Using AI to better understand and treat glioblastoma

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MULTIDISCIPLINARY APPROACHES IN HEALTH

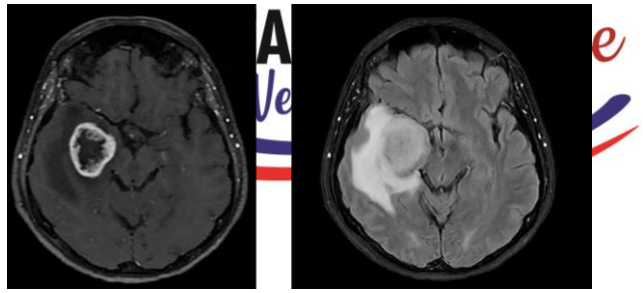
Conflicts of interest

- E Moyal :
  - Grants from Novocure; patent with Novocure; serves as member of advisory boards for Novocure
  - Member of scientific expert board for Servier
  - Research Grants from Astra-Zeneca, Incyte and Bayer.

- A Berjaoui :No COI

Glioblastoma : The north face of Oncology

Most frequent and agressive primary brain tumor

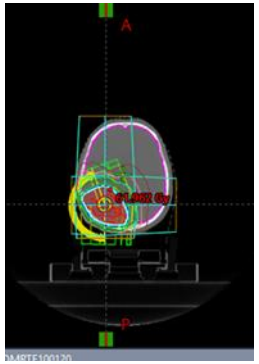


EF-14 trial (Stupp et al , 2017)

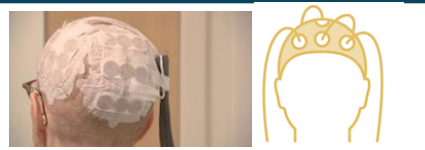
- PFS : from 4 m to 6,7 months
- OS : from 16 m to 20,9 months

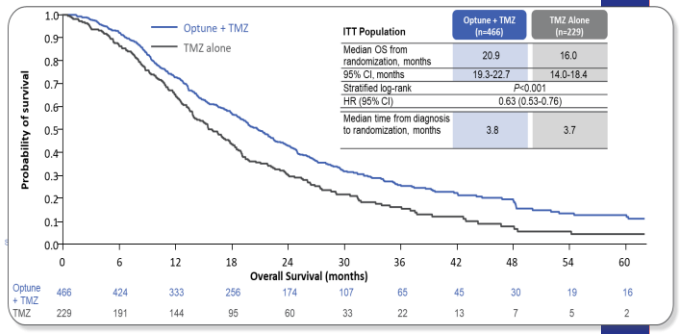


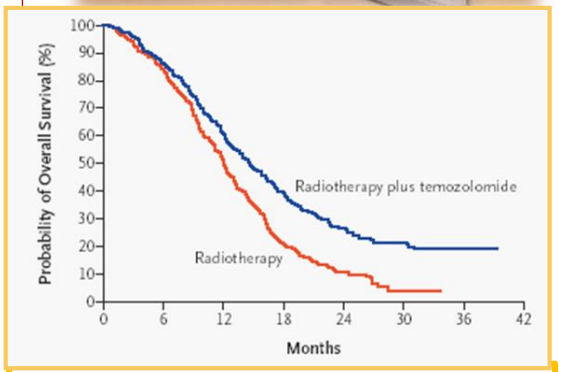
TMZ TMZ

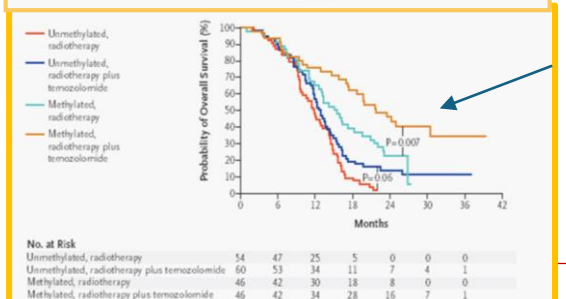


TMZ TMZ









(Stupp et al, 2005)

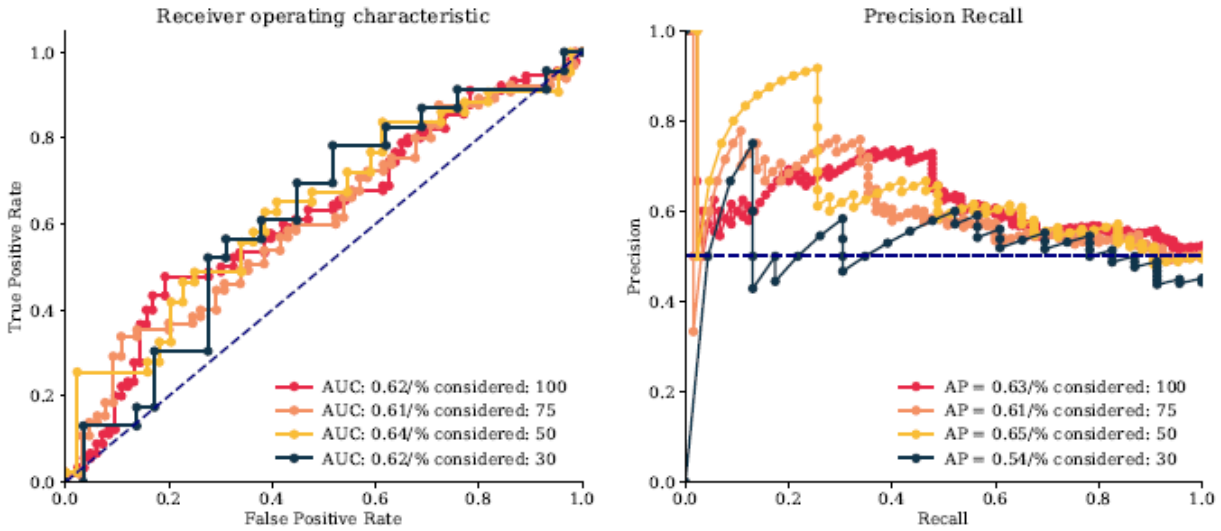
MGMT methylation : important pronostic factor but requires biopsies that are not necesseraly representative of the entire tumor and can vary at relapse

Methylated MGMT

Can AI applied to MRI determine precise MGMT methylation status ?

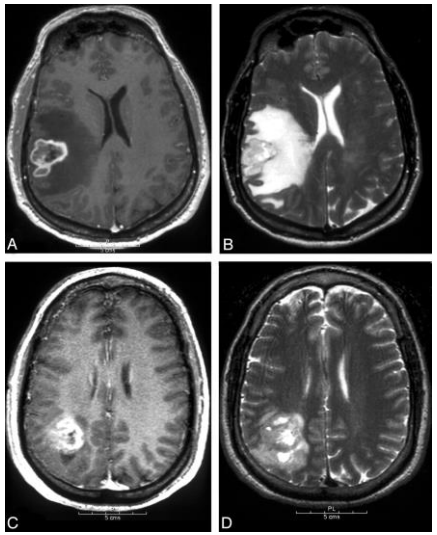
MGMT Methylation detection using MRI + AI ?

- Many published studies are in favor of using AI to determine MGMT methylation status…Many others are not !
- Using Deep learning classifiers (ResNet-50) trained on public datasets and data from IUCT-O, along with confidence metrics, we have determined that it is not currently possible with available MRI technology *(Robinet L…Berjaoui A, Moyal E. MRI-Based Deep Learning Tools for MGMT Promoter Methylation Detection: A Thorough Evaluation, Cancers, 2023)*

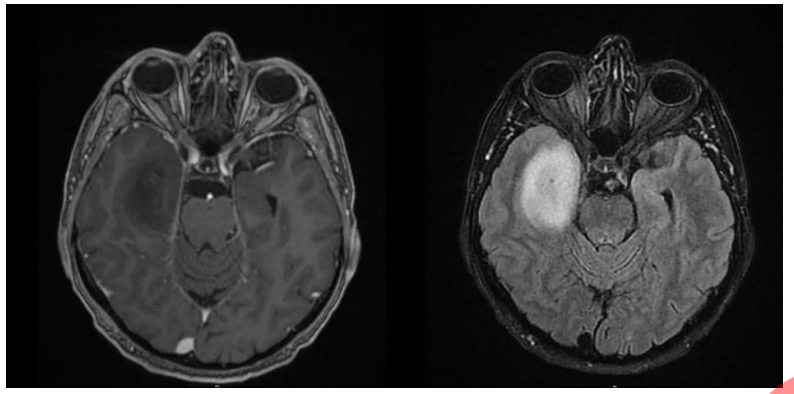


- The model was trained against various levels of methylation, assuming higher degrees where easier to spot than lower ones: **also not possible using mere imagery!**

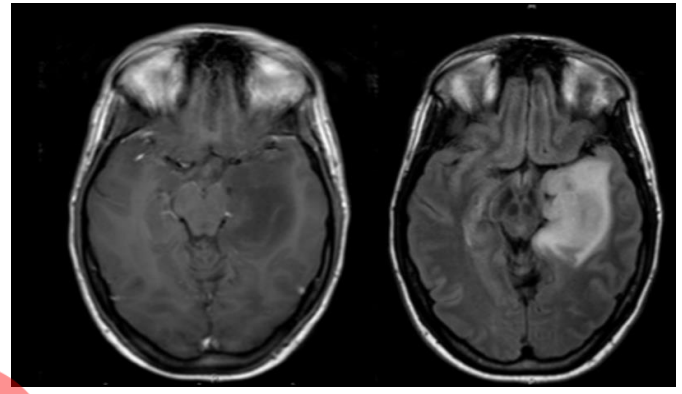
Glioblastoma : an heterogenous landscape



Typical glioblastoma
(necrosis+ endothelial proliferation)
Contrast enhancemement on T1Gado MRI)



Molecular glioblastoma
(7+/10-, EGFR amplification, TERT mutation)

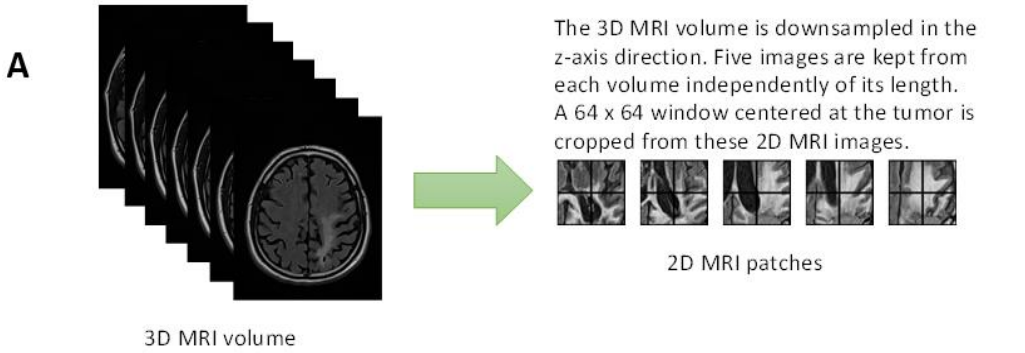


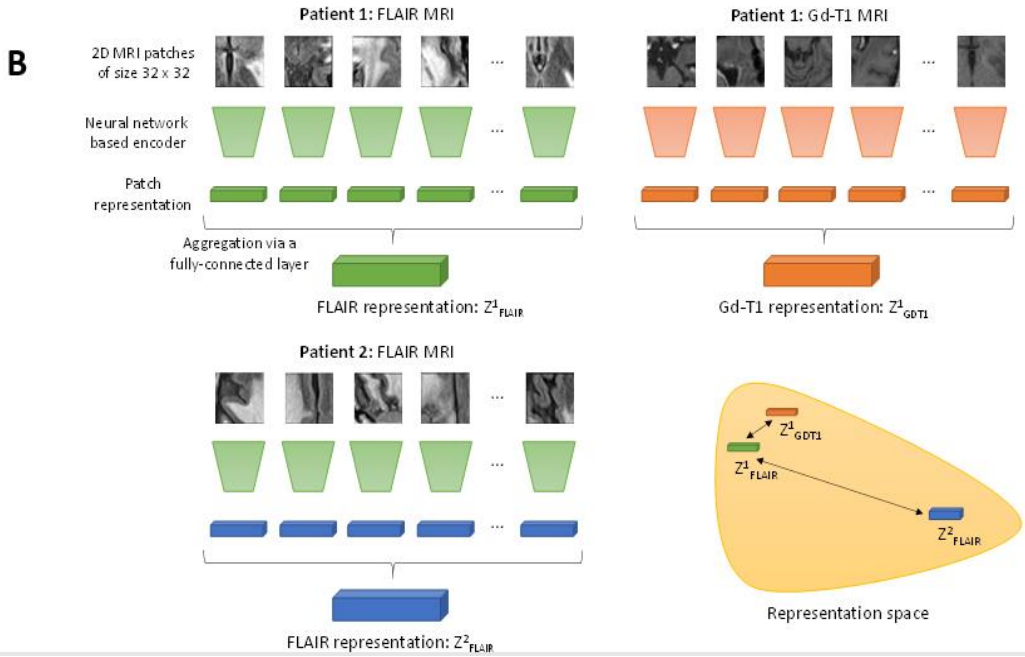
Low grade glioma

Look the same but totally different prognosis !

Can AI applied to MRI see something the professional naked eye cannot ?

GlioMol: Differential diagnosis of molecular glioblastoma using AI and MRI

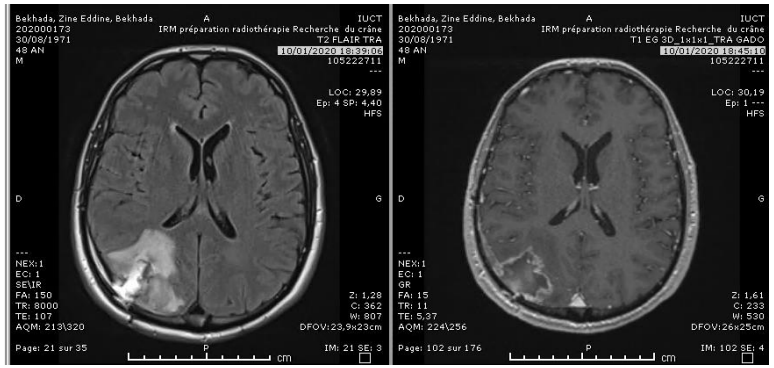




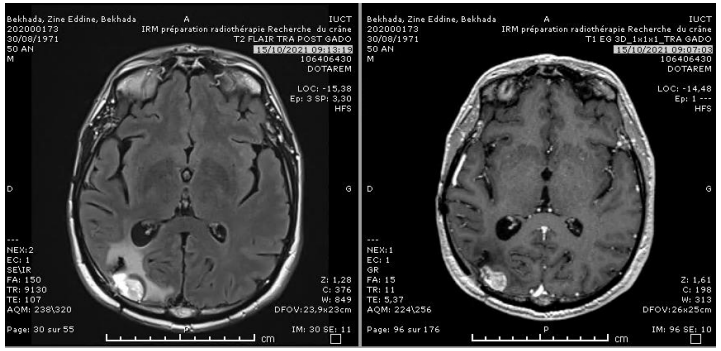
ResNet10-3D was pre-trained on public data using contrastive learning (a patient's MRI are matched with augmented versions and against other patients' MRI). A simple neural network classifier is then trained by supervised learning.

Current results show at least 70% accuracy: Zerbib C, Robinet L…Berjaoui A, Moyal E. Survival assessment and MRI features in patients with glioblastoma lacking necrosis or vascular proliferation (molecular glioblastoma), *Zerbib, Robinet et al. The Oncologist 2025*

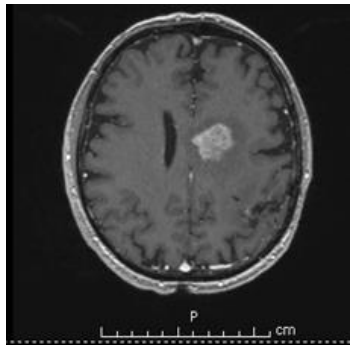
Systematic Recurrence because of tumor heterogeneity



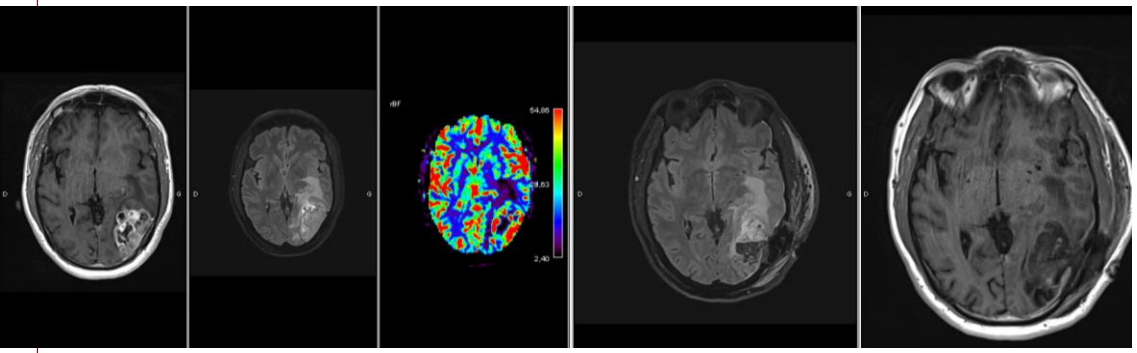
Primary tumor

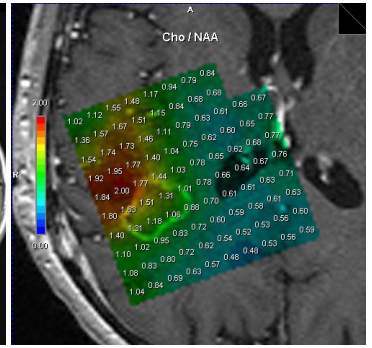


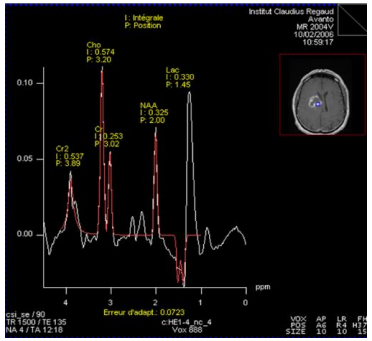
Local relapse

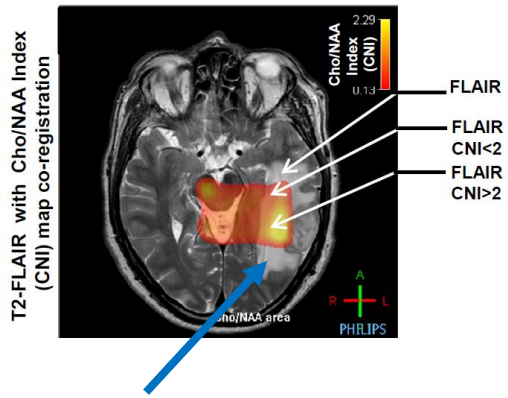


Distant relapse







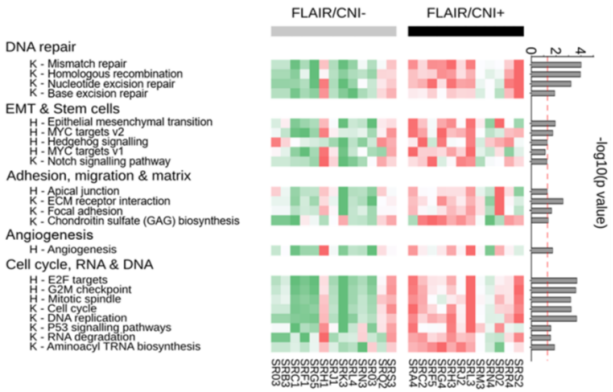


Predictive of the site of relapse

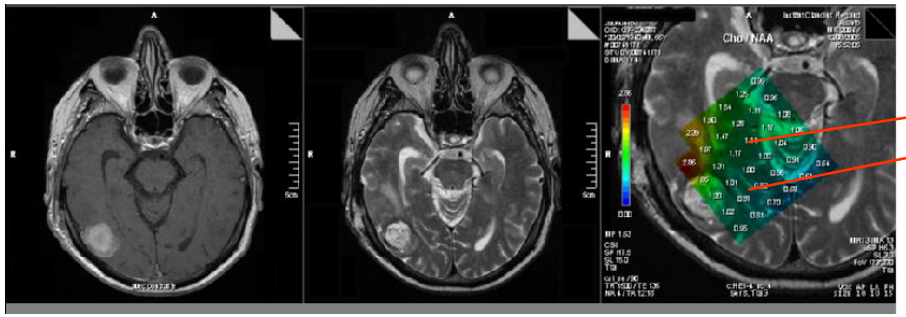
(Laprie …Cohen-Jonathan Moyal, Int J Radiat Biol Phys 2008)

Enriched in glioblastoma stem cells?

Determine the underlying molecular pathways that drive aggressivity and relapse pattern (**STEMRI trial**)

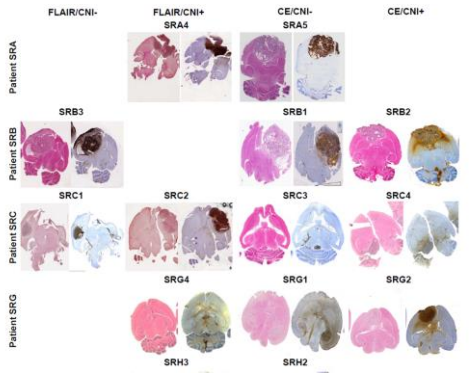


- Is the metabolic zone on MRI spectroscopy enriched in GBM stem cells expressing aggressive gene pathways ? YES
- 16 patients; biopsies and resection guided by multimodal MRI and MRI spectroscopy *(Lemarié A …Moyal E , Science Advances 2023)*



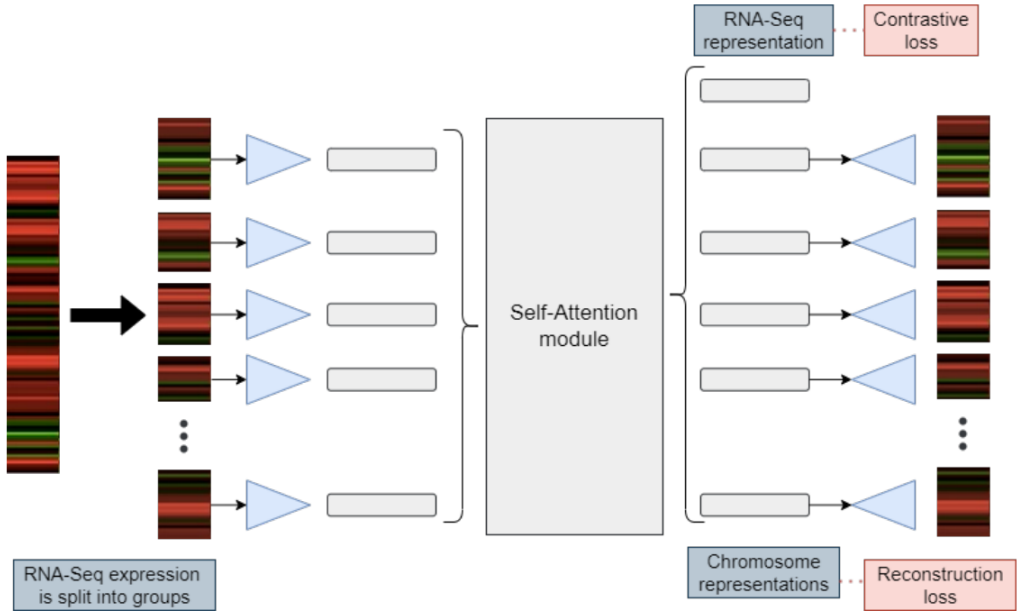
Available data

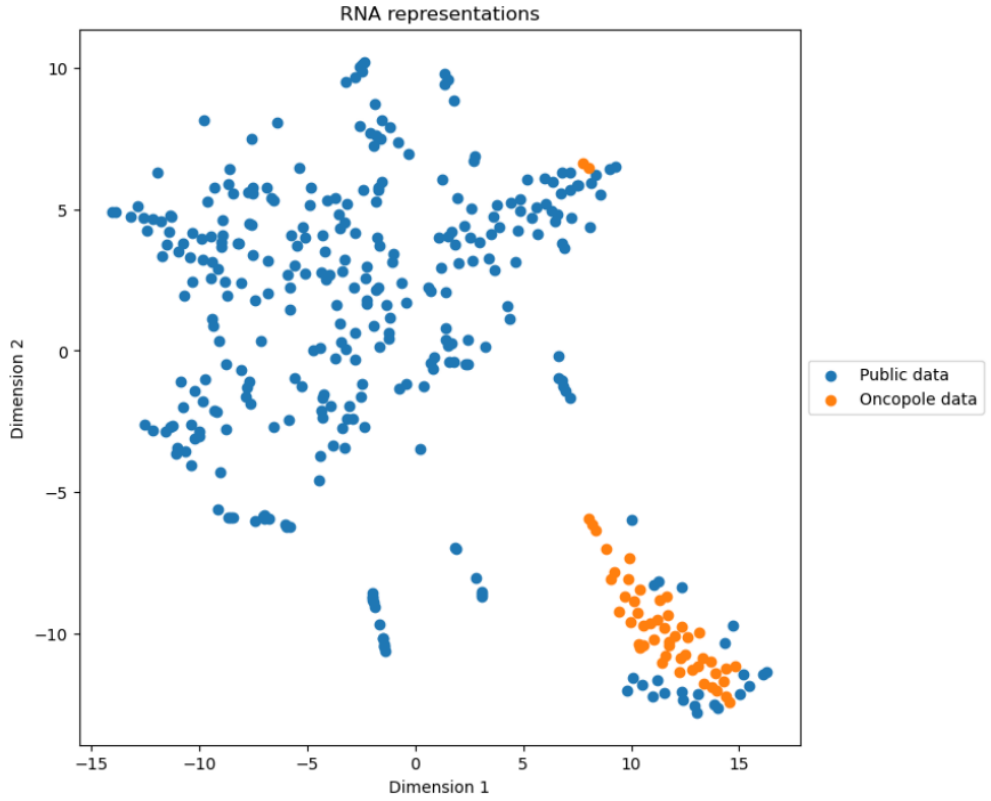
- RNA Seq genes expressions on biopsies
- RNAseq genes expression in all the GBMSC
- Orthotopic implantation in mice brain of all the GBMSC
- Mice survival
- Patients survival and MRI relapse pattern



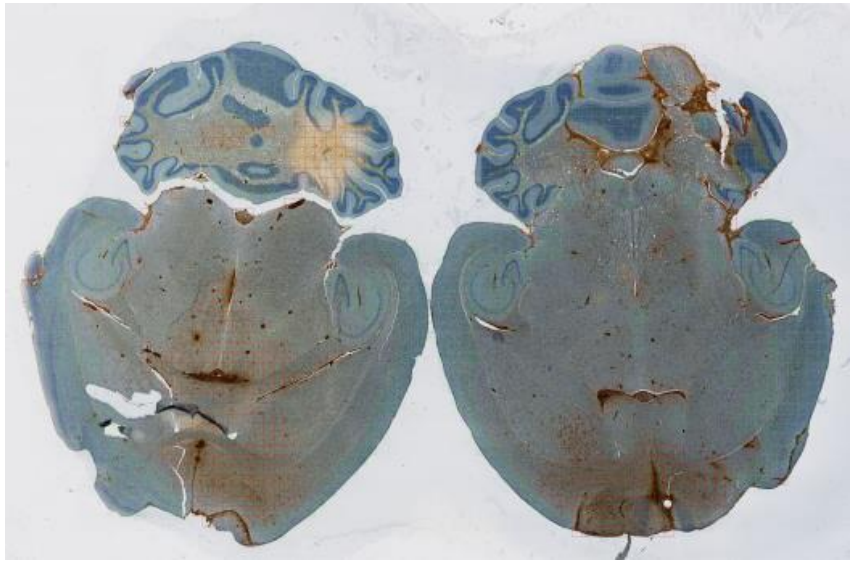
Biological pathways/genes driving Individual tumor agressiveness or relapse pattern?

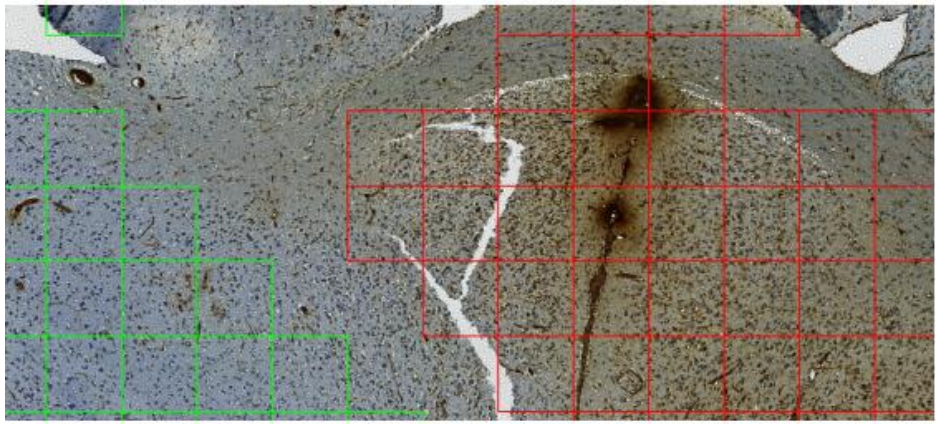
Encoding RNAseq data

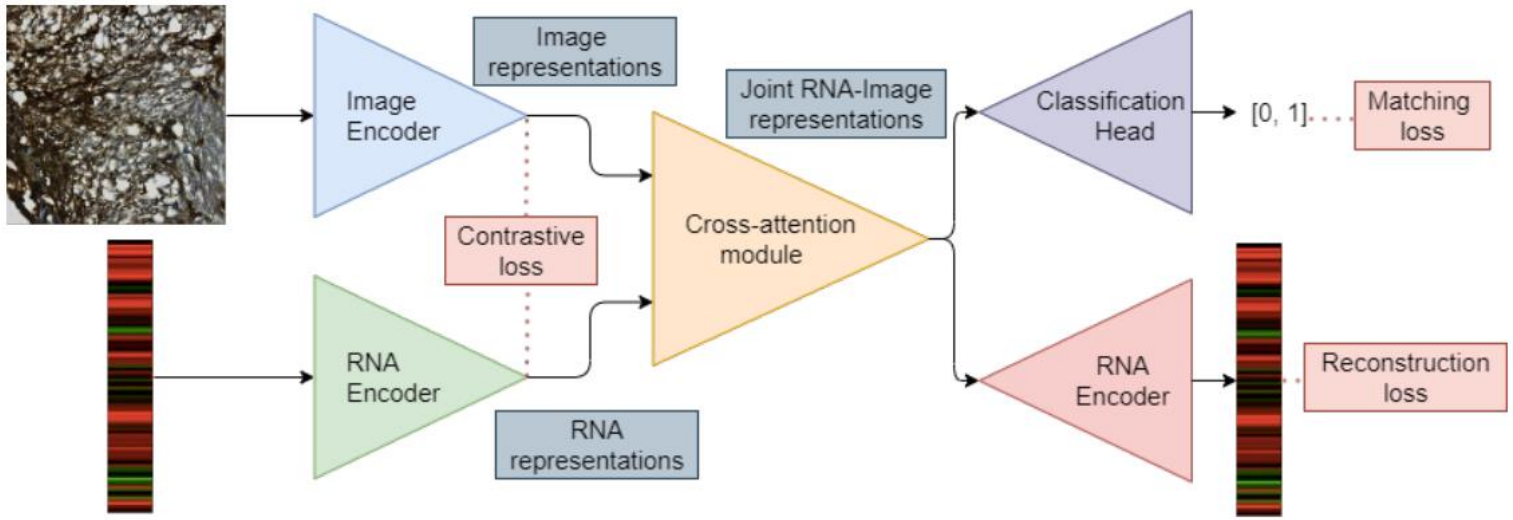




Multimodal alignment







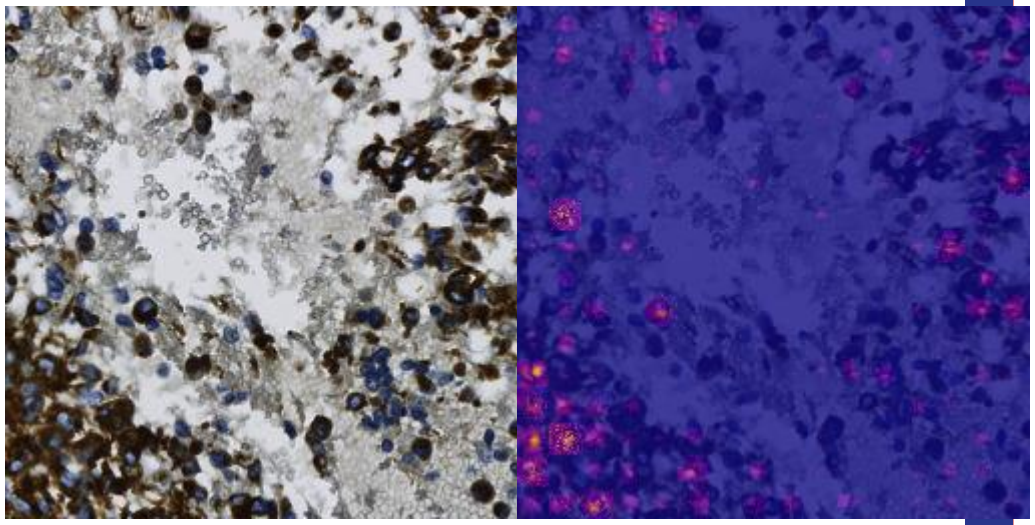
- Encoded RNAseq data and microscopic image patches are aligned using cross-attention
- Merged modalities are trained against available mice and clinical data (survival, GBMSC lineage etc.)
- GradCAM was used to determine key pathways associated with each obervation

Model	Accuracy (patient)	Accuracy (lineage)
Random initialization	0.050	0.006
$\mathcal{L}^{r}_{MM} + \mathcal{L}^{c}_{MM} + \mathcal{L}^{m}_{MM}$ (frozen RNA-Image encoders)	0.29	0.199
$\mathcal{L}^{r}_{MM} + \mathcal{L}^{c}_{MM} + \mathcal{L}^{m}_{MM}$ (all modules are trainable)	0.946	0.941
$\mathcal{L}^{c}_{MM} + \mathcal{L}^{m}_{MM}$ (all modules are trainable/chromosome gene groups)	0.890	0.913
$\mathcal{L}^{c}_{MM} + \mathcal{L}^{m}_{MM}$ (all modules are trainable/pathways gene groups)	**0.970**	**0.968**

Key genes identified so far…

- These genes have been determined as the most relevant for matching clinical, mice survival and RNAseq data

- Patient relapse pattern on MRI still needs to be matched with this data

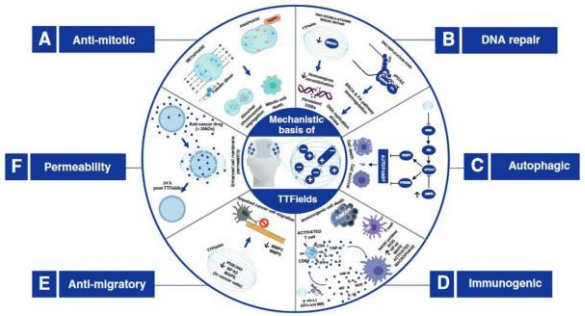


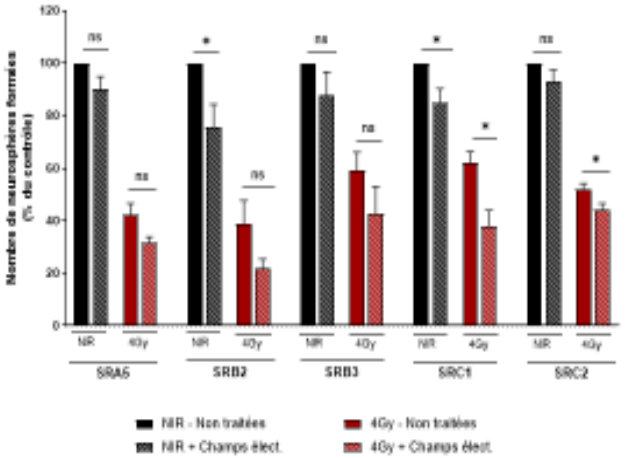
	Gene	Occurrence	Symbol
0	ENSG00000198964.14	2344	SGMS1
1	ENSG00000120008.16	2151	WDR11
2	ENSG00000111670.16	1759	GNPTAB
3	ENSG00000078098.14	1669	FAP
4	ENSG00000143147.14	1639	GPR161
5	ENSG00000070061.16	1463	ELP1
6	ENSG00000139624.14	1350	CERS5
7	ENSG00000077254.14	1347	USP33
8	ENSG00000138614.15	1249	INTS14
9	ENSG00000090054.15	1202	SPTLC1
10	ENSG00000183036.11	1187	PCP4
11	ENSG00000130717.13	1177	UCK1
12	ENSG00000184164.15	1157	CRELD2
13	ENSG00000125633.11	1138	CCDC93
14	ENSG00000128829.12	1112	EIF2AK4

Berjaoui A., … , Moyal E. : *Uncovering the Genetic Basis of Glioblastoma Heterogeneity through Multimodal Analysis of Whole Slide Images and RNA Sequencing Data, accepted in Artificial Intelligence in Medicine*

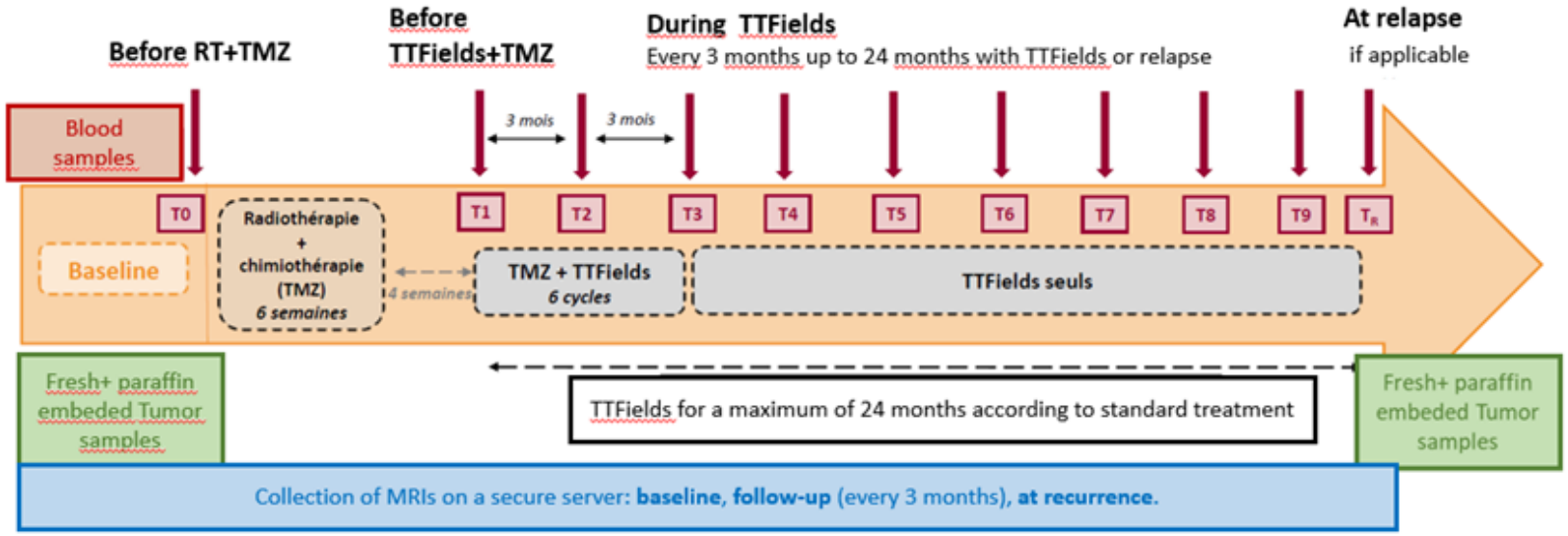
Determing key success and resistance factors of clinical response to TTFields







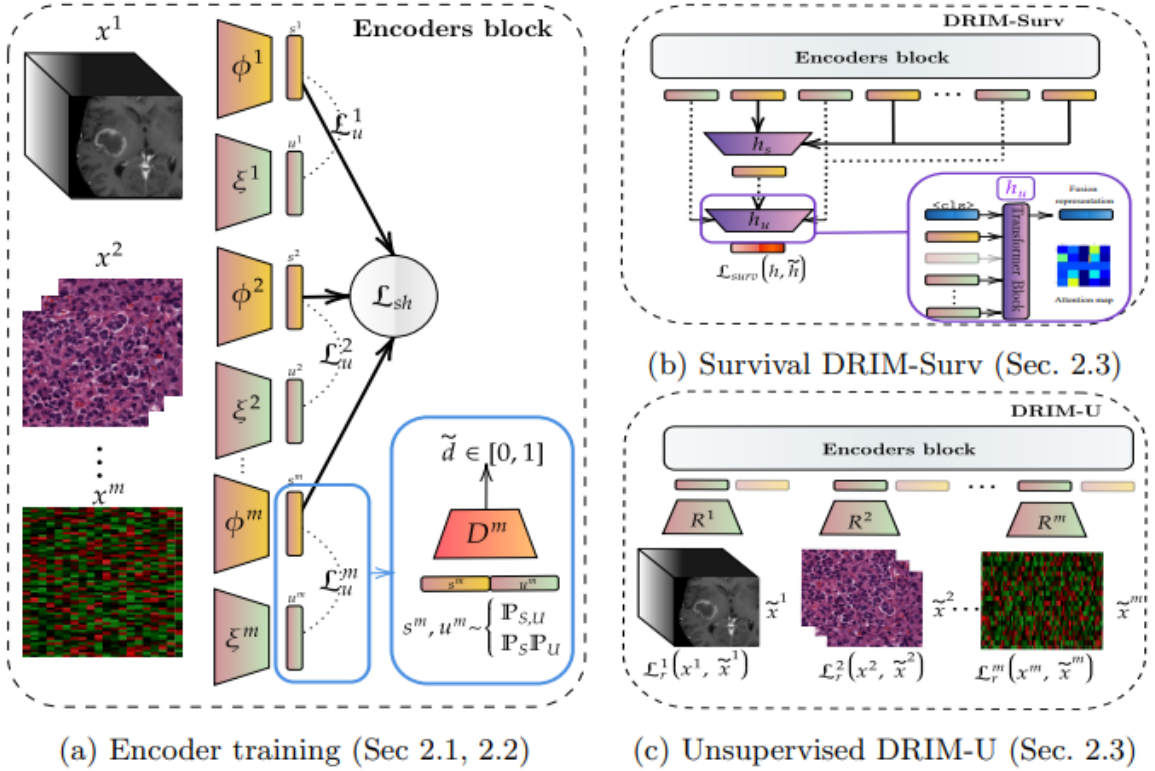
Common Radioresistance a
TTFields resistance mechanisms
(Patent with Novocure)
(Deshors et al, Cell Death Discovery 2025)



Exofields Trial

Multimodal AI algorithms for prediction of sensitivity /resistance to TTFields

Handling Incomplete Multimodal Healthcare Data



(a) Encoder training (Sec 2.1, 2.2)

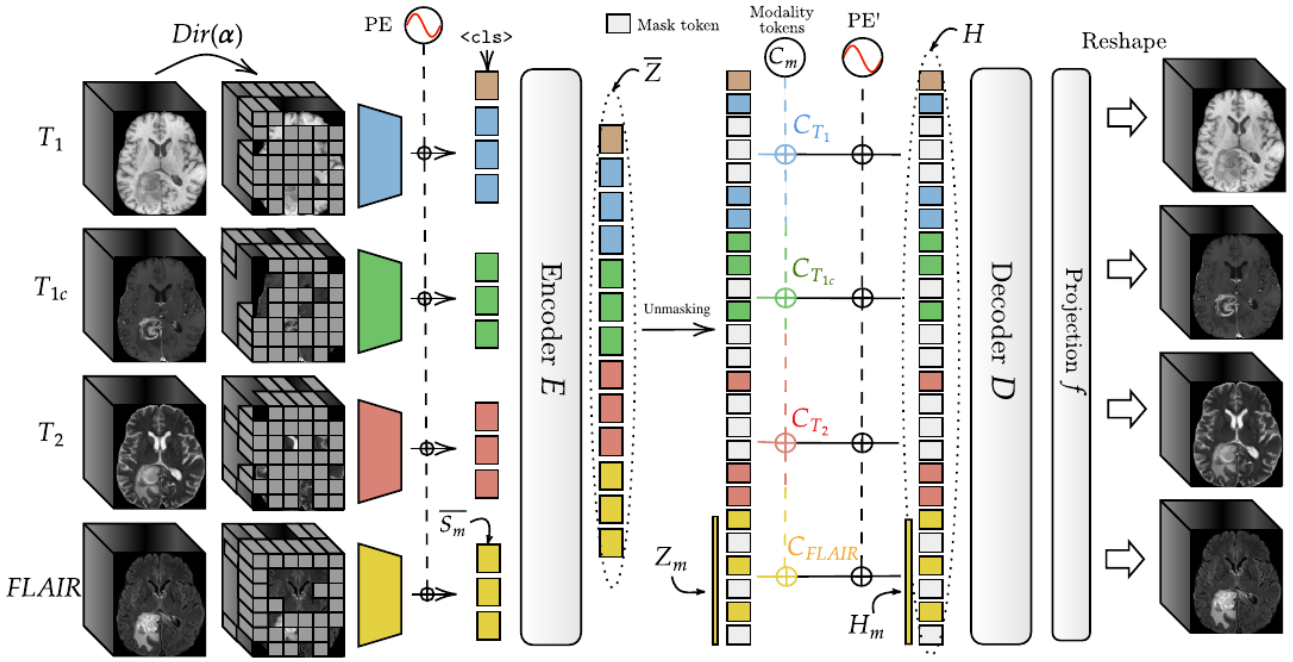
(b) Survival DRIM-Surv (Sec. 2.3)

(c) Unsupervised DRIM-U (Sec. 2.3)

- Everyday patient data are often incomplete
- Using multimodal distentanglement to obtain information shared betwen patients and modality specific features, it is possible to handle missing modalities (e.g. missing RNA-seq or T1 MRI)
- Survival prediction remains highly accurate despite missing modalities, ranging from 80% to 90% accuracy (exceeding other existing techniques)

Robinet L., Berjaoui A., Kheil Z., Moyal E. : DRIM: Learning Disentangled Representations from Incomplete Multimodal Healthcare Data, MICCAI 2024

Towards multipurpose foundation models



Foundation model

- Large model
- Long and costly to train
- Self-supervised training (lots of data, e.g. more than 1M samples)

OS prediction

PFS prediction

Segmentation

...

Small specialized models

- Specific tasks
- Very fast and cheap to train
- Supervised training (reduced data points, e.g. less than 1K samples)

Thanks to our patients and their families

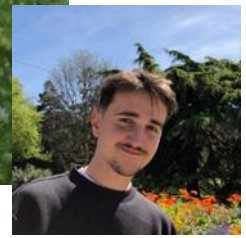












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Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

Fondation ARC pour la recherche sur le cancer

LA LIGUE CONTRE LE CANCER

ARTC Association pour la Recherche sur les Tumeurs Cérébrales

INSTITUT NATIONAL DU CANCER

novocure

MoGlimaging

PLAN CANCER 2014-2019

Incyte

AstraZeneca

Oncopole CLAUDIUS REGAUD

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

BAYER

AIRBUS

IRT SAINT EXUPÉRY

Clinical trial Unit

M Mounier
M Poublanc
T Filleron

Thank you for your attention