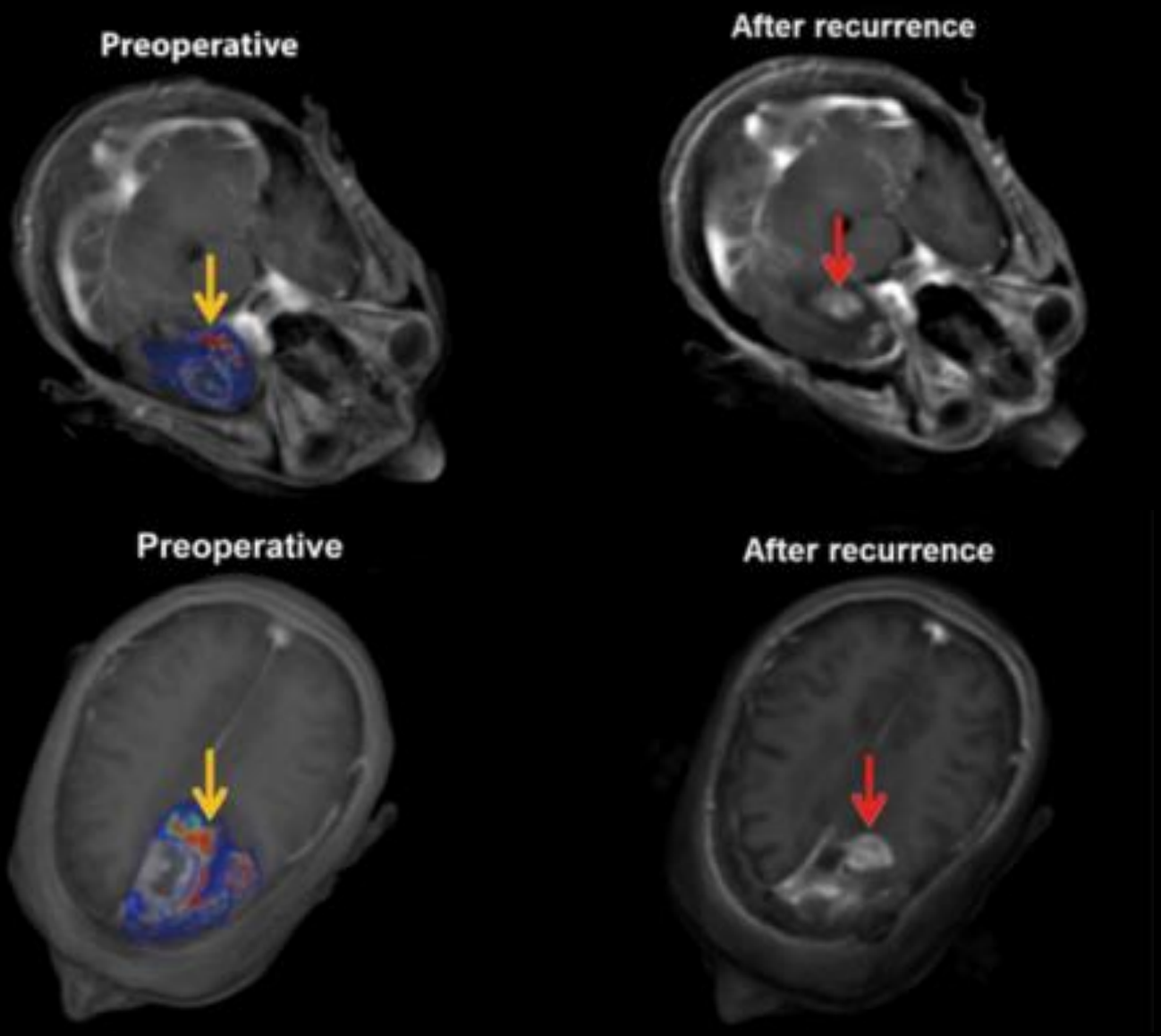
Discovery Set

Replication Set

Environnement péri-tumoral

Plannification Thérapeutique

Akbari et al. 2016
Rathore et al. 2017



Discovery Set

Replication Set

Environnement péri-tumoral

Plannification Thérapeutique

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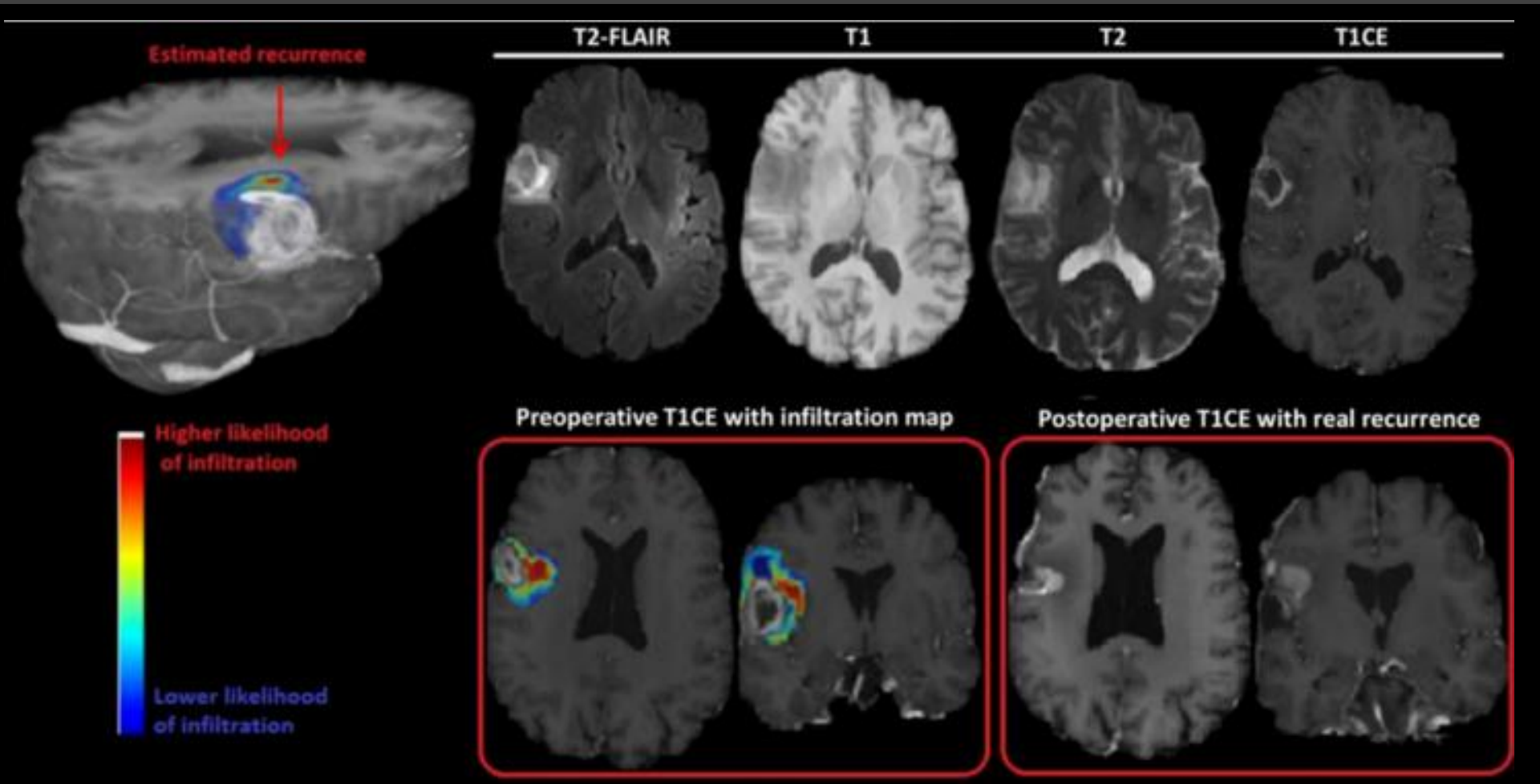


Théranostique

Exemple du Bevacizumab

- Bevacizumab
- Phase III (AVAglio, RTOG-0825, EORTC-26101)
- Absence de bénéfice sur population non sélectionnée

- Hétérogénéité des réponses
- AVAglio et RTOG 0825 : sous-type proneural ?
- Biomarqueur prédictif : sélection des patients

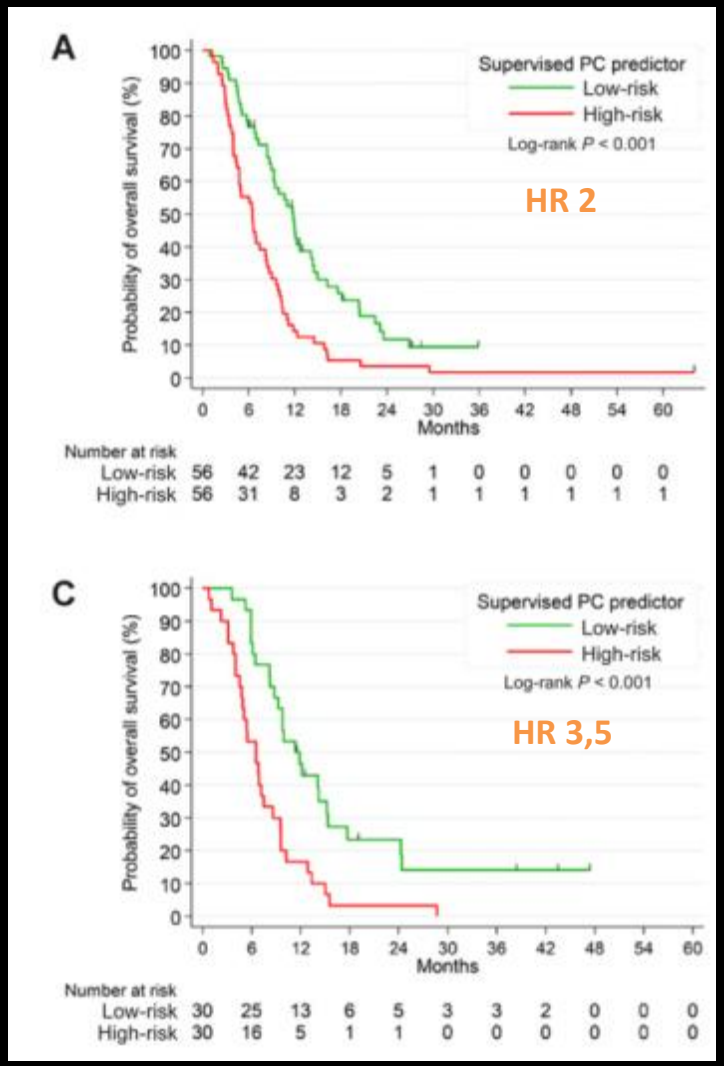
Théranostique

Exemple du Bevacizumab

Kickingereder et al. *Clin Cancer* 2016
Grossmann et al. *Neuro-Oncology* 2017

Absence =/= critères cliniques

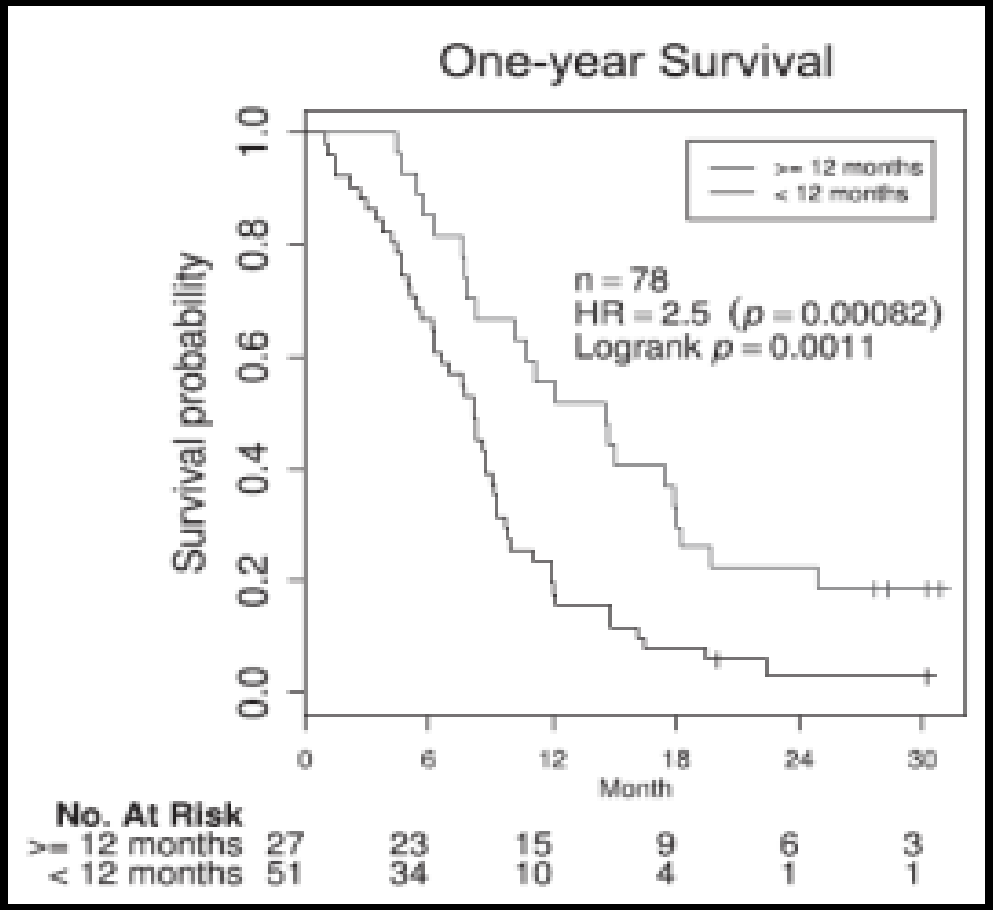
- Discovery vs validation
- H-R vs L-R
- *Signature radiomique indépendante*
- *Bio-information nouvelle*

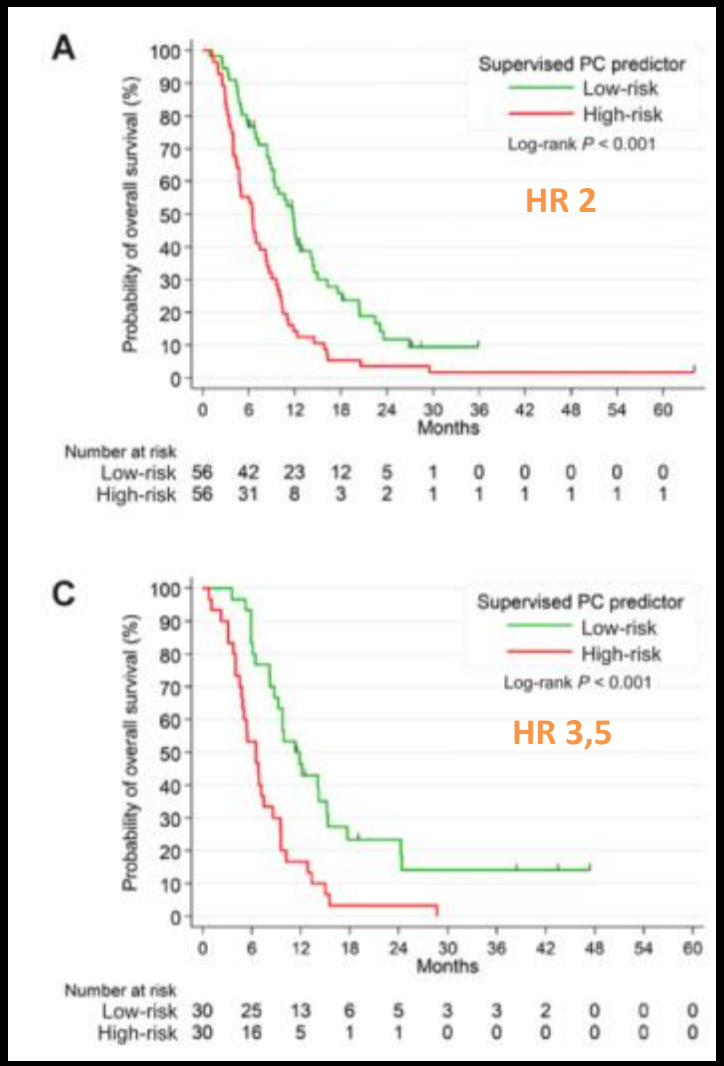


Théranostique

Exemple du Bevacizumab

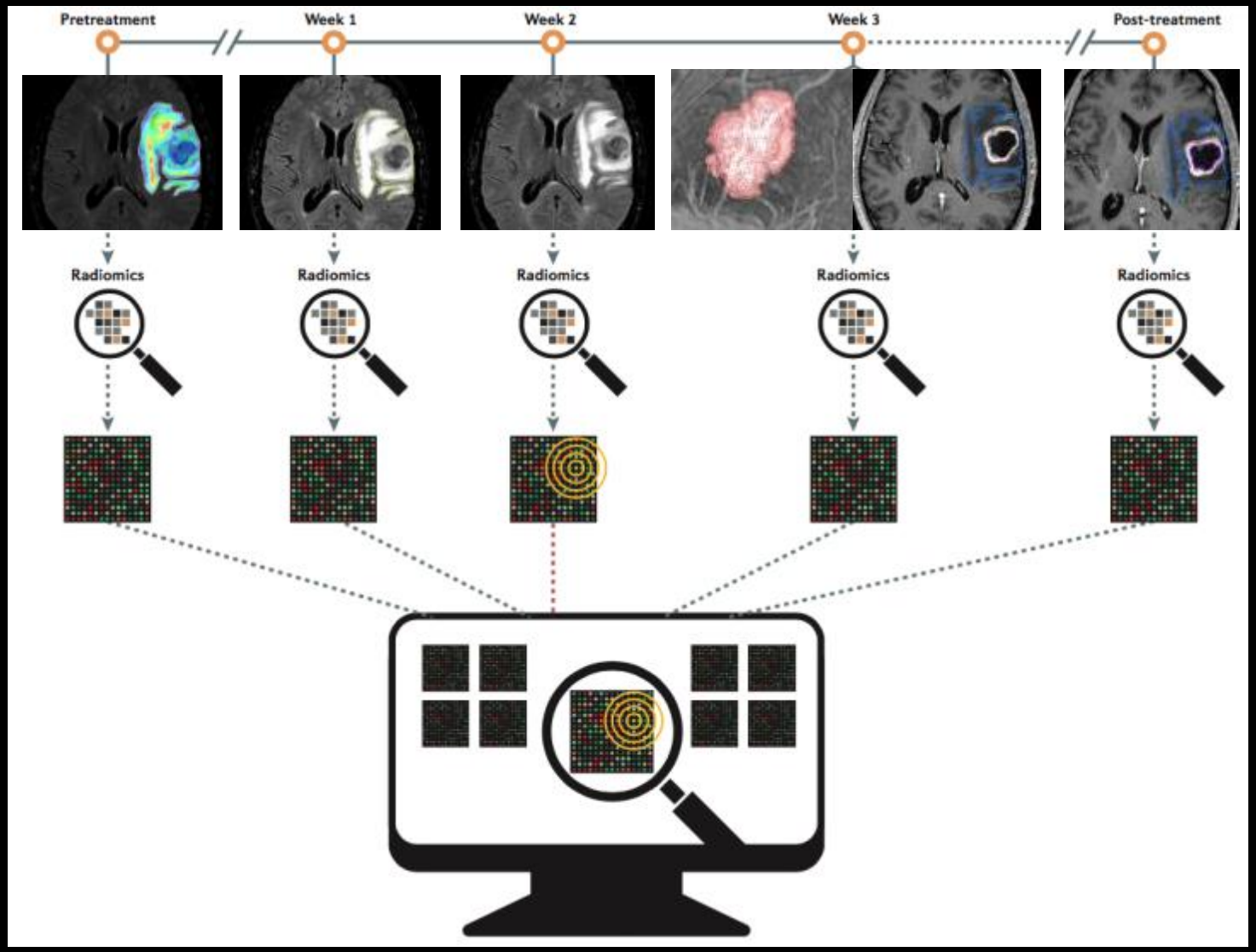
Kickingereder et al. *Clin Cancer* 2016
Grossmann et al. *Neuro-Oncology* 2017





D'après Lambin et al. 2017

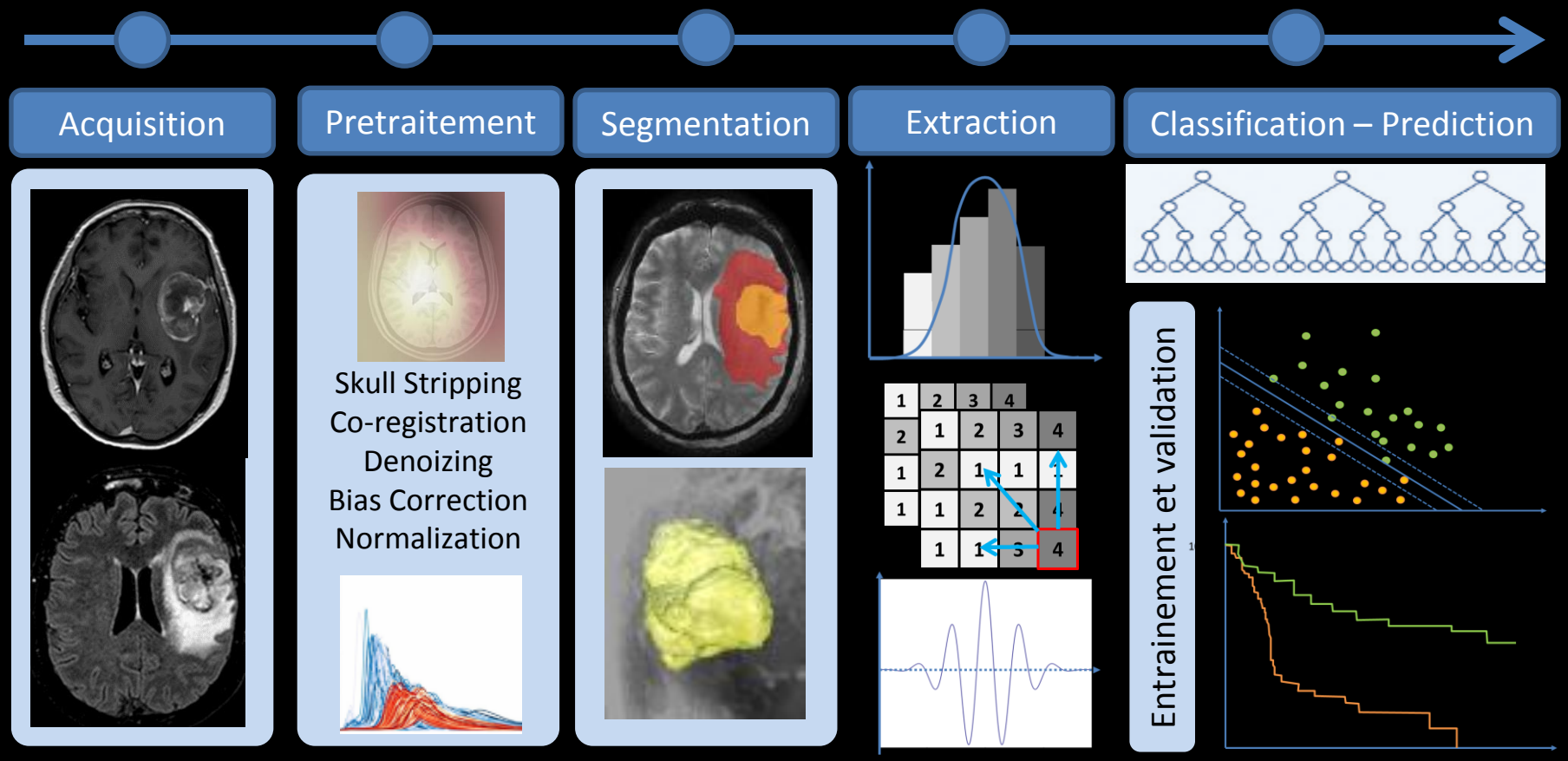
Δ-Radiomics



Sommaire

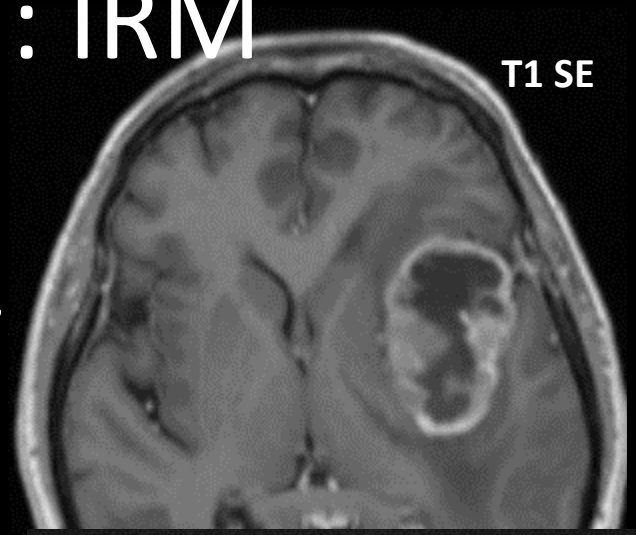
- Contextualisation & Définitions
- Recherche et applications en Neuro-Oncologie
- “Worklow” : Limites et solutions
- Synthèse

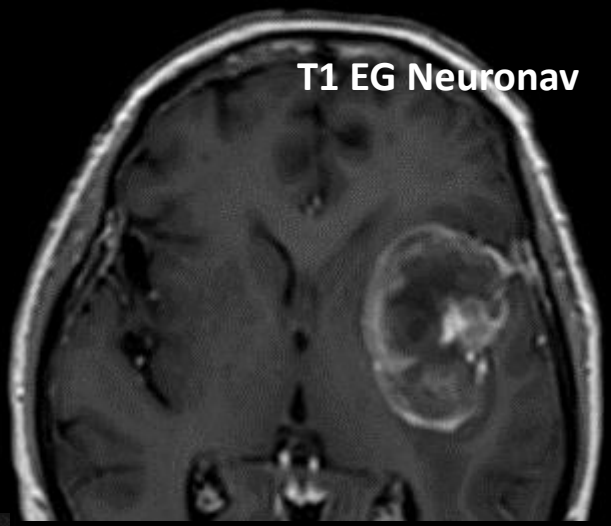
General Worklow

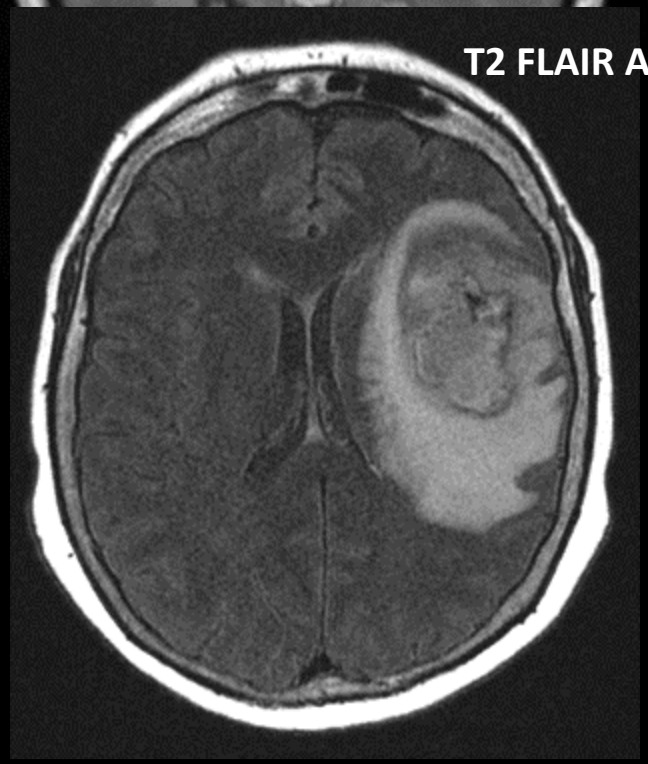


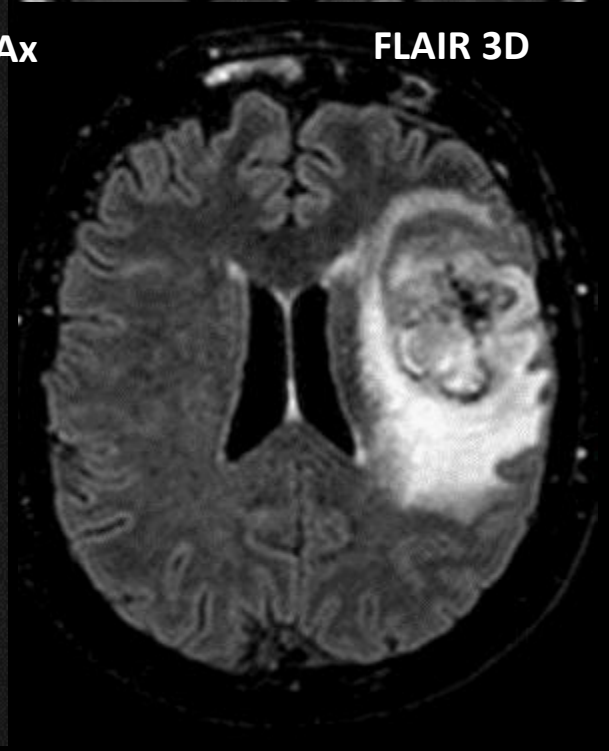
Acquisition : IRM

- Hétérogénéités de protocoles : standard, DSC, DWI, DTI …
- Paramètres des séquences : TE, TR, FOV, angle, épaisseur de coupe…
- Intensité de champ magnétique









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Acquisition : IRM

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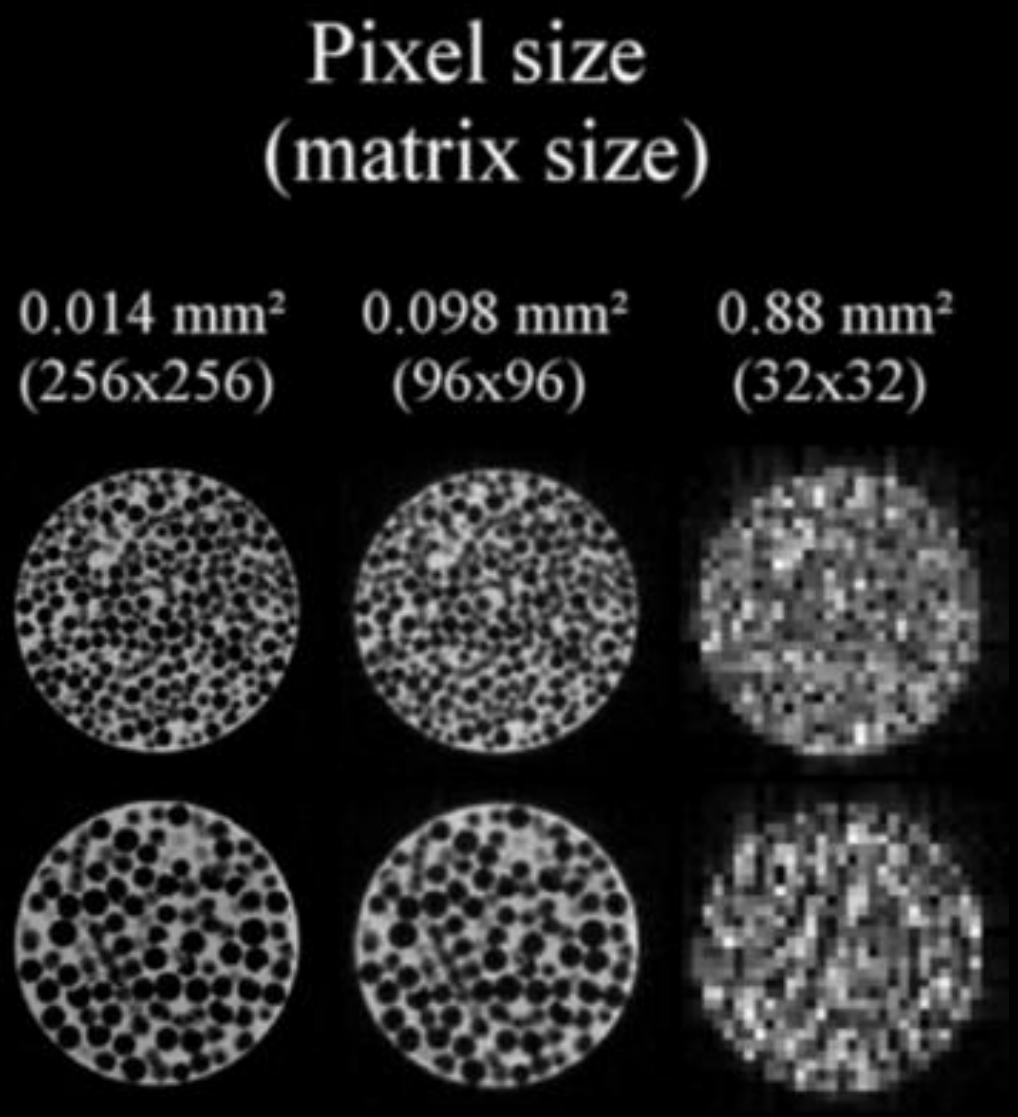
- Paramètres des séquences : TE, TR, FOV, angle, épaisseur de coupe… **taille voxel**
- Intensité de champ magnétique



Acquisition : IRM

- Hétérogénéités de protocoles : standard, DSC, DWI, DTI …
- Paramètres des séquences : TE, TR, FOV, angle, épaisseur de coupe… **taille voxel**
- Intensité de champ magnétique

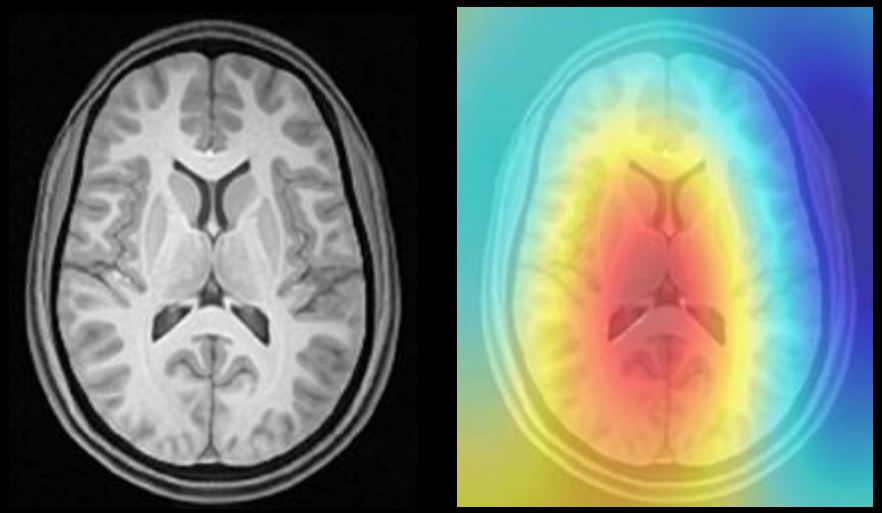
Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials **2015**

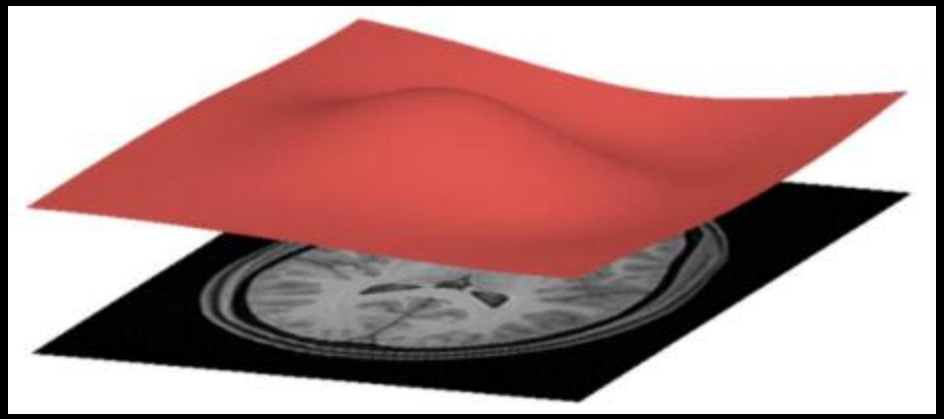
- Intensités arbitraires → **Normalisation**
- Distorsion spatiale → **Coregistration**

Pre-Processing

- Skull-stripping
- Co-registration
- Bias Correction (N4ITK)
- Denoizing
- Normalization

(White Stripe ++)



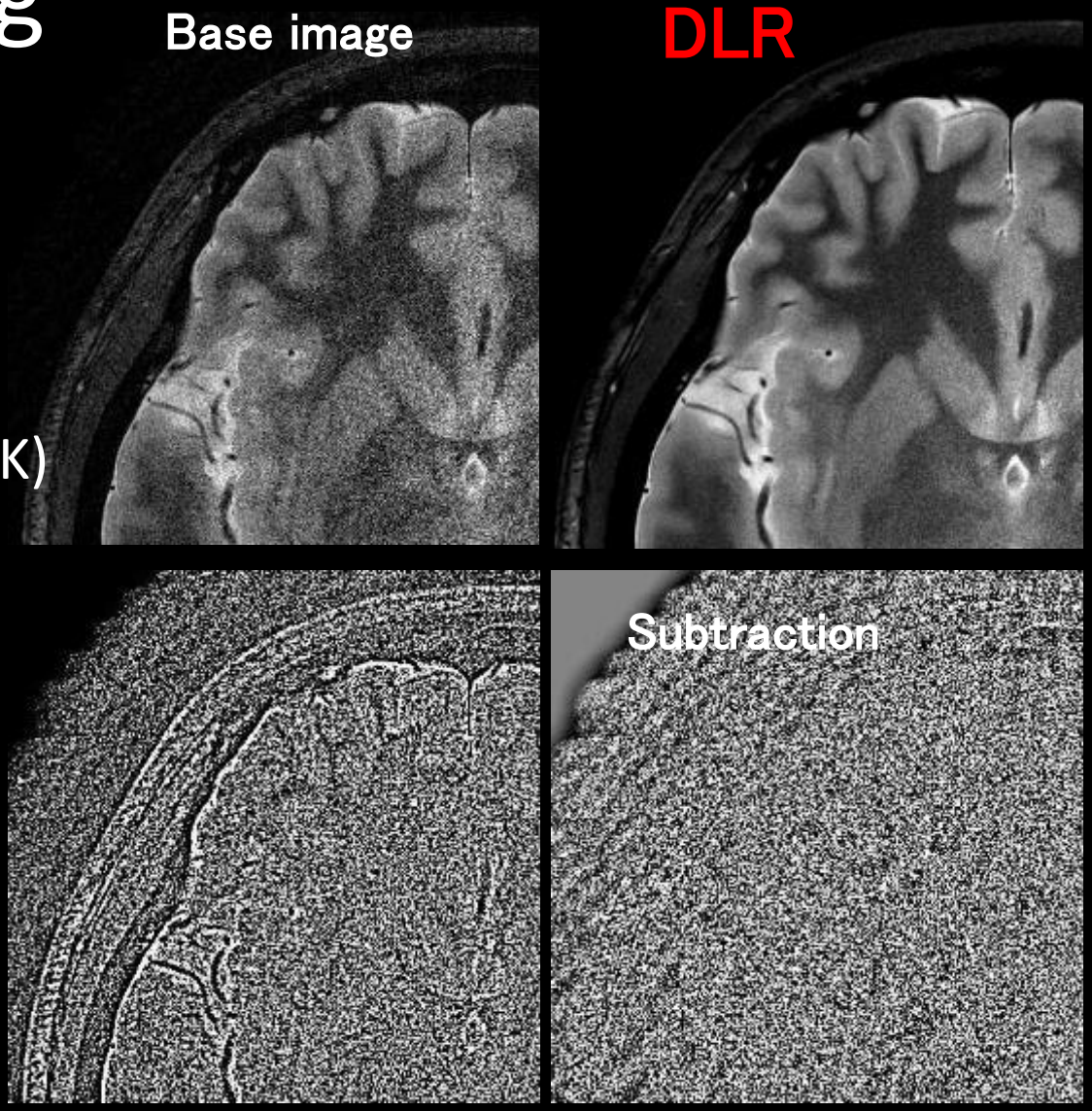


Tutison et al. 2010

Pre-Processing

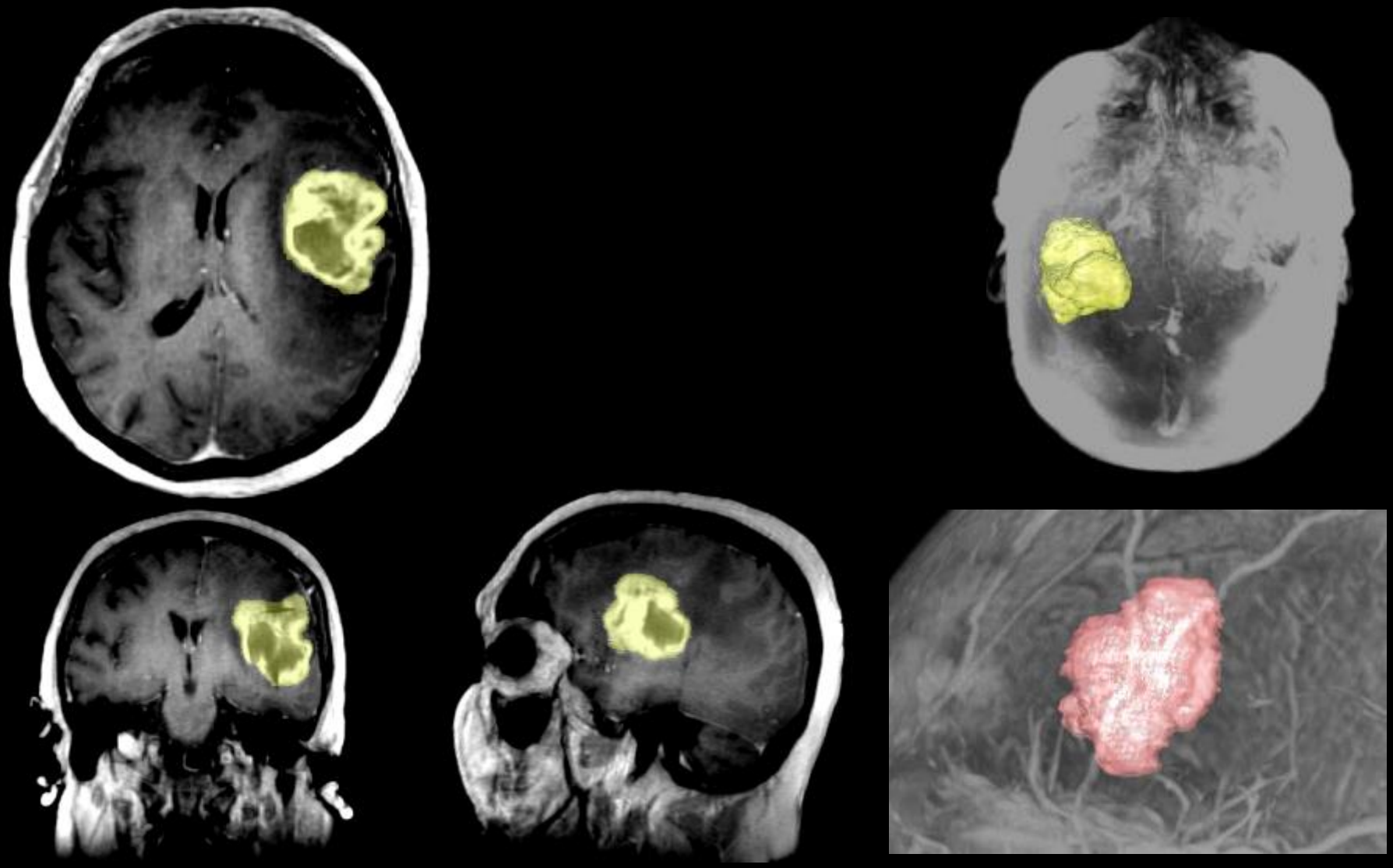
- Skull-stripping
- Co-registration
- Bias Correction (N4ITK)
- Denoizing
- Normalization

(White Stripe ++)

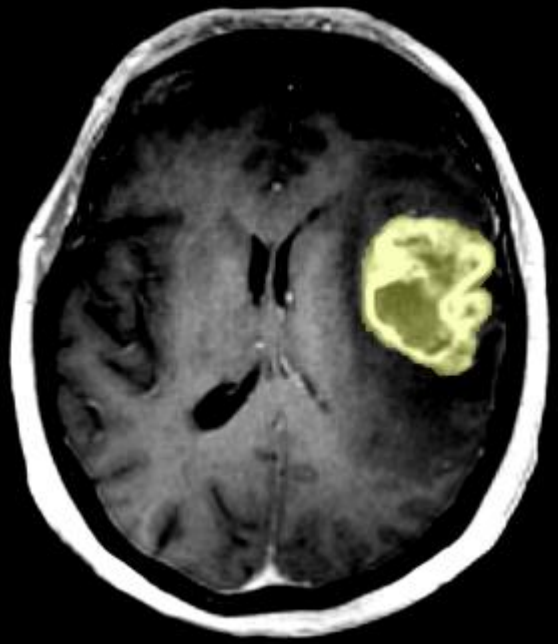


Canon Imaging – Pr. Dousset

Segmentation



Segmentation



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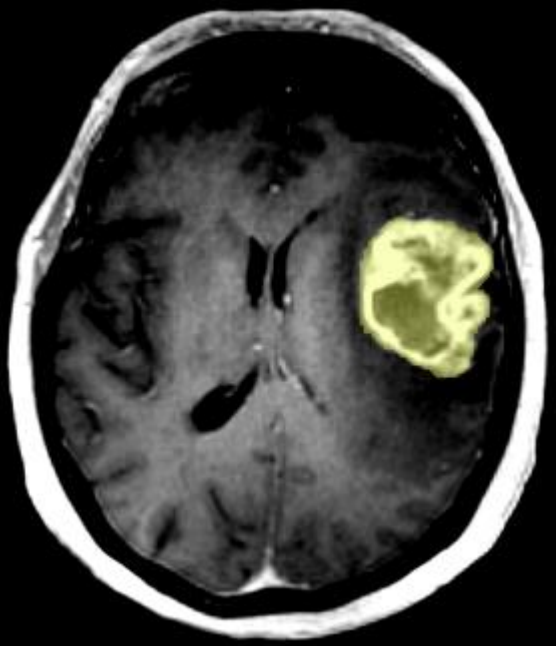

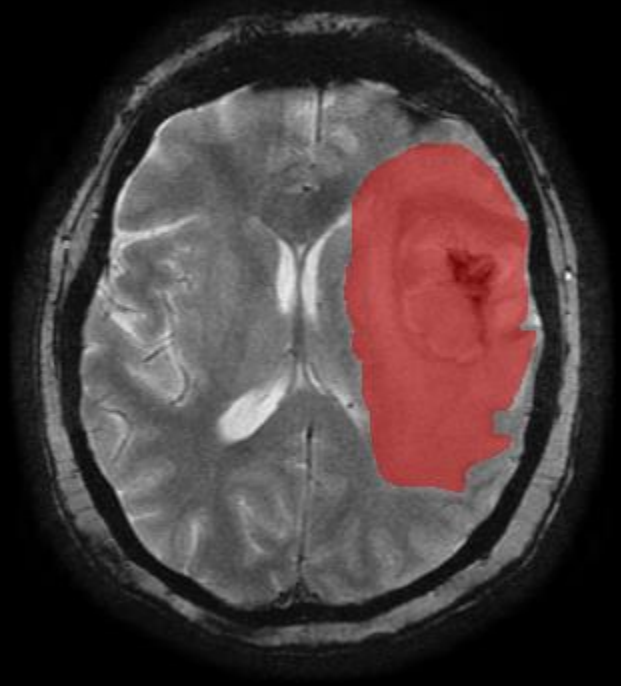

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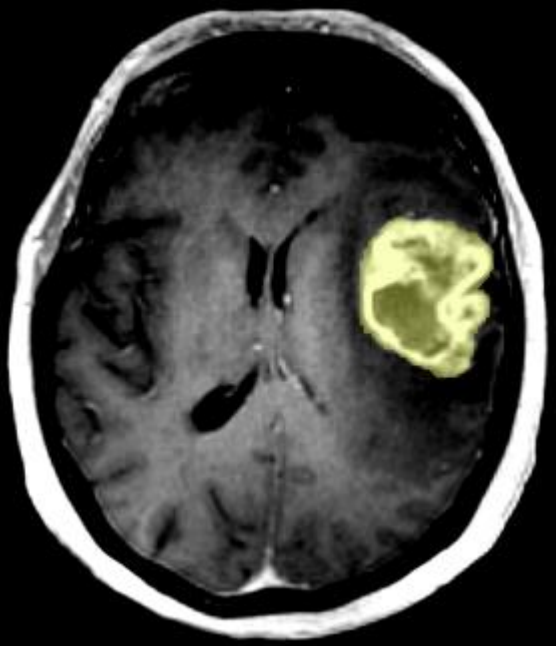

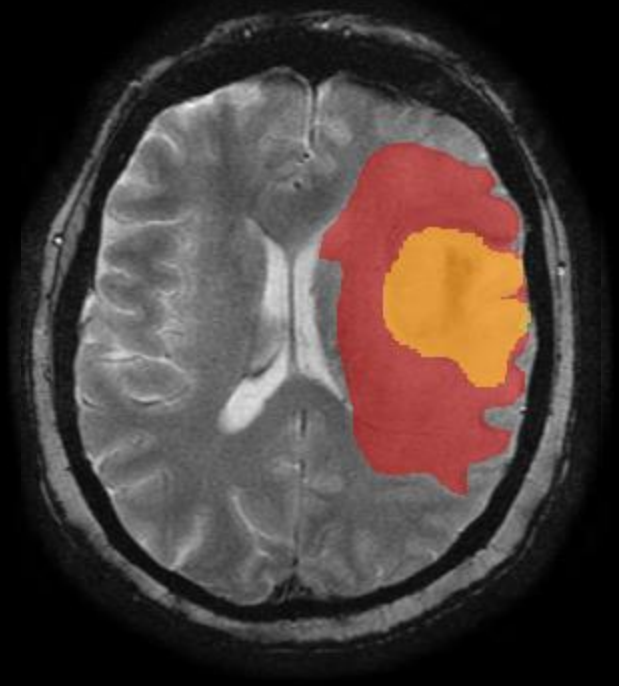

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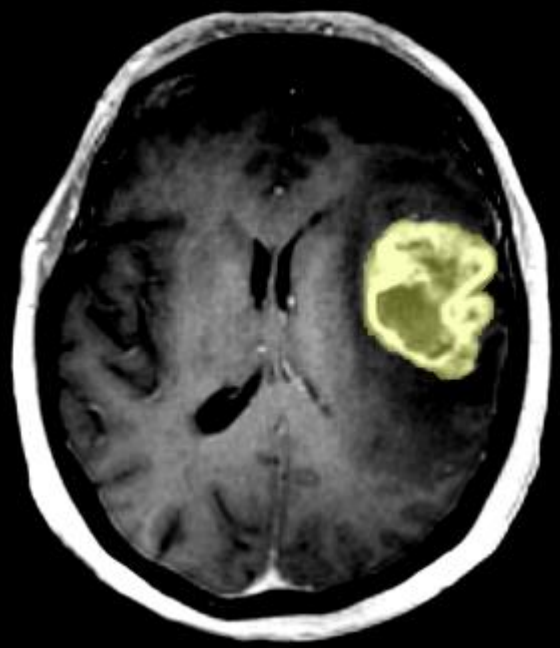

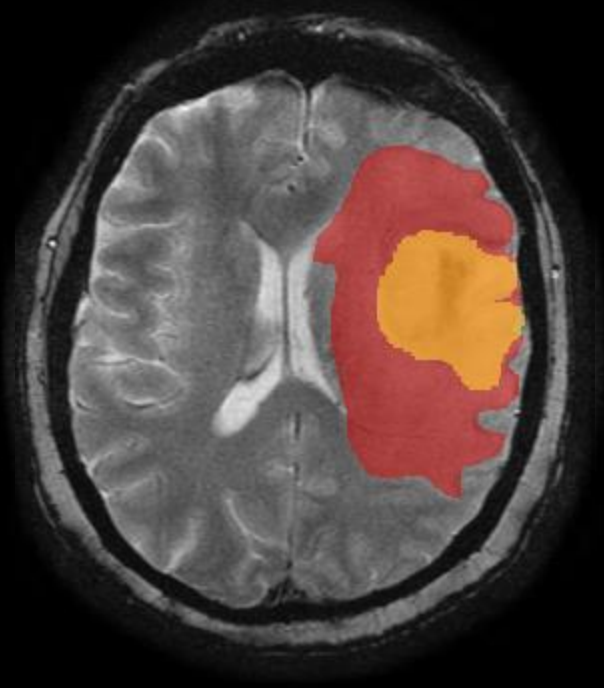

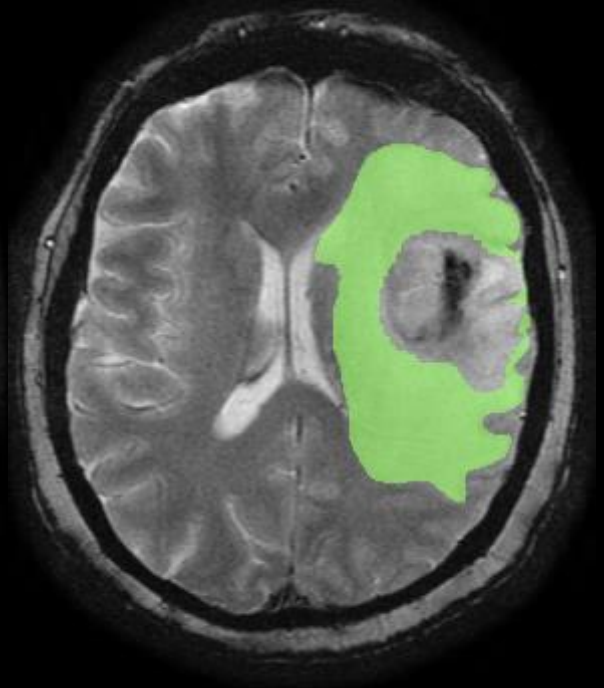

Segmentation

- Manuelle
- Automatique
- Semi-automatique

PET feature	50% SUVmax Value	40% SUVmax Value	40% SUVmax Change	FLAB Value	FLAB Change
Volume	26.59	34.61	+30%	40.36	+51%
Entropy	3.64	3.89	+7%	3.98	+10%
Total energy	$4.72 \cdot 10^4$	$5.28 \cdot 10^4$	+12%	$5.57 \cdot 10^4$	+18%
Homogeneity	0.29	0.25	-12%	0.24	-17%
Dissimilarity	2.97	3.60	+21%	3.95	+33%
Zone percentage	0.35	0.39	+9%	0.39	+10%
Size-zone variability	0.36	0.38	+6%	0.38	+4%
Intensity variability	0.09	0.08	-15%	0.07	-18%

Lerue et Defraene. 2017

Segmentation

- Manuelle
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- Semi-automatique

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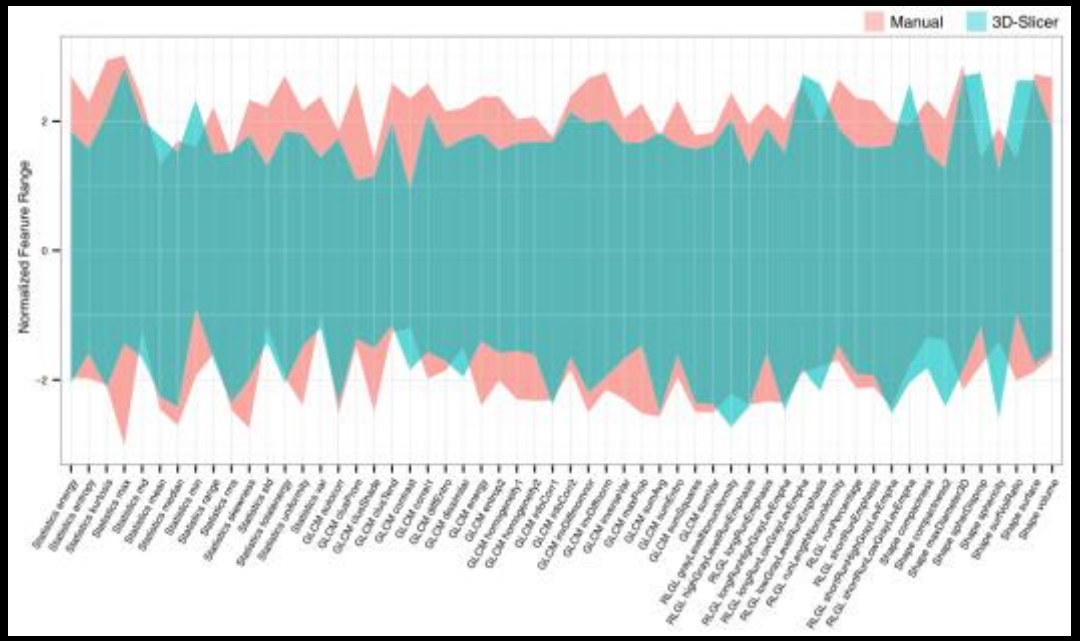
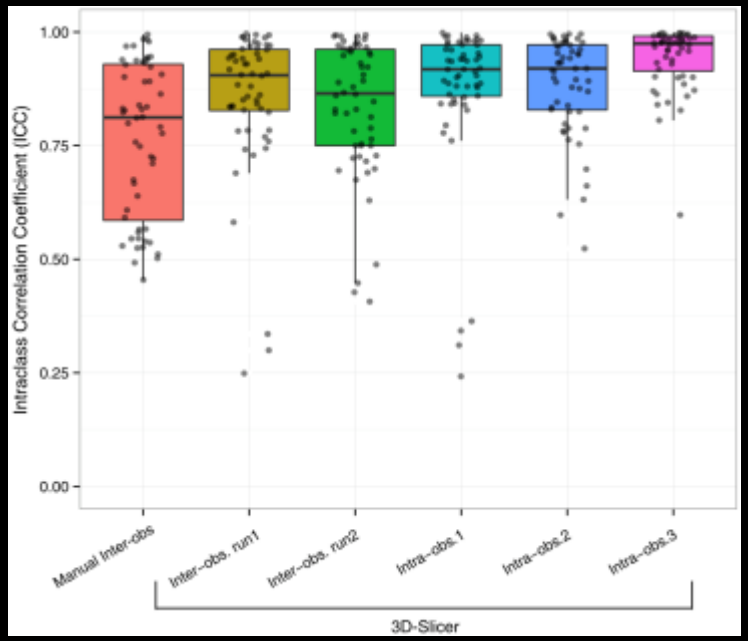
Lerue et Defraene. 2017

Parmar et al. 2014

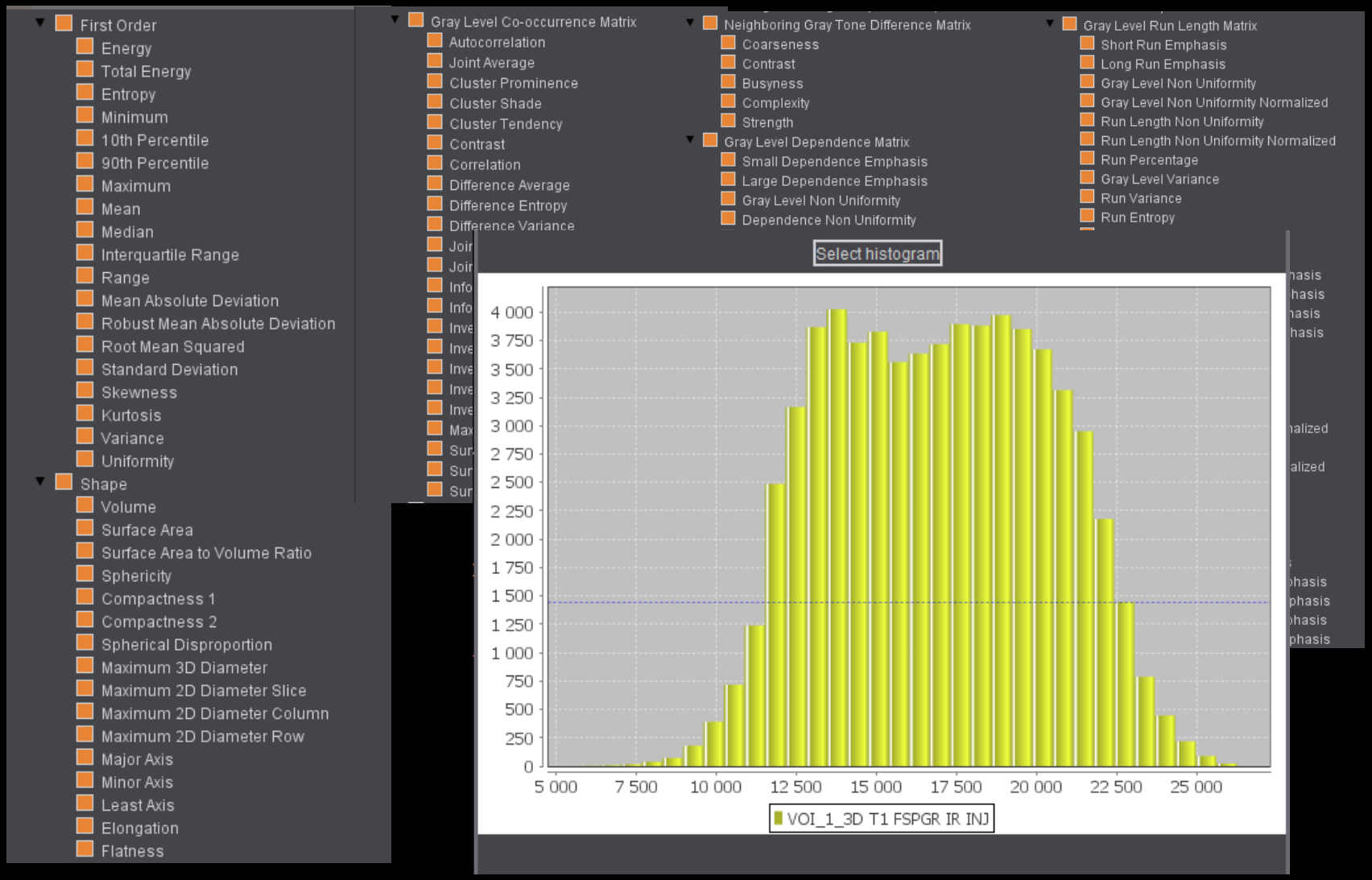




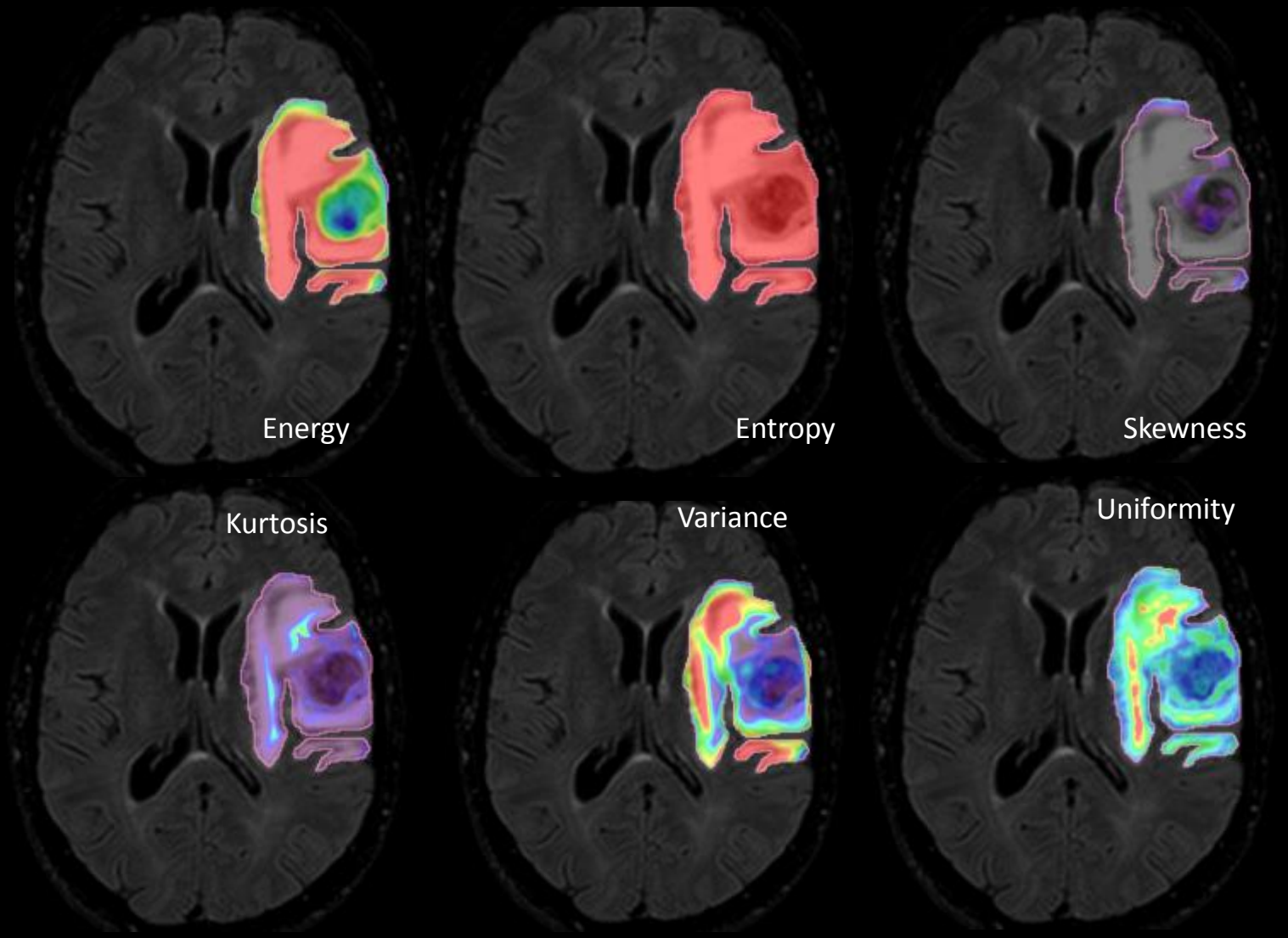
Extraction

- First Order
  - Energy
  - Total Energy
  - Entropy
  - Minimum
  - 10th Percentile
  - 90th Percentile
  - Maximum
  - Mean
  - Median
  - Interquartile Range
  - Range
  - Mean Absolute Deviation
  - Robust Mean Absolute Deviation
  - Root Mean Squared
  - Standard Deviation
  - Skewness
  - Kurtosis
  - Variance
  - Uniformity
- Shape
  - Volume
  - Surface Area
  - Surface Area to Volume Ratio
  - Sphericity
  - Compactness 1
  - Compactness 2
  - Spherical Disproportion
  - Maximum 3D Diameter
  - Maximum 2D Diameter Slice
  - Maximum 2D Diameter Column
  - Maximum 2D Diameter Row
  - Major Axis
  - Minor Axis
  - Least Axis
  - Elongation
  - Flatness
- Gray Level Co-occurrence Matrix
  - Autocorrelation
  - Joint Average
  - Cluster Prominence
  - Cluster Shade
  - Cluster Tendency
  - Contrast
  - Correlation
  - Difference Average
  - Difference Entropy
  - Difference Variance
  - Joint Energy
  - Joint Entropy
  - Informal Measure of Correlation 1
  - Informal Measure of Correlation 2
  - Inverse Difference Moment
  - Inverse Difference Moment Normali
  - Inverse Difference
  - Inverse Difference Normalized
  - Inverse Variance
  - Maximum Probability
  - Sum Average
  - Sum Entropy
  - Sum of Squares
- Neighboring Gray Tone Difference Matrix
  - Coarseness
  - Contrast
  - Busyness
  - Complexity
  - Strength
- Gray Level Dependence Matrix
  - Small Dependence Emphasis
  - Large Dependence Emphasis
  - Gray Level Non Uniformity
  - Dependence Non Uniformity
  - Dependence Non Uniformity Normalized
  - Gray Level Variance
  - Dependence Variance
  - Dependence Entropy
  - Low Gray Level Emphasis
  - High Gray Level Emphasis
  - Small Dependence Low Gray Level Emphasis
  - Small Dependence High Gray Level Emphasis
  - Large Dependence Low Gray Level Emphasis
  - Large Dependence High Gray Level Emphasis
- Gray Level Run Length Matrix
  - Short Run Emphasis
  - Long Run Emphasis
  - Gray Level Non Uniformity
  - Gray Level Non Uniformity Normalized
  - Run Length Non Uniformity
  - Run Length Non Uniformity Normalized
  - Run Percentage
  - Gray Level Variance
  - Run Variance
  - Run Entropy
  - Low Gray Level Run Emphasis
  - High Gray Level Run Emphasis
  - Short Run Low Gray Level Emphasis
  - Short Run High Gray Level Emphasis
  - Long Run Low Gray Level Emphasis
  - Long Run High Gray Level Emphasis
- Gray Level Size Zone Matrix
  - Small Area Emphasis
  - Large Area Emphasis
  - Gray Level Non Uniformity
  - Gray Level Non Uniformity Normalized
  - Size Zone Non Uniformity
  - Size Zone Non Uniformity Normalized
  - Zone Percentage
  - Gray Level Variance
  - Zone Variance
  - Zone Entropy
  - Low Gray Level Zone Emphasis
  - Small Area Low Gray Level Emphasis
  - Small Area High Gray Level Emphasis
  - Large Area Low Gray Level Emphasis
  - Large Area High Gray Level Emphasis

Extraction


First Order
Energy
Total Energy
Entropy
Minimum
10th Percentile
90th Percentile
Maximum
Mean
Median
Interquartile Range
Range
Mean Absolute Deviation
Robust Mean Absolute Deviation
Root Mean Squared
Standard Deviation
Skewness
Kurtosis
Variance
Uniformity
Shape
Volume
Surface Area
Surface Area to Volume Ratio
Sphericity
Compactness 1
Compactness 2
Spherical Disproportion
Maximum 3D Diameter
Maximum 2D Diameter Slice
Maximum 2D Diameter Column
Maximum 2D Diameter Row
Major Axis
Minor Axis
Least Axis
Elongation
Flatness
Gray Level Co-occurrence Matrix
Autocorrelation
Joint Average
Cluster Prominence
Cluster Shade
Cluster Tendency
Contrast
Correlation
Difference Average
Difference Entropy
Difference Variance
Neighboring Gray Tone Difference Matrix
Coarseness
Contrast
Busyness
Complexity
Strength
Gray Level Dependence Matrix
Small Dependence Emphasis
Large Dependence Emphasis
Gray Level Non Uniformity
Dependence Non Uniformity
Gray Level Run Length Matrix
Short Run Emphasis
Long Run Emphasis
Gray Level Non Uniformity
Gray Level Non Uniformity Normalized
Run Length Non Uniformity
Run Length Non Uniformity Normalized
Run Percentage
Gray Level Variance
Run Variance
Run Entropy
Select histogram
4 000
3 750
3 500
3 250
3 000
2 750
2 500
2 250
2 000
1 750
1 500
1 250
1 000
750
500
250
0
5 000
7 500
10 000
12 500
15 000
17 500
20 000
22 500
25 000
VOI_1_3D T1 FSPGR IR INJ

Extraction



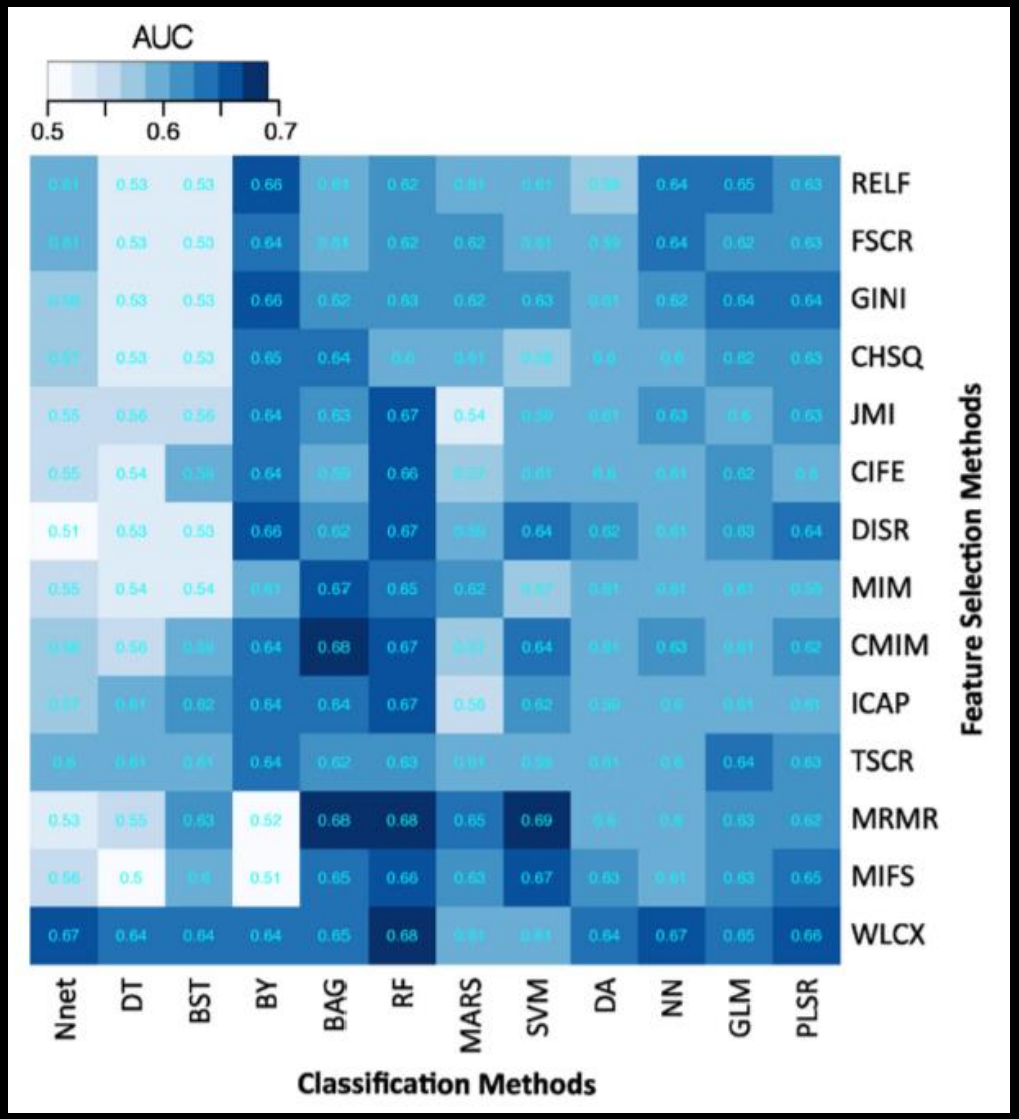
DataManagement

Feature Selection method acronym	Feature selection method name
RELF	Relief
FSCR	Fisher score
GINI	Gini index
CHSQ	Chi-square score
JMI	Joint mutual information
CIFE	Conditional infomax feature extraction
DISR	Double input symmetric relevance
MIM	Mutual information maximization
CMIM	Conditional mutual information maximization
ICAP	Interaction capping
TSCR	T-test score
MRMR	Minimum redundancy maximum relevance
MIFS	Mutual information feature selection
WLCX	Wilcoxon

Classification method acronym	Classification method name
Nnet	Neural network
DT	Decision Tree
BST	Boosting
BY	Bayesian
BAG	Bagging
RF	Random Forset
MARS	Multi adaptive regression splines
SVM	Support vector machines
DA	Discriminant analysis
NN	Neirest neighbour
GLM	Generalized linear models
PLSR	Partial least squares and prinicipal componenet regression

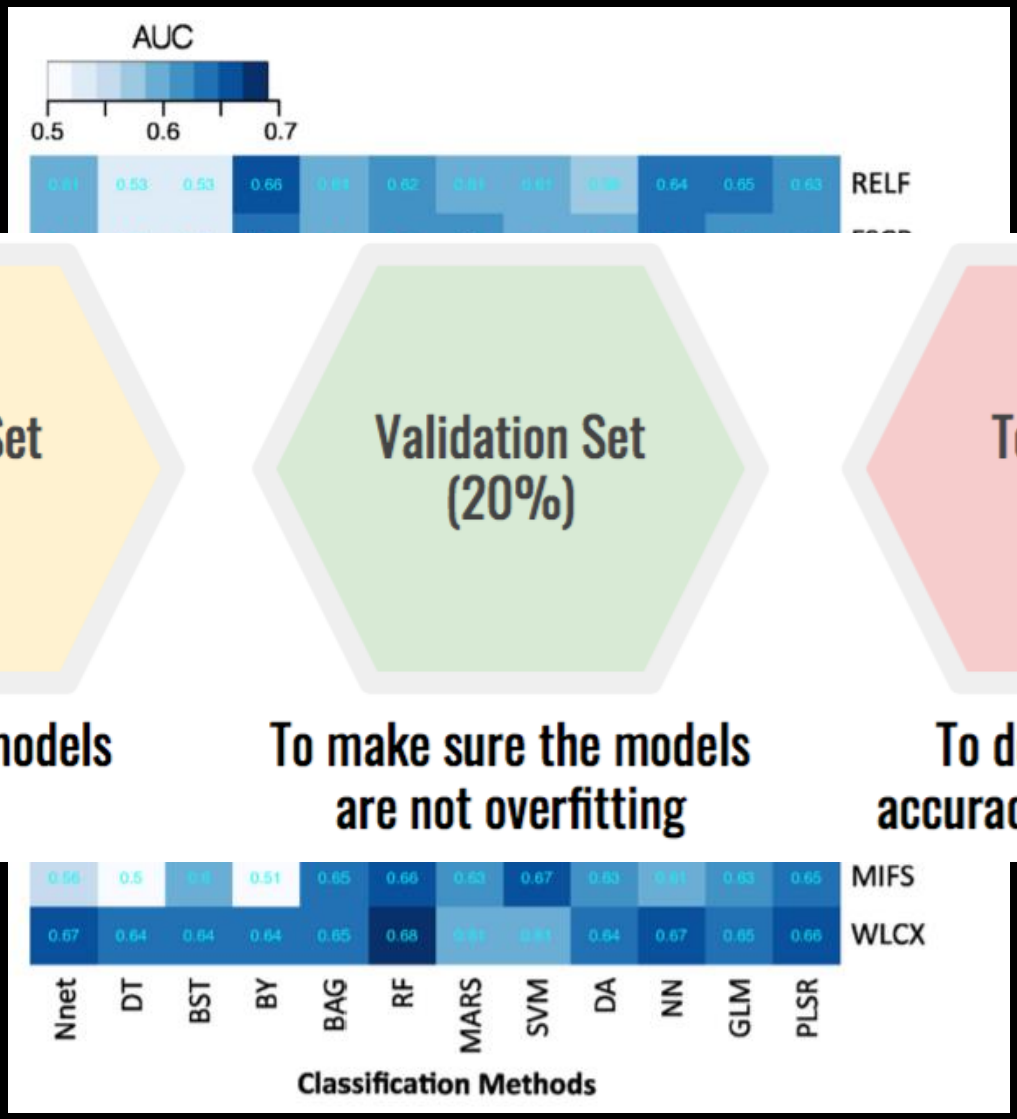
Parmar et al. *Nature* 2015

DataManagement



Parmar et al. *Nature* 2015

DataManagement



Training Set (60%)

To train the models

Validation Set (20%)

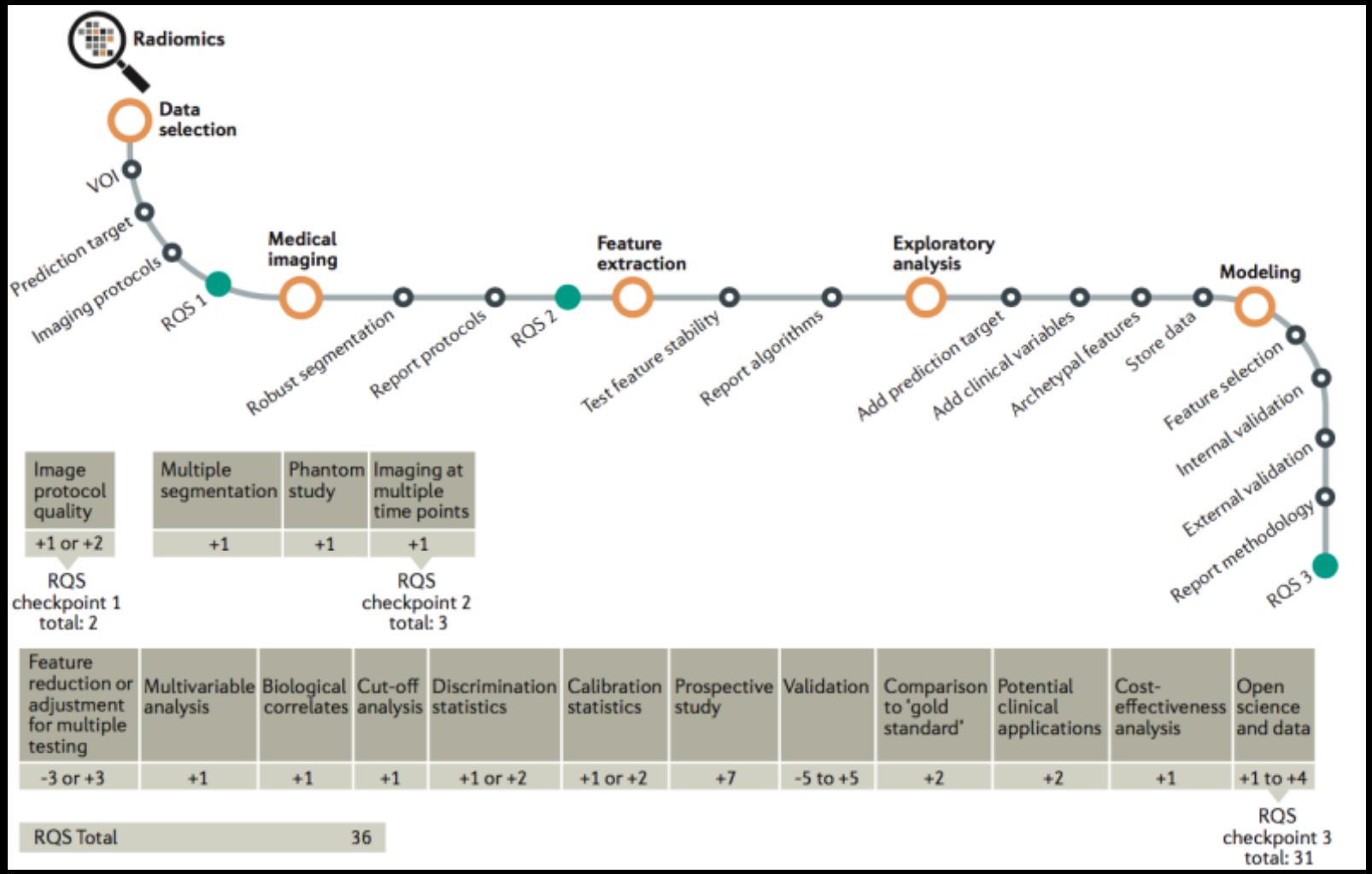
To make sure the models are not overfitting

Testing Set (20%)

To determine the accuracy of the models

Parmar et al. *Nature* 2015

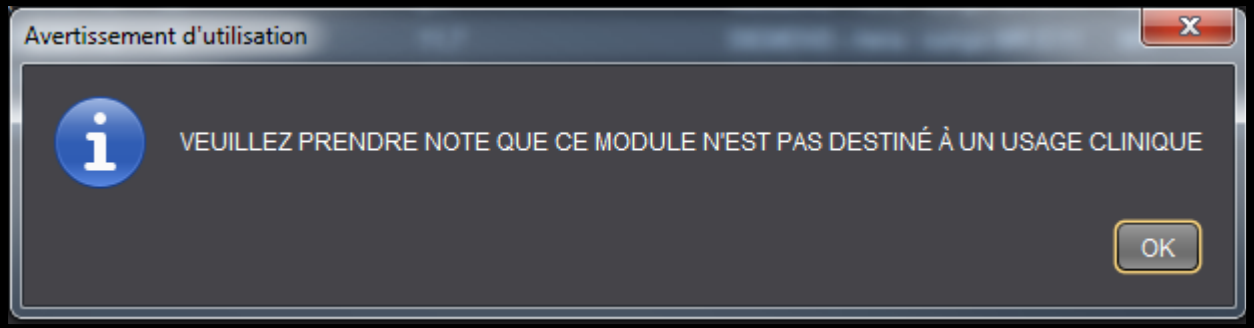
Limites ?



Lambin et al. 2017

Radiomics

HYPE or HOPE ?

Radiomics

HYPE or HOPE ?