



Institut du thorax  
Curie - Montsouris

PSL  
RESEARCH UNIVERSITY PARIS

Epione  
e-patient / e-medicine

informatics mathematics  
Inria

# Radiomique : pièges et promesses

## applications au cancer pulmonaire

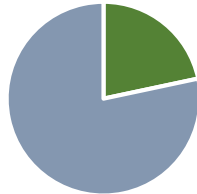
Dr Alain Livartowski, PH  
Direction des Data  
Institut Curie

Fanny Orlhac, PhD  
Equipe-projet Epione  
Inria Sophia Antipolis

# Le cancer du poumon, un enjeu de santé publique

## L'un des cancers les plus fréquents

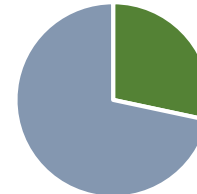
50 000 nouveaux cas par an



Un diagnostic  
toutes les  
10 minutes  
en France

## Le cancer le plus mortel

30 000 décès par an

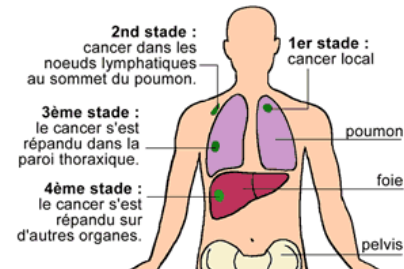


Un décès  
toutes les  
15 minutes  
en France

## Le tabagisme comme principal facteur de risque

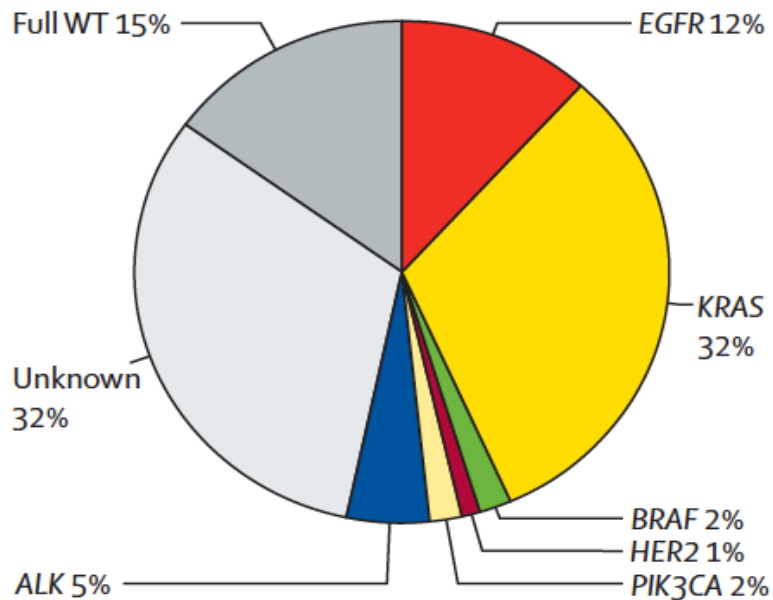


## Un diagnostic souvent tardif

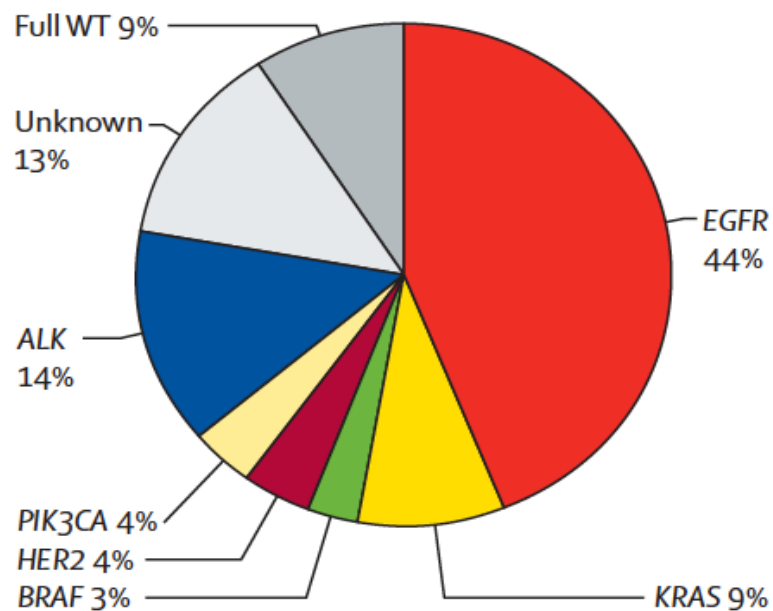


## Le cancer du poumon : de multiples maladies orphelines

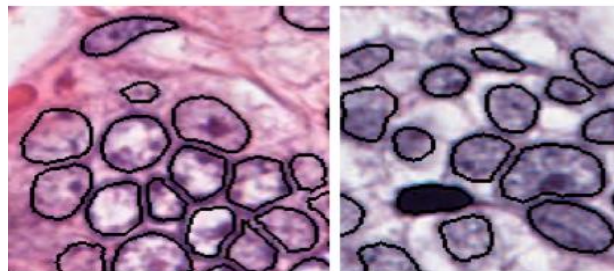
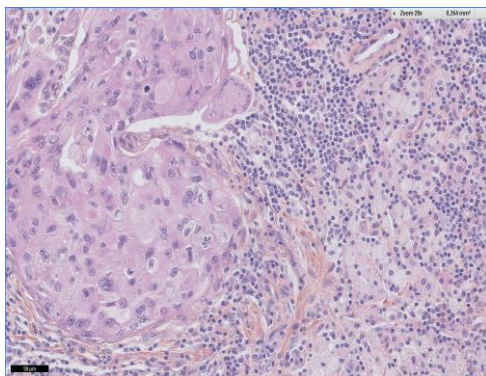
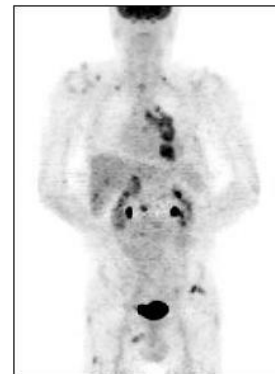
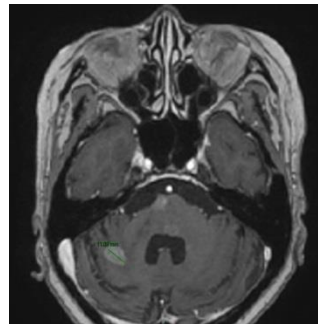
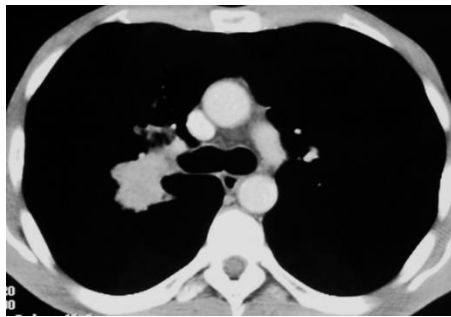
**B Adenocarcinoma**



**D Never smokers**



## L'importance des images dans la prise en charge du cancer

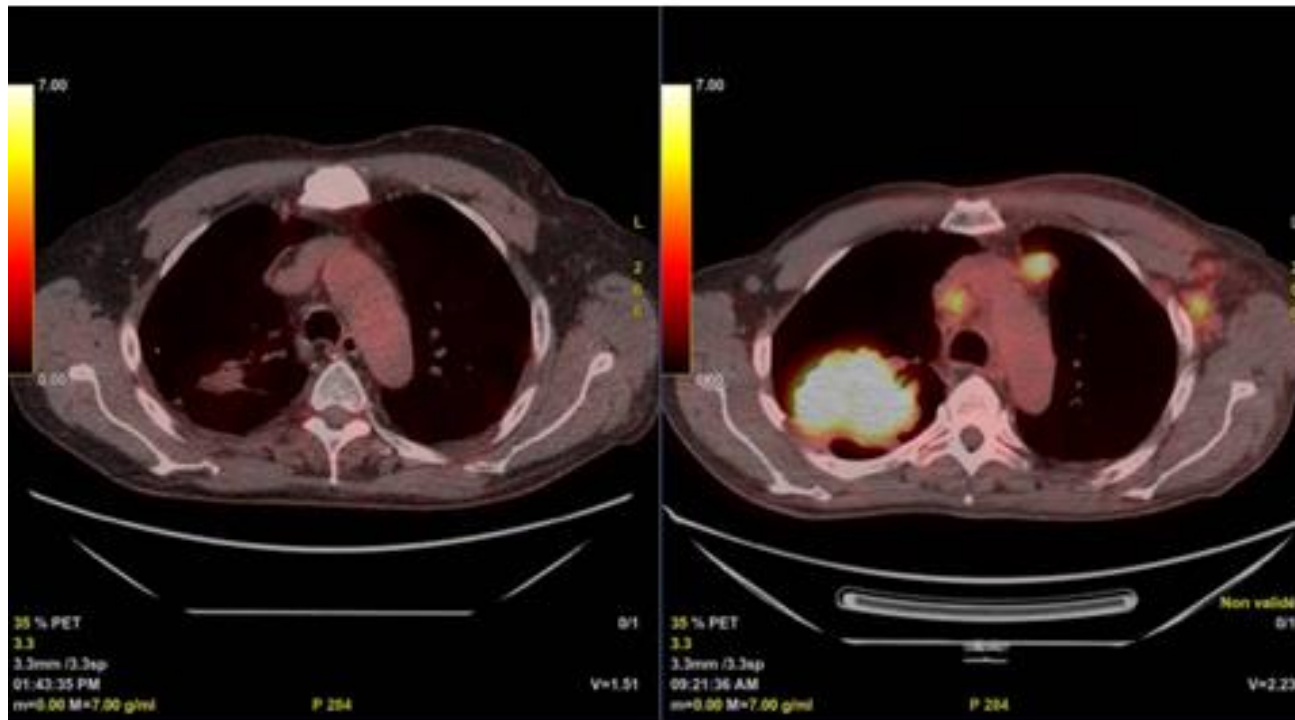


## L'imagerie en médecine

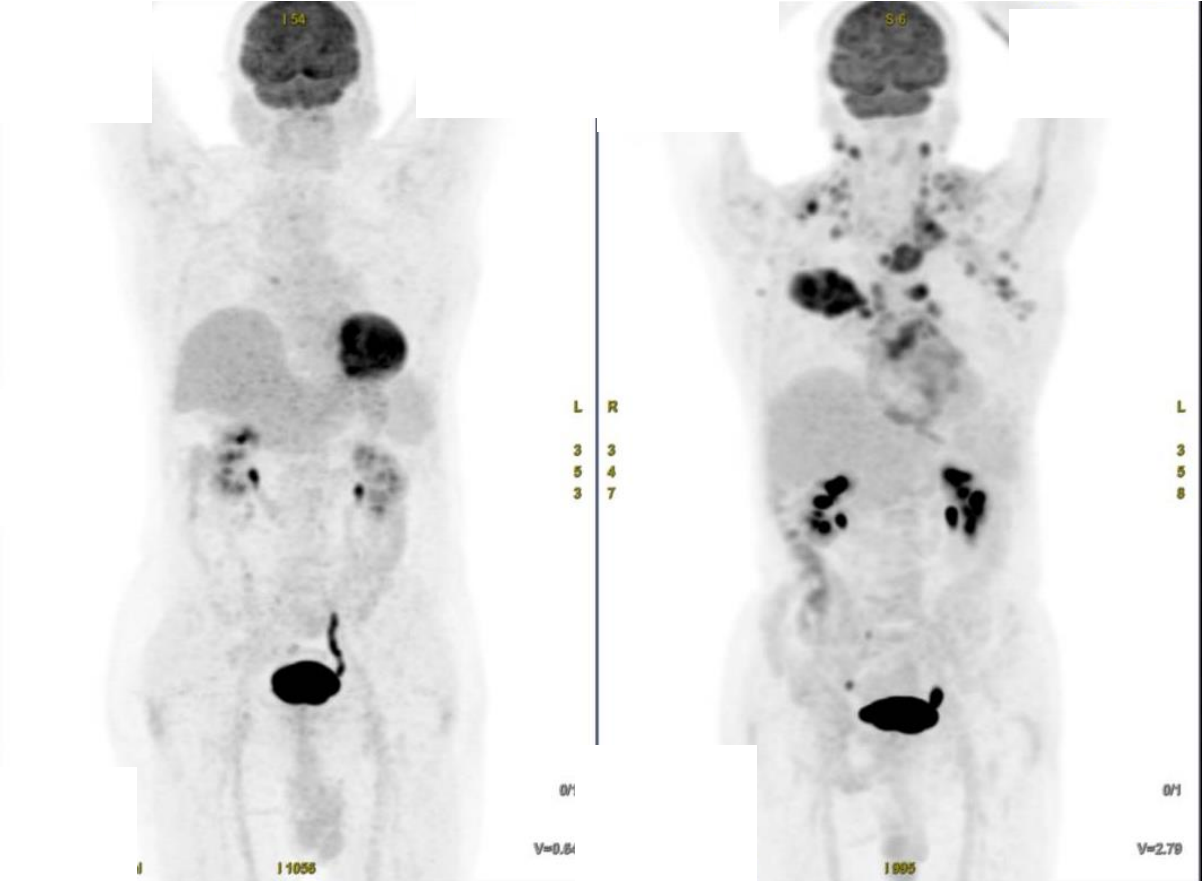




## La révolution de l'immunothérapie (1)



# La révolution de l'immunothérapie (1)

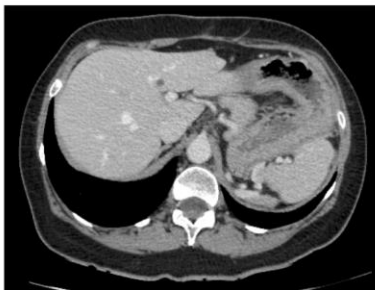




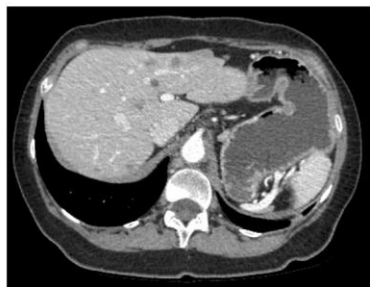
# L'hyperprogression sous immunothérapie

1A

CT evaluations



Before  
(-8 weeks)

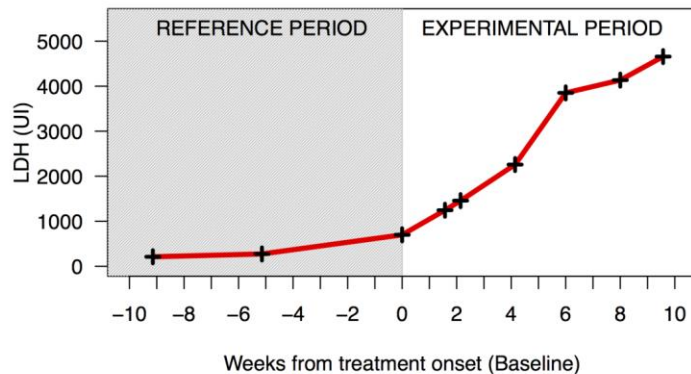


Baseline

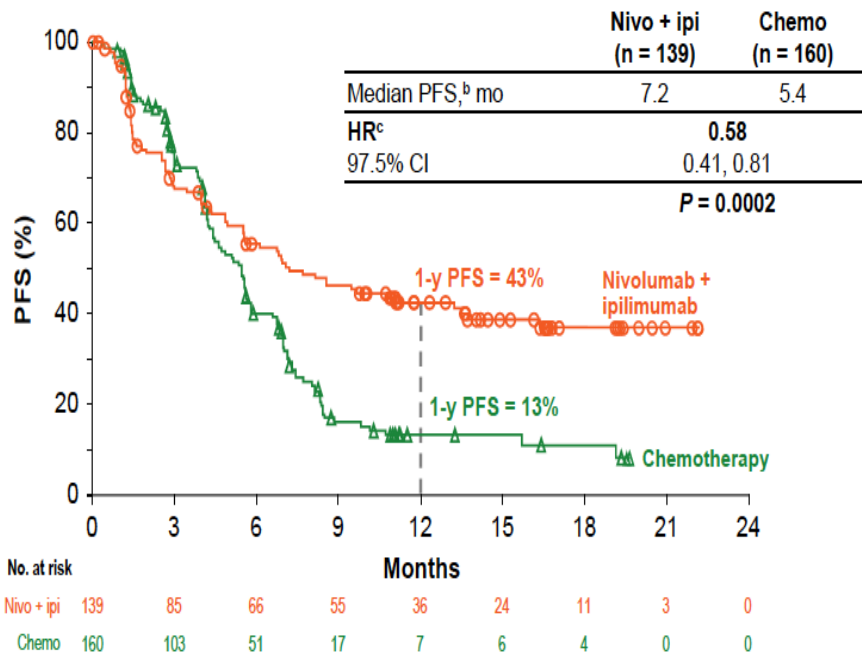


1<sup>st</sup> Evaluation  
(+8 weeks)

1B



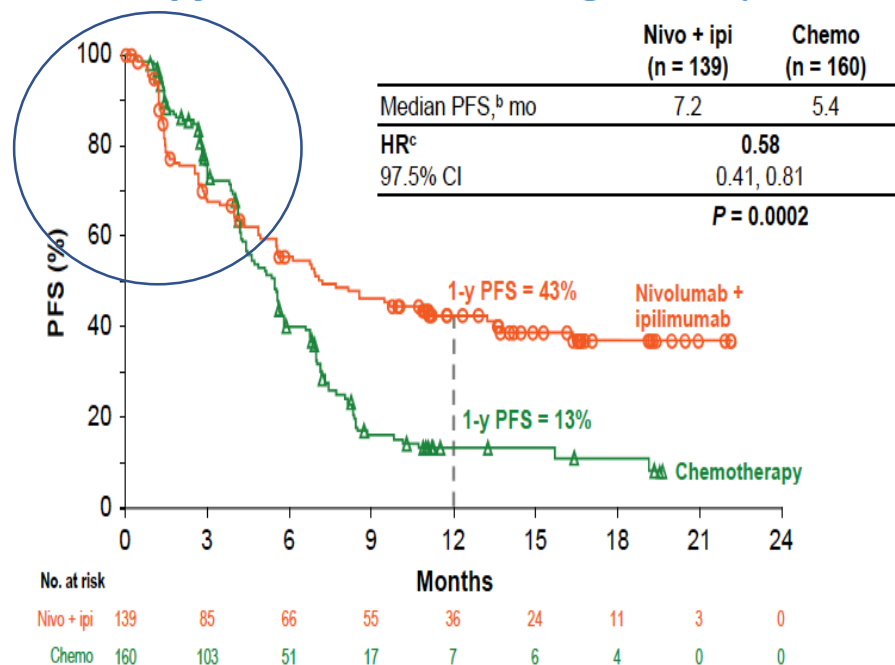
## Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB ( $\geq 10$ mut/Mb)<sup>a</sup>



- In patients with TMB  $< 10$  mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)<sup>d</sup>

<sup>a</sup>Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo; <sup>b</sup>95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo); <sup>c</sup>95% CI: 0.43, 0.77 mo; <sup>d</sup>The P-value for the treatment interaction was 0.0018

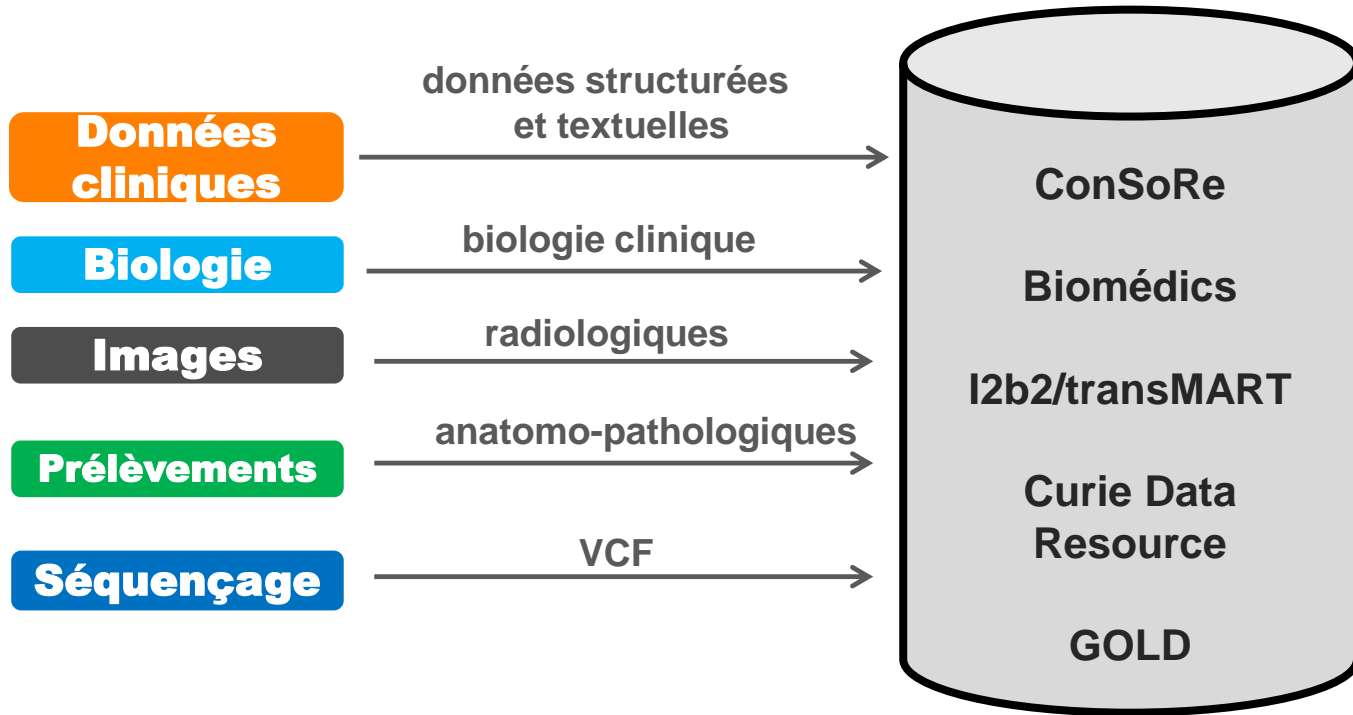
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# Des soins à la recherche : les entrepôts de données



# Les problèmes liés aux données

## Les données cliniques

- Données textuelles, données structurées
- Hétérogénéité des données (interopérabilité technique et sémantique)
- Qualité des données
- Modélisation de la maladie
- Données de grands volumes, longitudinales et récentes

## Les images

- Modalités différentes
- Annotation des images par les autres données
- Etc.


## Les autres problèmes

- Informatique, juridique, éthique, économique, soin/recherche, etc.




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- Définition des questions cliniques
- Données annotées
- Validation en clinique



IMIV  
Imagerie Moléculaire In Vivo

- Analyse radiomique (LIFEx)
- Harmonisation multi-centrique



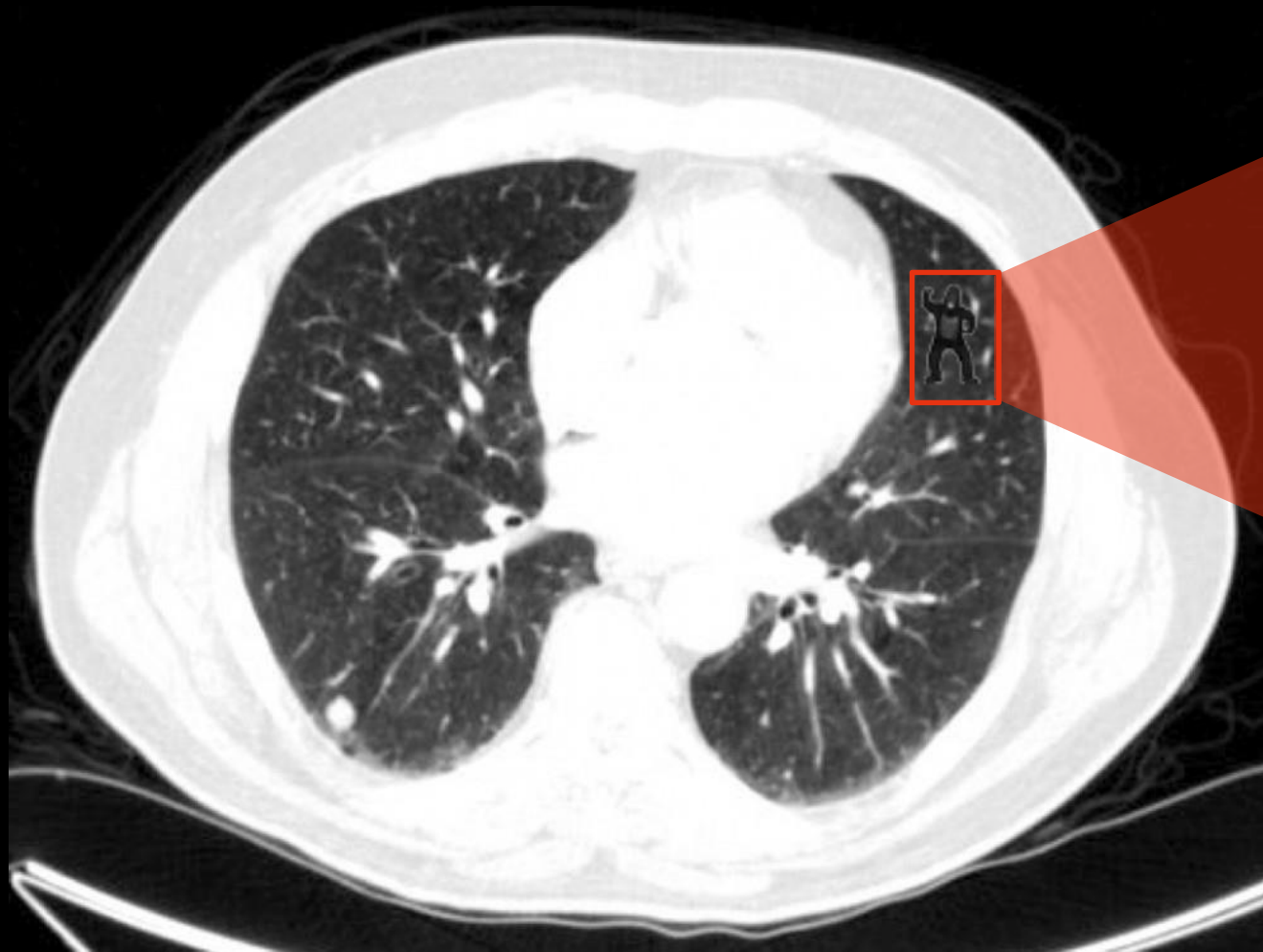
Epione  
e-patient / e-medicine

- Apprentissage profond
- Analyse statistique en grande dimension



**Question clinique** : prédire la réponse au traitement à partir de l'imagerie TEP au diagnostic



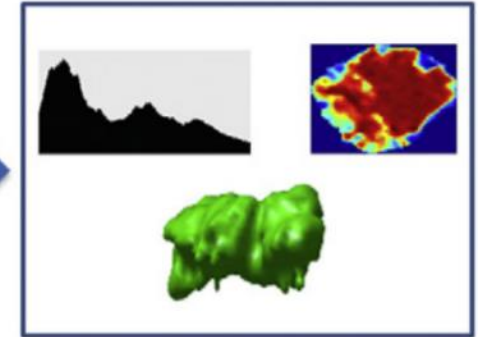
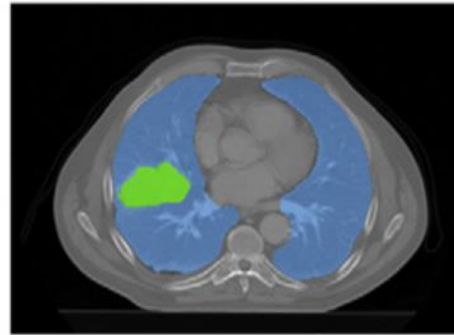




**Constat** : les images médicales sous-exploitées par l'évaluation visuelle

## Radiomique (*radiomics*)

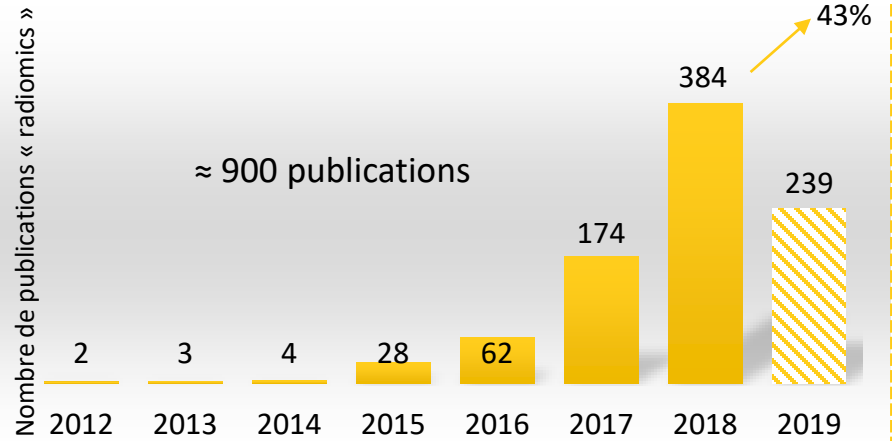
Extraction automatique d'index  
issus des images médicales



[Eur J Cancer](#). 2012 Mar;48(4):441-6. doi: 10.1016/j.ejca.2011.11.036. Epub 2012 Jan 16.

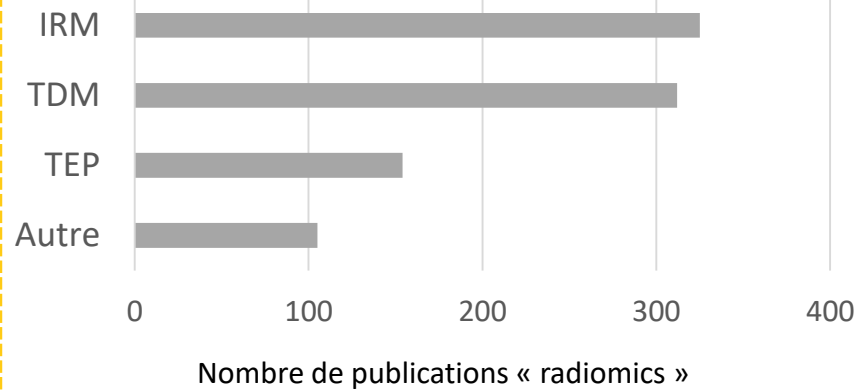
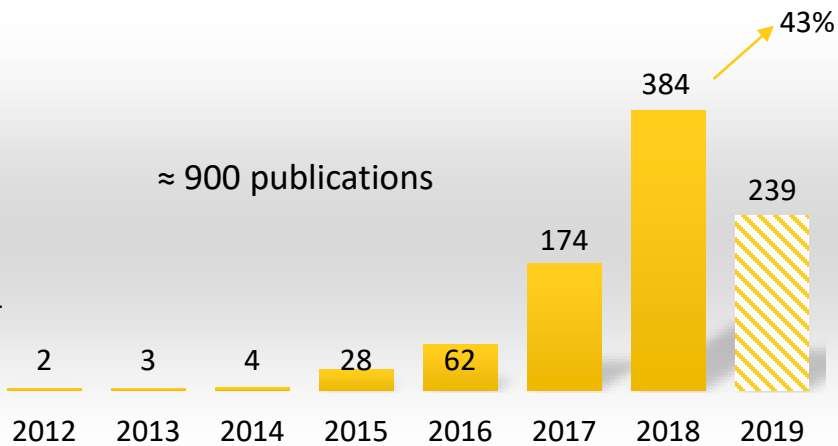
**Radiomics: extracting more information from medical images using advanced feature analysis.**

Lambin P<sup>1</sup>, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, Zegers CM, Gillies R, Boellard R, Dekker A, Aerts HJ.

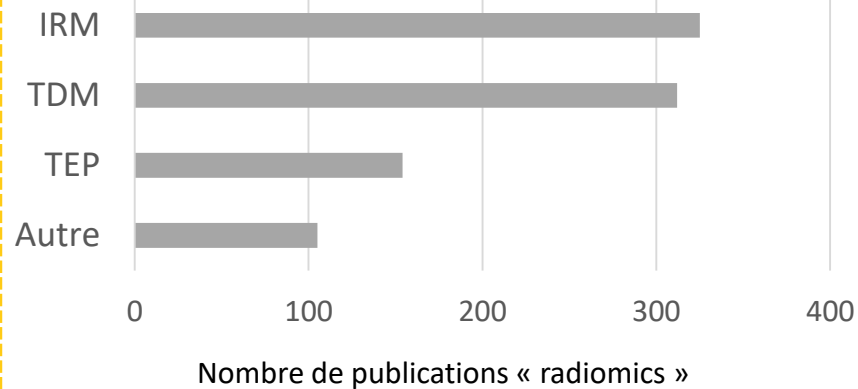
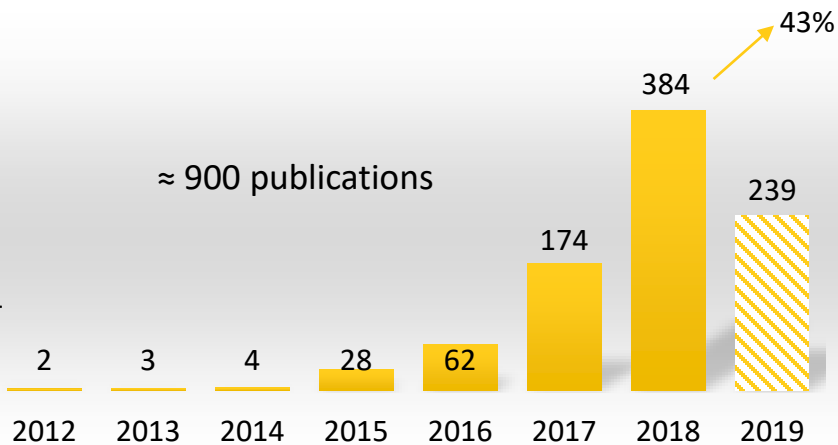


## Radiomique : statistiques

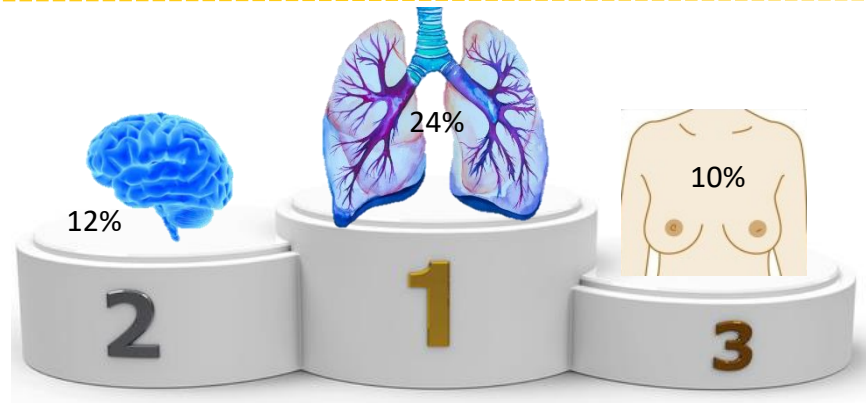
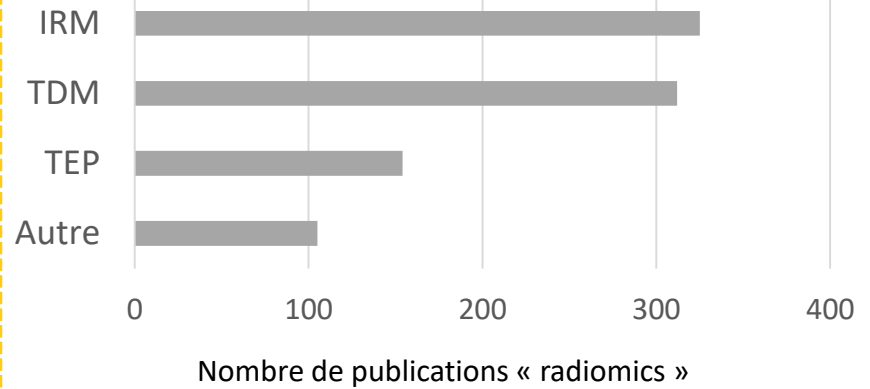
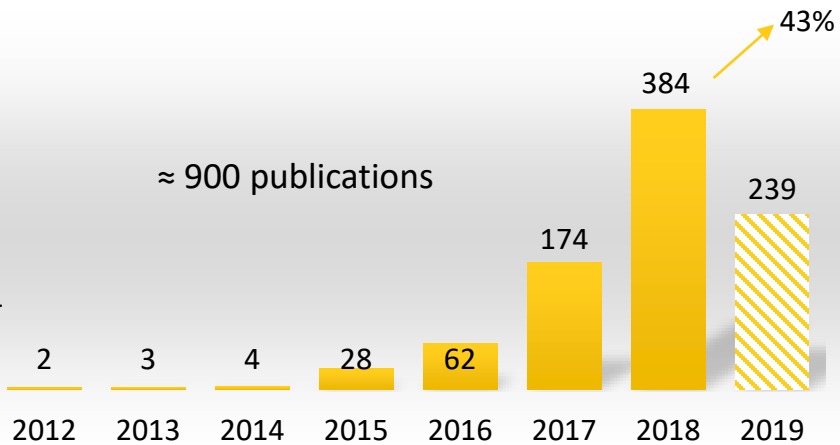
Nombre de publications « radiomics »

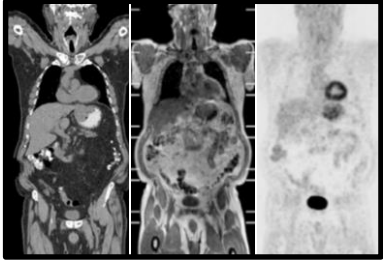


Nombre de publications « radiomics »



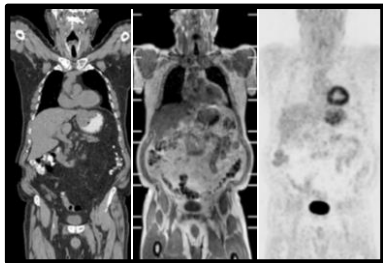
Nombre de publications « radiomics »



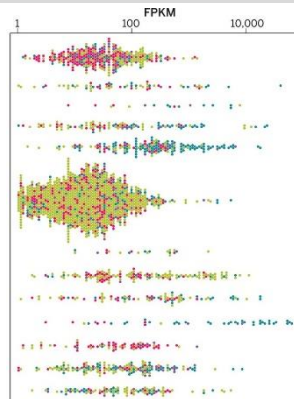


$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \dots \\ x_n \end{bmatrix}$$

**Radiome**



$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \dots \\ x_n \end{bmatrix}$$

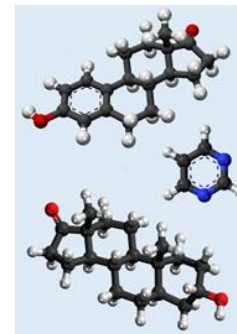
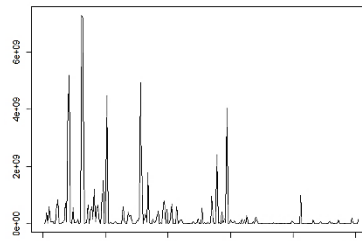
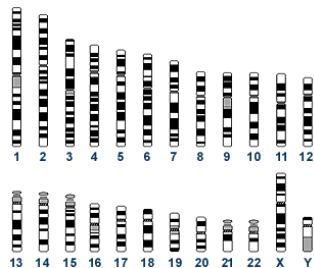
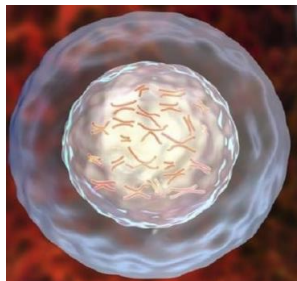


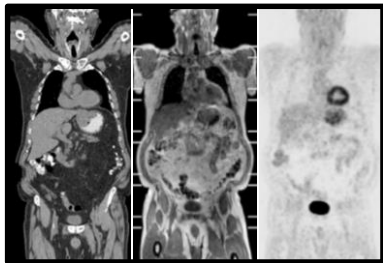
Radiome

Protéome

Génome

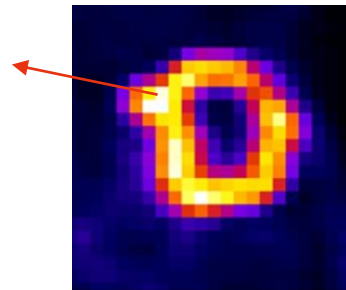
Métabolome





$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \dots \\ x_n \end{bmatrix}$$

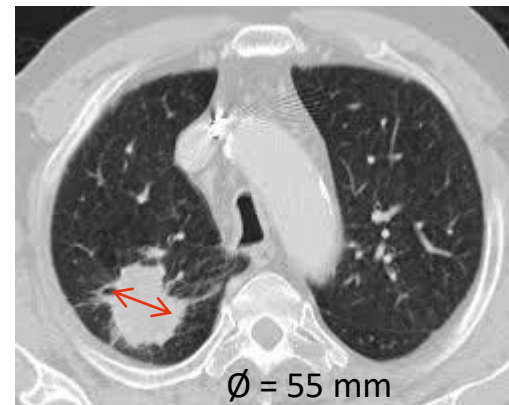
SUVmax = 22,9



Radiome en soin courant :

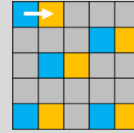
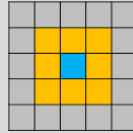
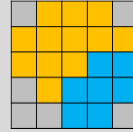
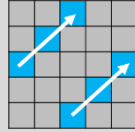
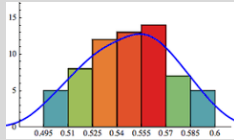
- SUVmax en TEP
- Plus grand diamètre en TDM
- ...

[O'Connor et al. *Nat Rev Clin Oncol* 2017]

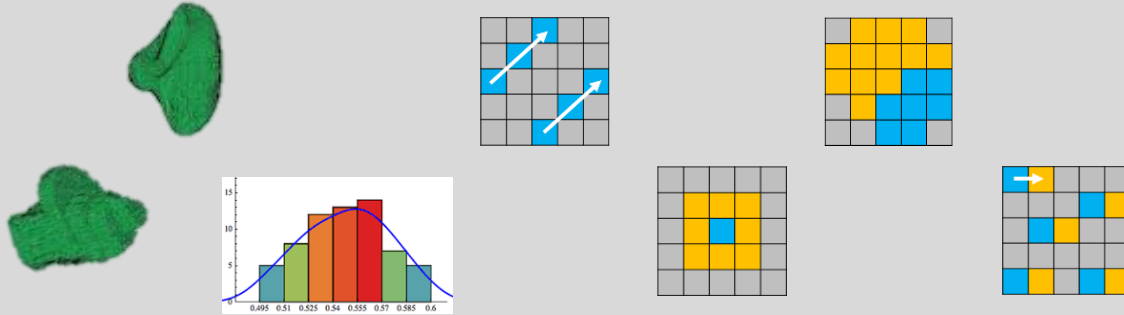




**Attributs construits manuellement** (*Hand-crafted features*)



### Attributs construits manuellement (*Hand-crafted features*)

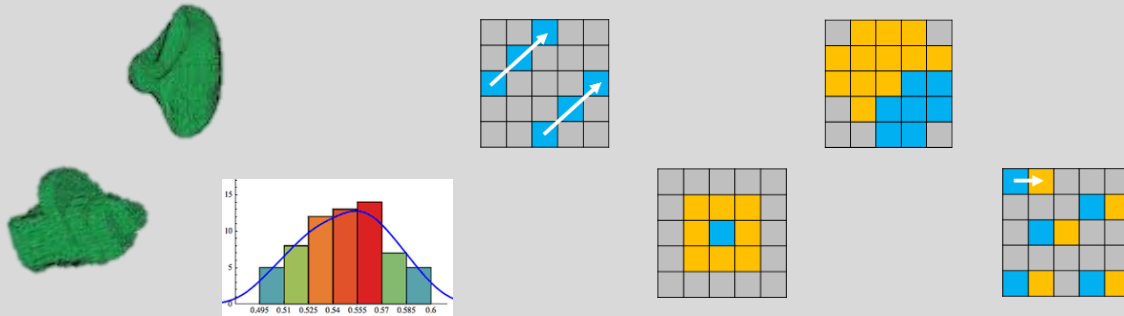


Compréhension du calcul



Segmentation requise

### Attributs construits manuellement (*Hand-crafted features*)

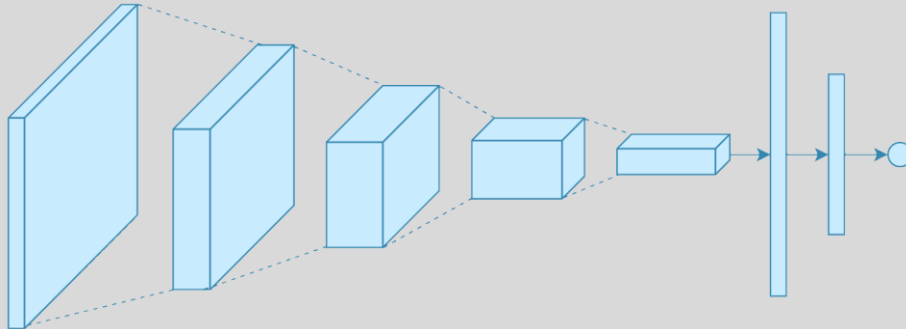


Compréhension du calcul

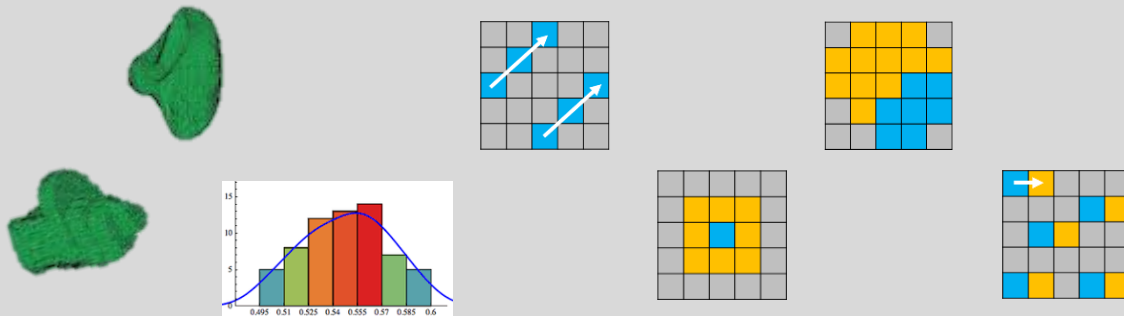


Segmentation requise

### Attributs profonds (*Deep features*)



### Attributs construits manuellement (*Hand-crafted features*)

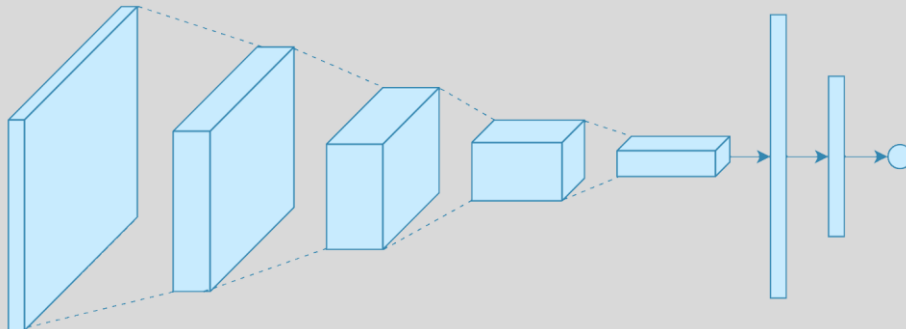


Compréhension du calcul



Segmentation requise

### Attributs profonds (*Deep features*)



Sans segmentation  
Nombre illimité  
d'index



Explicabilité ?

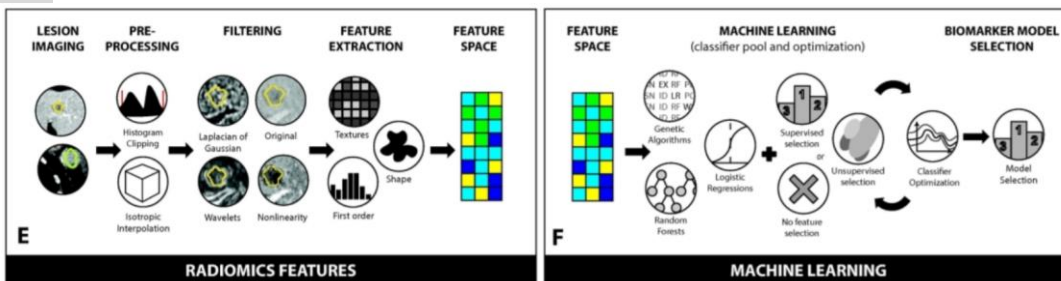


Ann Oncol. 2019 Mar 21. pii: mdz108. doi: 10.1093/annonc/mdz108. [Epub ahead of print]

## Predicting Response to Cancer Immunotherapy using Non-invasive Radiomic Biomarkers.

Trebeschi S<sup>1,2,3</sup>, Drago SG<sup>1,4</sup>, Birkbak NJ<sup>5</sup>, Kurilova I<sup>1,2</sup>, Călin AM<sup>1,6</sup>, Pizzi AD<sup>1,7</sup>, Lalezari F<sup>1</sup>, Lambregts DMJ<sup>1</sup>, Roahaan M<sup>8</sup>, Parmar C<sup>3</sup>, Hartemink KJ<sup>9</sup>, Swanton C<sup>5</sup>, Haanen JBAG<sup>8</sup>, Blank CU<sup>8</sup>, Smit EF<sup>10</sup>, Beets-Tan RGH<sup>1,2</sup>, Aerts HJWL<sup>1,3</sup>.

- 123 patients CPNPC\* avec 572 lésions (réponse positive au traitement : 27%)
- Images TDM
- 5 865 index radiomiques



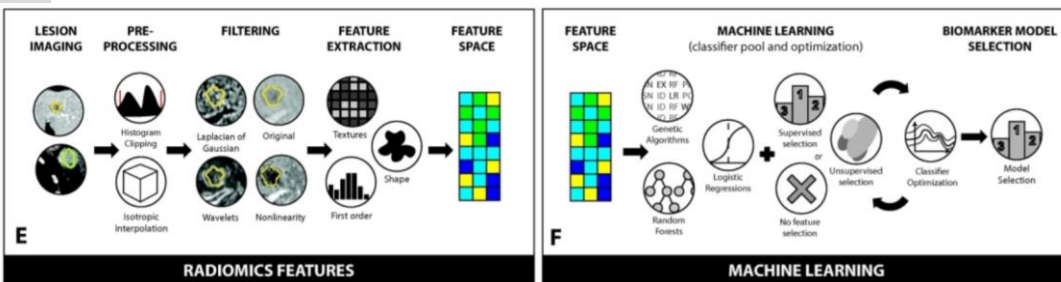
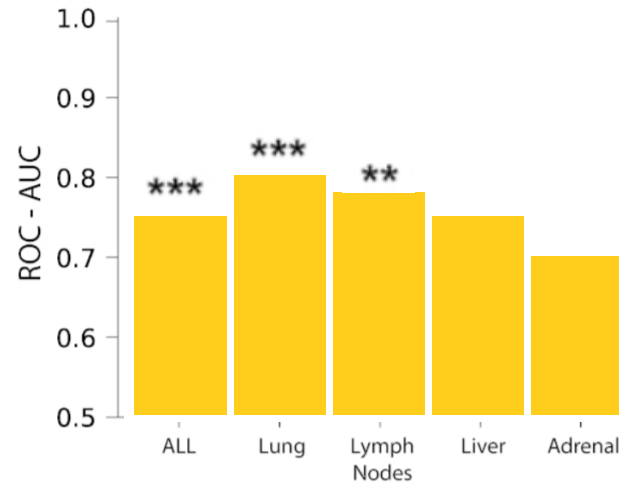
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Lesion Response Prediction Non-Small Cell Lung Cancer



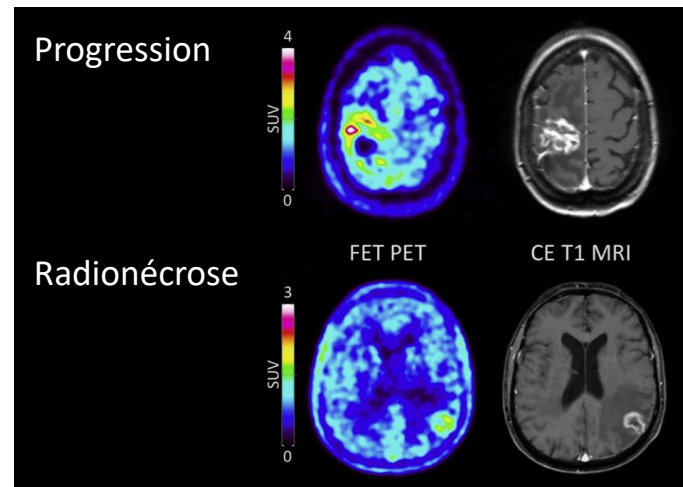
Prédire la réponse à l'immunothérapie à partir du TDM : lésions hétérogènes et sphériques de meilleurs pronostics

Neuroimage Clin. 2018 Aug 19;20:537-542. doi: 10.1016/j.nicl.2018.08.024. eCollection 2018.

### Combined FET PET/MRI radiomics differentiates radiation injury from recurrent brain metastasis.

Lohmann P<sup>1</sup>, Kocher M<sup>2</sup>, Ceccon G<sup>3</sup>, Bauer EK<sup>3</sup>, Stoffels G<sup>4</sup>, Viswanathan S<sup>4</sup>, Ruge M<sup>5</sup>, Neumaier B<sup>4</sup>, Shah NJ<sup>6</sup>, Fink GR<sup>7</sup>, Langen KJ<sup>8</sup>, Galldiks N<sup>9</sup>.

- 52 patients (27% avec CPNPC\*)
- Métastases cérébrales après radiothérapie
- Images IRM et TEP au 18F-FET
- 42 index radiomiques



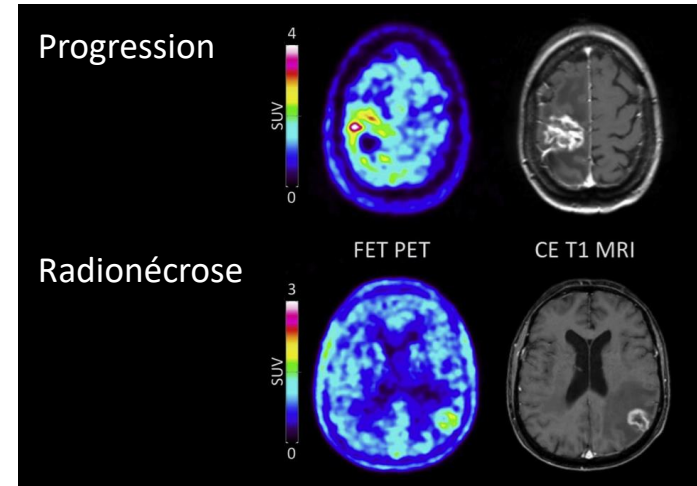


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Distinction entre progression et radionécrose avec AUC = 0,84

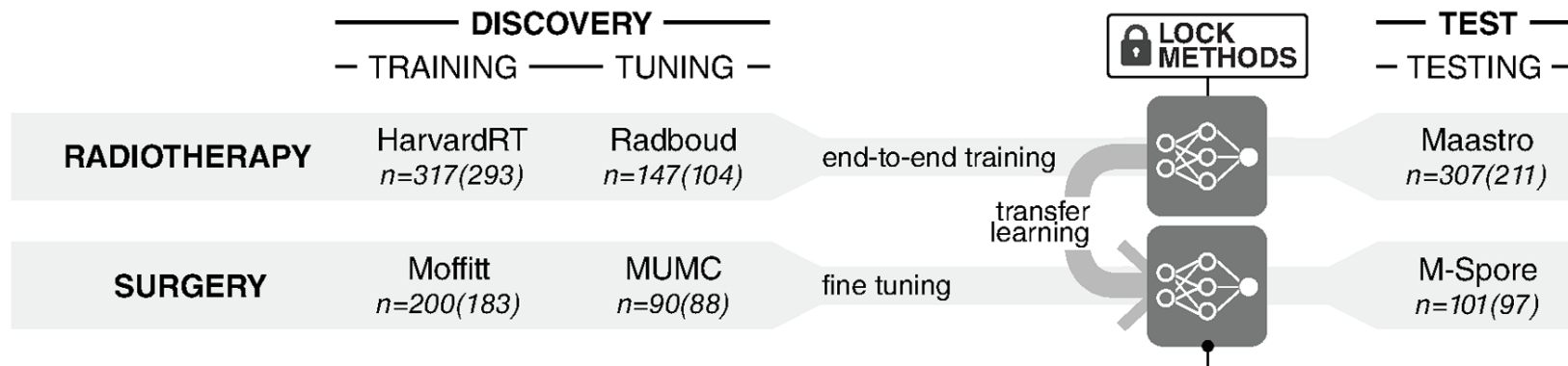
	FET PET	CE-MRI	Combined
Included features	PET_Volume	T1_stdValue	T1_LZE
	PET_GLNUr	T1_Volume	T1_GLNUz
	PET_RLNU	T1_Compacity	T1_ZLNU
	PET_LZHGE	T1_RLNU	T1_DWT3_GLNUz
	PET_GLNUz	T1_LoG_ZLNU	PET_SRE
10-fold CV			
Accuracy	76%	74%	83%
Sensitivity	85%	81%	81%
Specificity	65%	62%	85%
AUC	0.79	0.77	0.84

PLoS Med. 2018 Nov 30;15(11):e1002711. doi: 10.1371/journal.pmed.1002711. eCollection 2018 Nov.

## Deep learning for lung cancer prognostication: A retrospective multi-cohort radiomics study.

Hosny A<sup>1</sup>, Parmar C<sup>1</sup>, Coroller TP<sup>1</sup>, Grossmann P<sup>1</sup>, Zeleznik R<sup>1</sup>, Kumar A<sup>1</sup>, Bussink J<sup>2</sup>, Gillies RJ<sup>3</sup>, Mak RH<sup>4</sup>, Aerts HJWL<sup>1,4</sup>.

- 1 194 patients avec CPNPC\*
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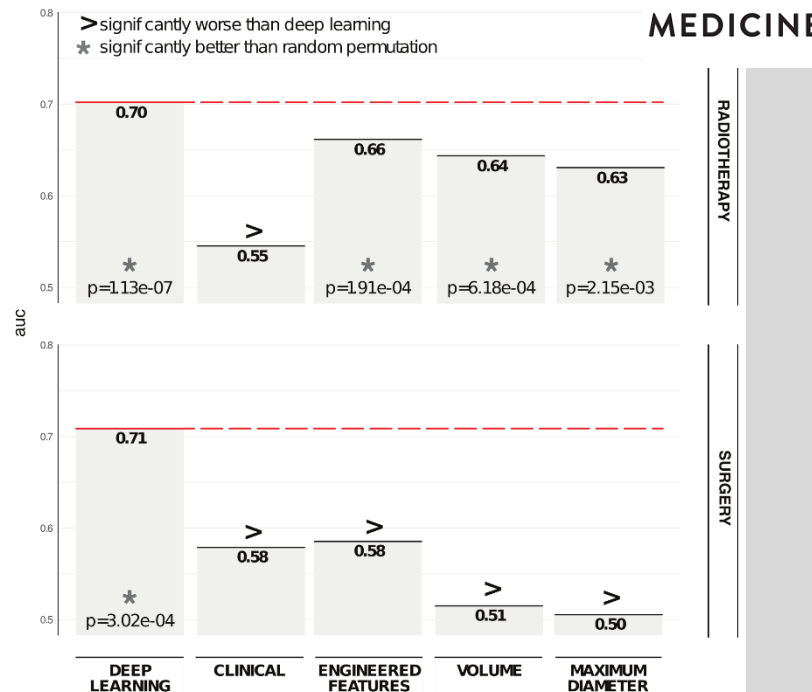


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- 1 194 patients avec CPNPC\*
- Images TDM



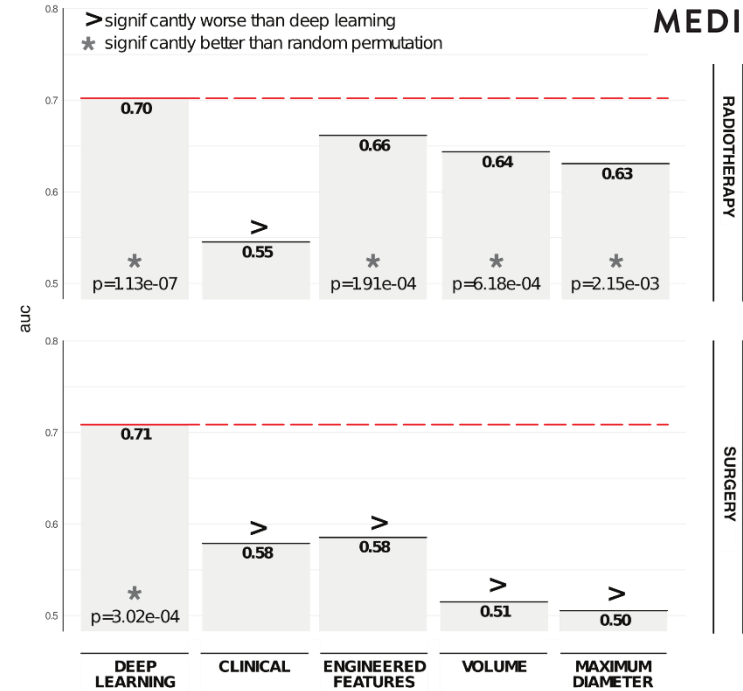
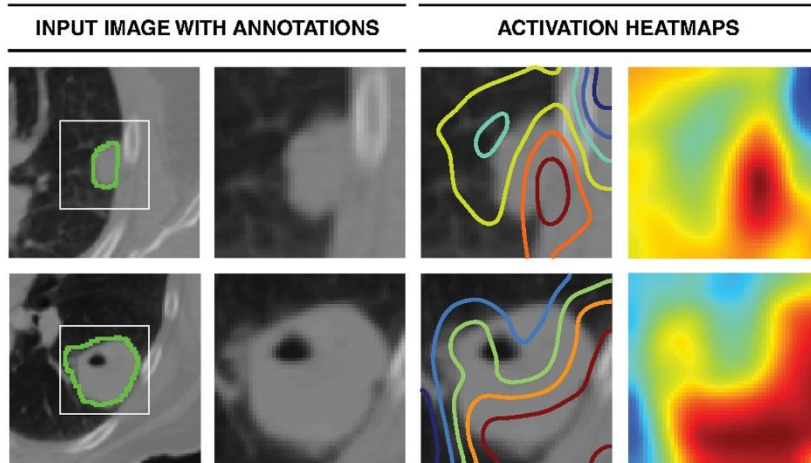
Prédiction de la survie à 2 ans  
(AUC=0,70-0,71) > variables cliniques

PLoS Med. 2018 Nov 30;15(11):e1002711. doi: 10.1371/journal.pmed.1002711. eCollection 2018 Nov.

## Deep learning for lung cancer prognostication: A retrospective study

Hosny A<sup>1</sup>, Parmar C<sup>1</sup>, Coroller TP<sup>1</sup>, Grossmann P<sup>1</sup>, Zeleznik R<sup>1</sup>, Kumar A<sup>1</sup>, Bussink J<sup>2</sup>, Gillies RJ<sup>3</sup>, Mak R

- 1 194 patients avec CPNPC\*
- Images TDM



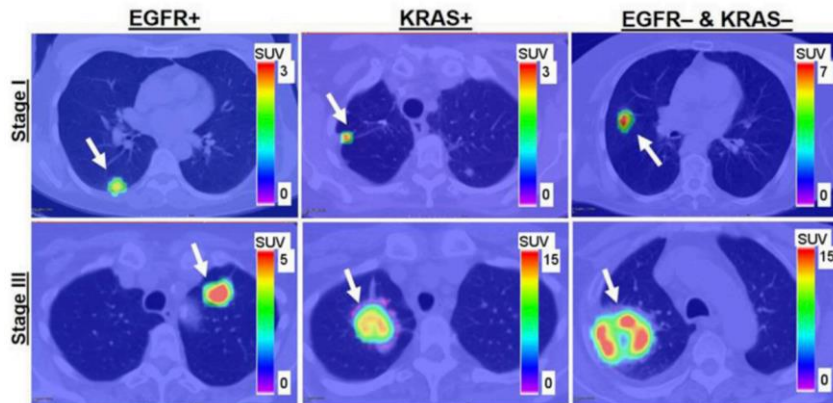
Prédiction de la survie à 2 ans (AUC=0,70-0,71) > variables cliniques

J Nucl Med. 2017 Apr;58(4):569-576. doi: 10.2967/jnumed.116.181826. Epub 2016 Sep 29.

## Associations Between Somatic Mutations and Metabolic Imaging Phenotypes in Non-Small Cell Lung Cancer.

Yip SS<sup>1</sup>, Kim J<sup>2</sup>, Coroller TP<sup>3</sup>, Parmar C<sup>3</sup>, Velazquez ER<sup>3</sup>, Huynh E<sup>3</sup>, Mak RH<sup>3</sup>, Aerts HJ<sup>3,4</sup>.

- 348 patients CPNPC\*
- Images TEP au 18F-FDG
- 73 index radiomiques

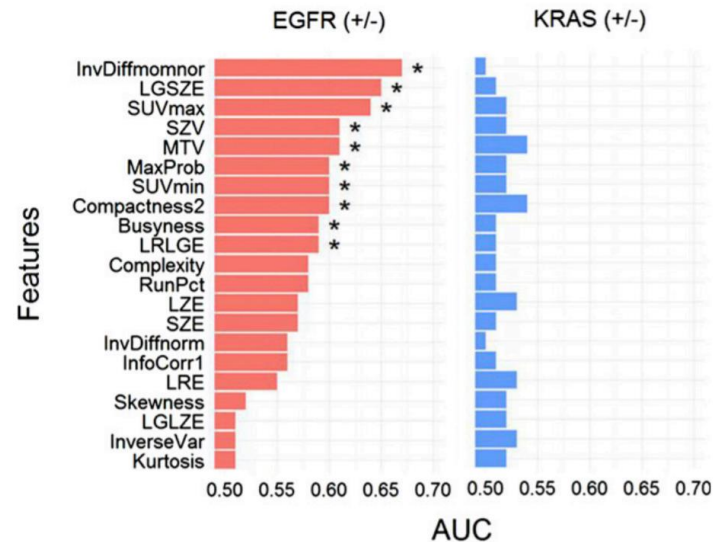
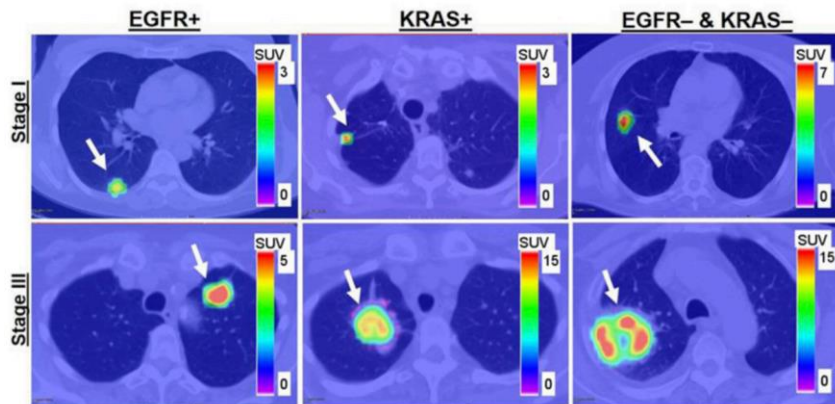


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- 348 patients CPNPC\*
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- 73 index radiomiques



Certains index mesurés en TEP sont sensibles au statut EGFR (≠KRAS)

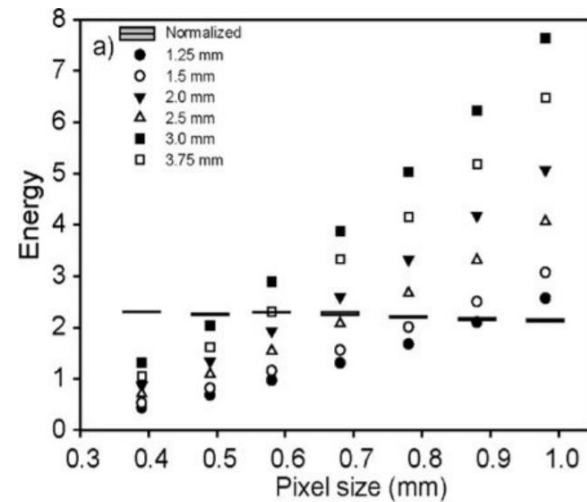


Impact des paramètres d'acquisition et de reconstruction des images

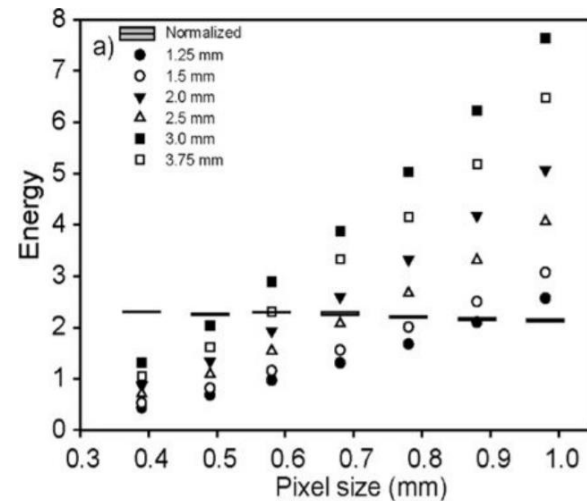
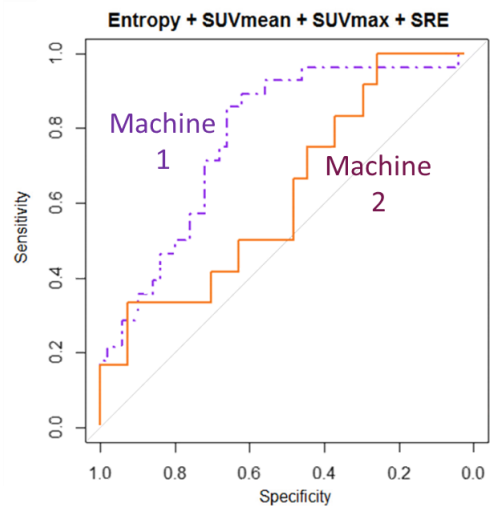




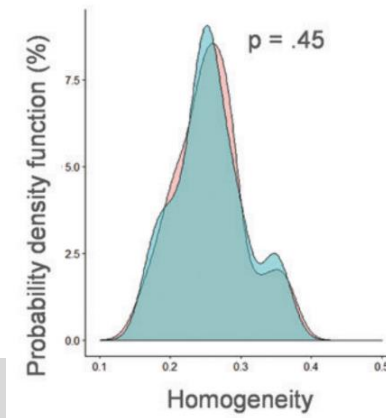
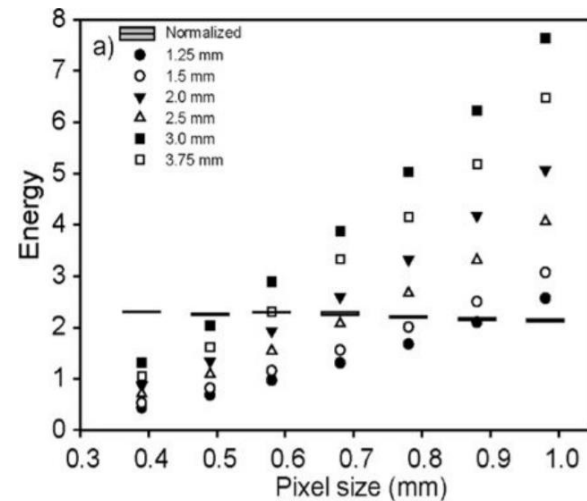
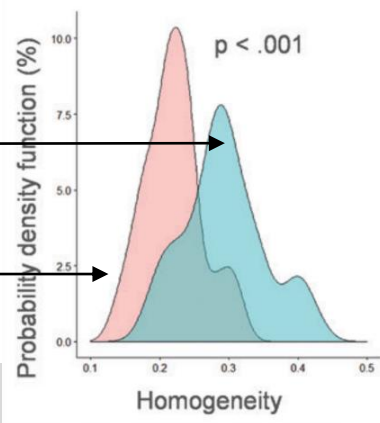
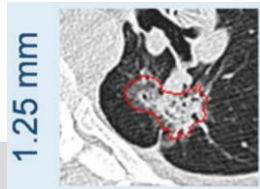
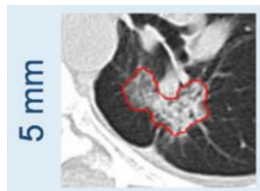
- Index radiomiques sensibles aux paramètres d'acquisition et de reconstruction des images



- Index radiomiques sensibles aux paramètres d'acquisition et de reconstruction des images
- Modèles radiomiques non transposables  
[Reuzé et al. *Oncotarget* 2017]



- Index radiomiques sensibles aux paramètres d'acquisition et de reconstruction des images
- Modèles radiomiques non transposables  
[Reuzé et al. *Oncotarget* 2017]
- Harmonisation des index radiomiques en TEP et en TDM  
[Orlhac et al. *J Nucl Med* 2018]  
[Orlhac et al. *Radiology* 2019]

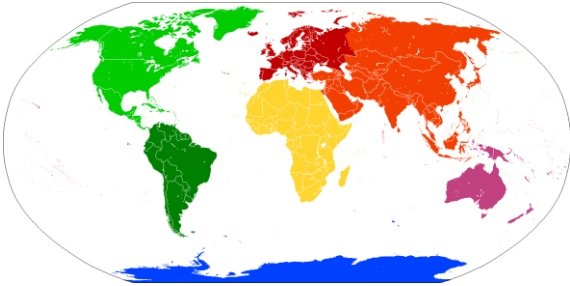




Impact des paramètres d'acquisition et de reconstruction des images

Biais dans le recrutement des patients

- Ethniques



Impact des paramètres d'acquisition et de reconstruction des images

Biais dans le recrutement des patients

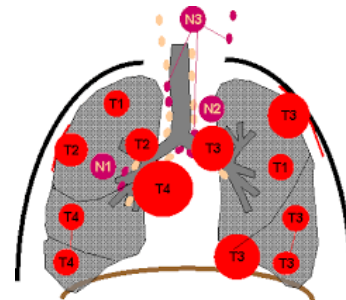
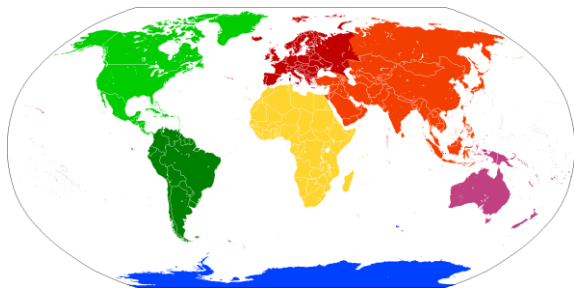
- Ethniques
- Sociaux



Impact des paramètres d'acquisition et de reconstruction des images

Biais dans le recrutement des patients

- Ethniques
- Sociaux
- Caractéristiques tumorales : stade T, sous-types, traitements

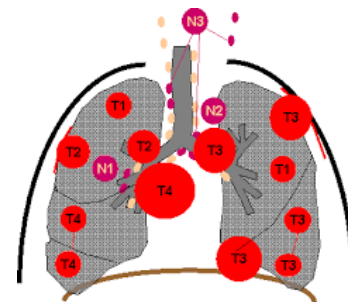
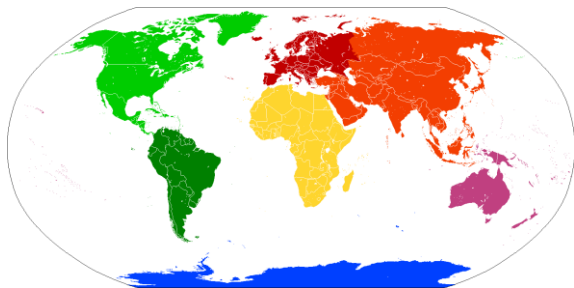


Impact des paramètres d'acquisition et de reconstruction des images

Biais dans le recrutement des patients

- Ethniques
- Sociaux
- Caractéristiques tumorales : stade T, sous-types, traitements

→ Adapter les modèles ?





Impact des paramètres d'acquisition et de reconstruction des images

Biais dans le recrutement des patients

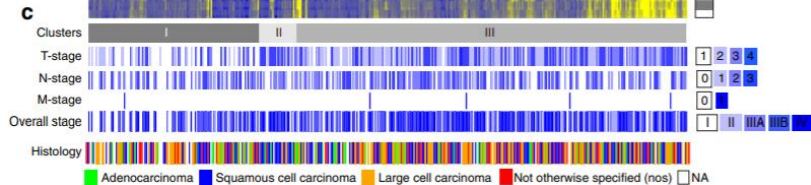
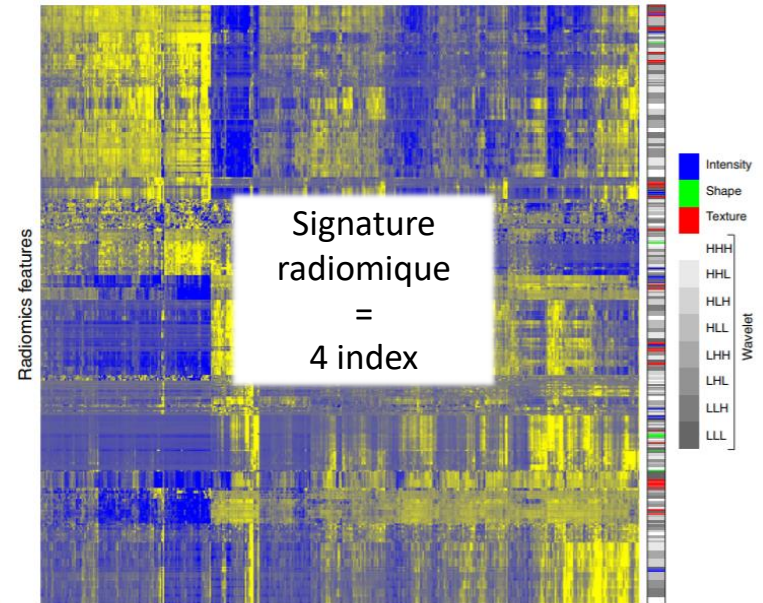
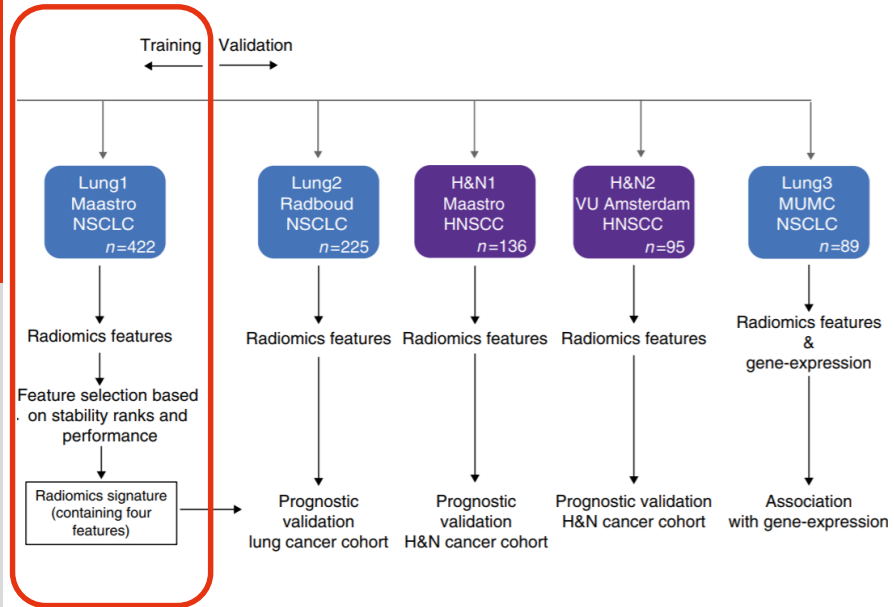
Ne pas décrypter les variables d'intérêt



Nat Commun. 2014 Jun 3;5:4006. doi: 10.1038/ncomms5006.

## Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach.

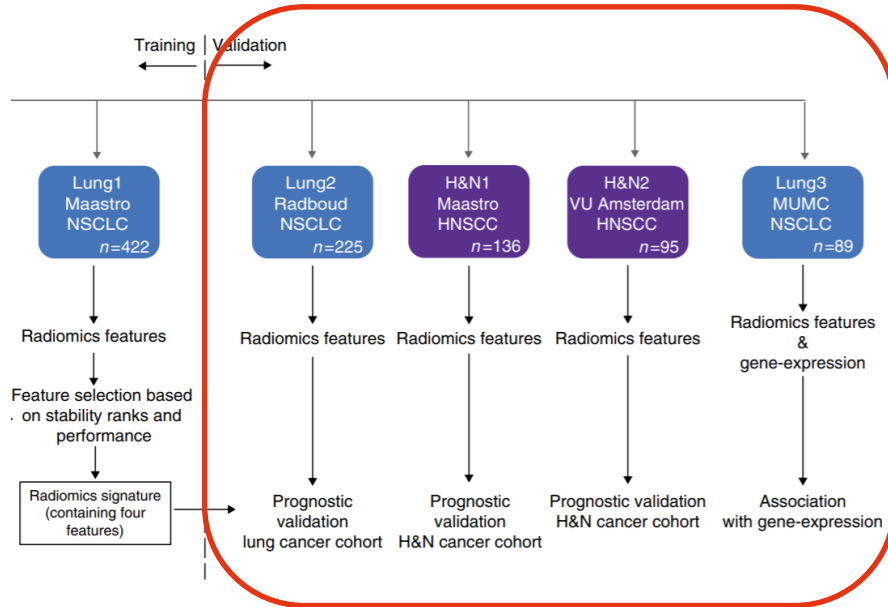
Aerts HJ<sup>1</sup>, Velazquez ER<sup>2</sup>, Leijenaar RT<sup>3</sup>, Parmar C<sup>4</sup>, Grossmann P<sup>5</sup>, Carvalho S, Bussink J<sup>6</sup>, Monshouwer R<sup>6</sup>, Haibe-Kains B<sup>7</sup>, Rietveld D<sup>8</sup>, Hoebers F<sup>3</sup>, Rietbergen MM<sup>9</sup>, Leemans CR<sup>9</sup>, Dekker A<sup>3</sup>, Quackenbush J<sup>10</sup>, Gillies RJ<sup>11</sup>, Lambin P<sup>3</sup>.



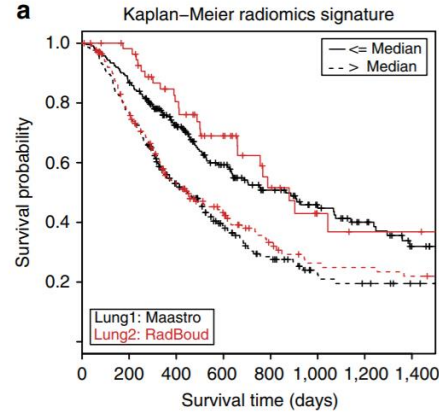
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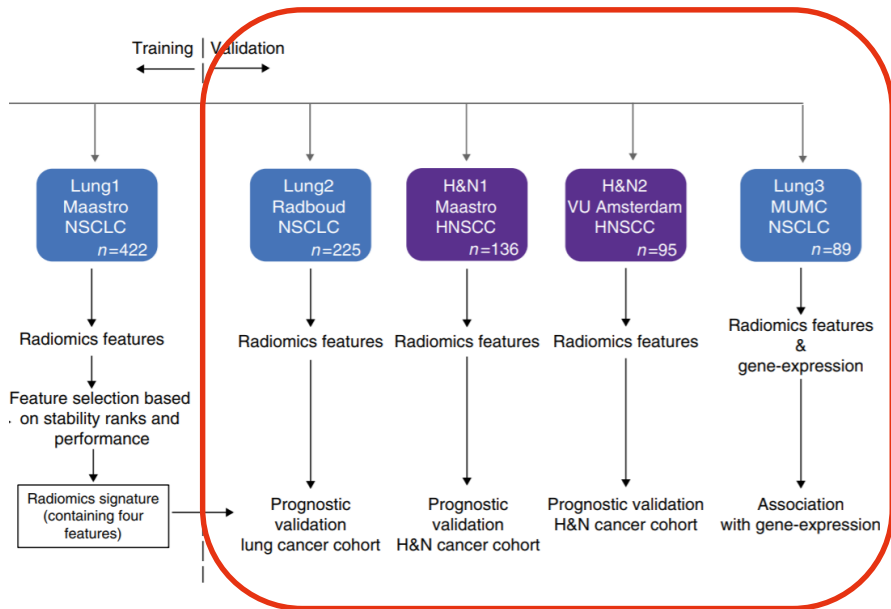
### Lésions pulmonaires



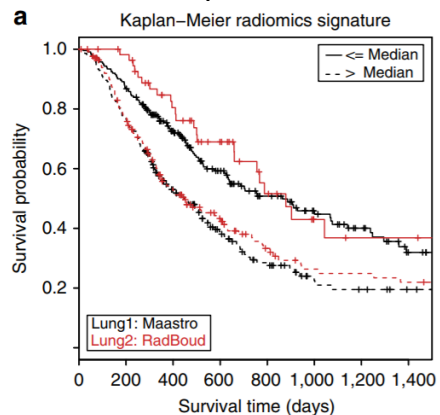
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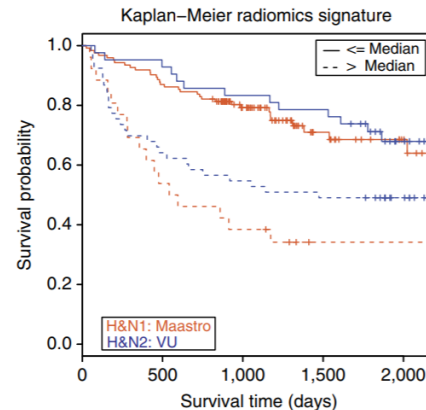
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### Lésions pulmonaires



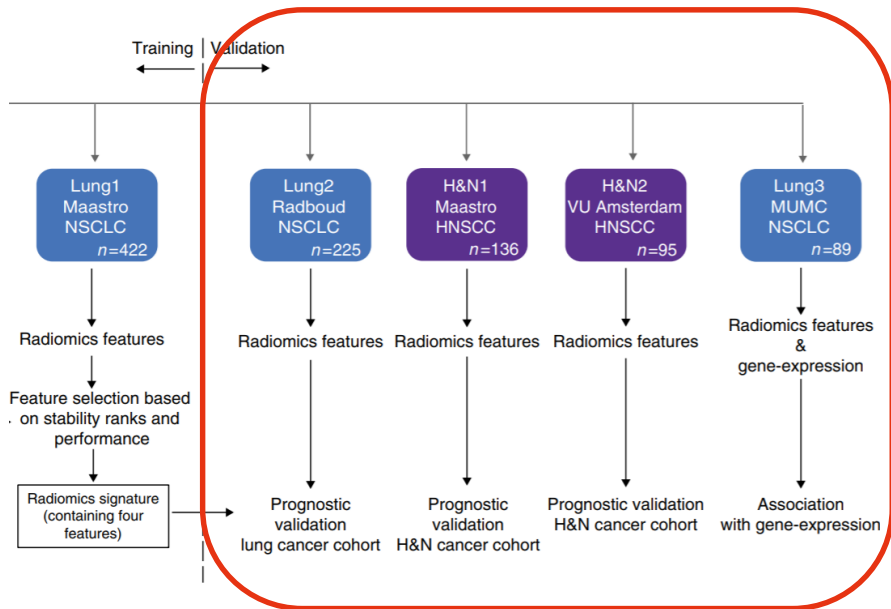
### Lésions ORL



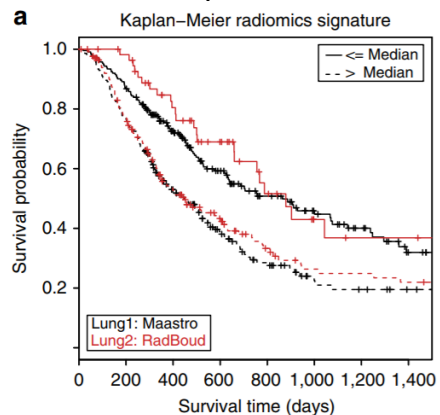
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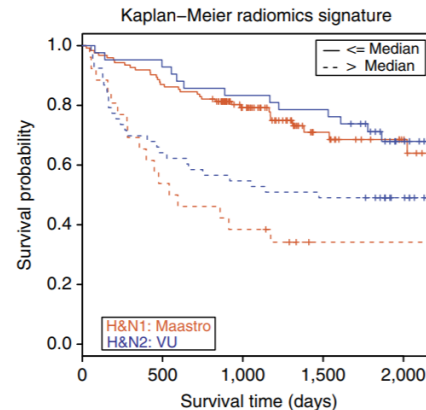
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### Lésions pulmonaires



### Lésions ORL

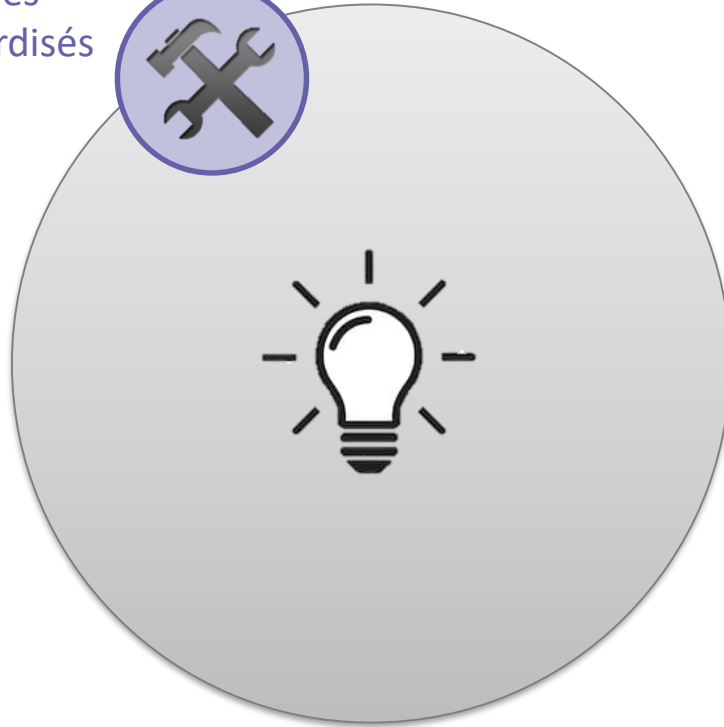


→ Performances expliquées par la corrélation avec le volume tumoral :  $R=[0,71-0,98]$

[Vallières et al. *SNMMI* 2018]

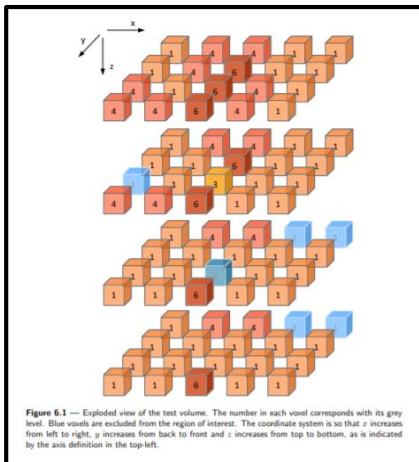


Outils/codes/modèles  
à disposition et standardisés



## Image biomarker standardisation initiative

Alex Zwanenburg, Stefan Leger, Martin Vallières, Steffen Löck (for the Image Biomarker Standardisation Initiative)



### PyRadiomics

Open-source toolbox for radiomic feature extraction



Outils/codes/modèles  
à disposition et standardisés



Méthodes  
statistiques  
spécifiques



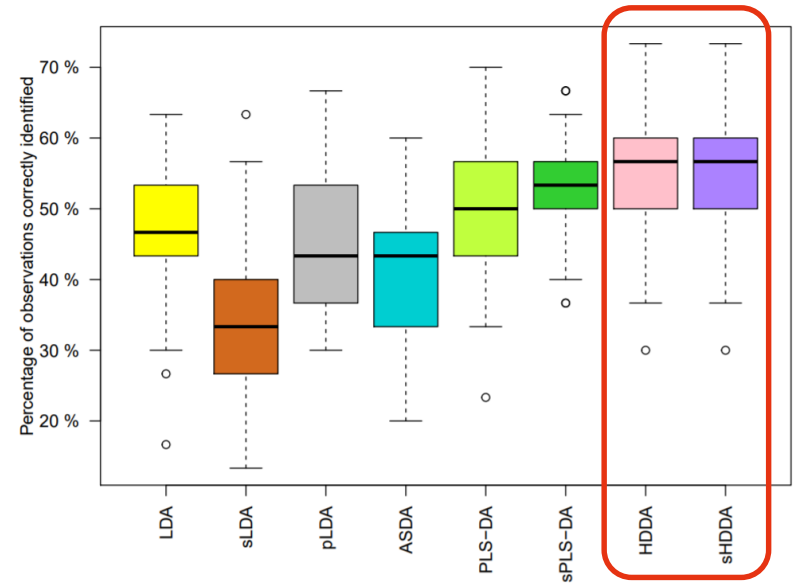


## Class-specific variable selection in high-dimensional discriminant analysis through Bayesian Sparsity

Fanny Orlhac, Pierre-Alexandre Mattei, Charles Bouveyron ✉, Nicholas Ayache

First published: 18 November 2018 | <https://doi.org/10.1002/cem.3097>

- 87 patients avec CPNPC\*
- Images TDM
- 636 index radiomiques
- Distinction en 3 sous-types tumoraux

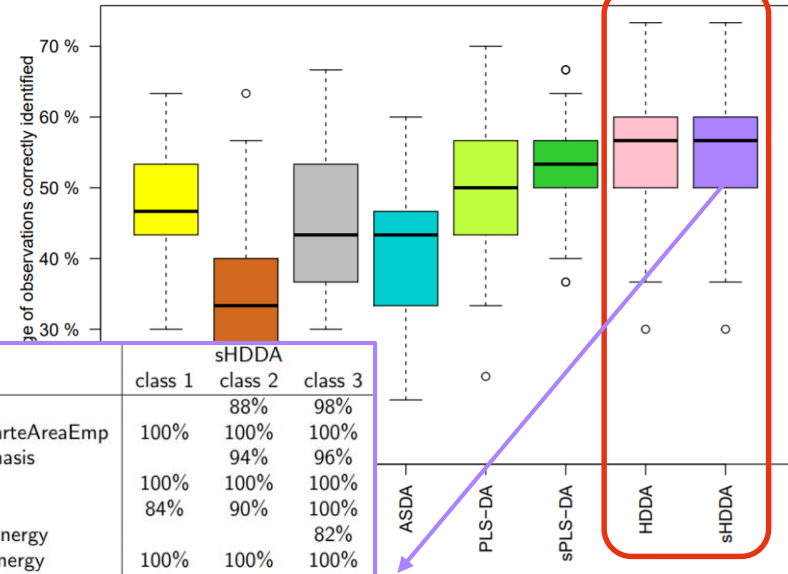


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- Distinction en 3 sous-types tumoraux



Radiomic features	sHDDA		
	class 1	class 2	class 3
GLCM_clusProm		88%	98%
GLSZM_highIntensityLarteAreaEmp	100%	100%	100%
GLSZM_largeAreaEmphasis		94%	96%
Stats_energy	100%	100%	100%
Stats_totalenergy	84%	90%	100%
Wavelet_HHH_stats_energy			82%
Wavelet_HHL_stats_energy	100%	100%	100%
Wavelet_HLH_stats_energy	96%	100%	100%
Wavelet_HLL_stats_energy	98%	100%	100%
Wavelet_LHH_stats_energy	80%	100%	98%
Wavelet_LHL_stats_energy	98%	96%	
Wavelet_LLH_stats_energy	98%	92%	
Wavelet_LLL_glcm_clusProm		88%	100%
Wavelet_LLL_stats_energy	100%	100%	100%
Wavelet_LLL_stats_totalenergy	90%	100%	100%
Wavelet_LLL_stats_var		82%	100%

Outils/codes/modèles  
à disposition et standardisés



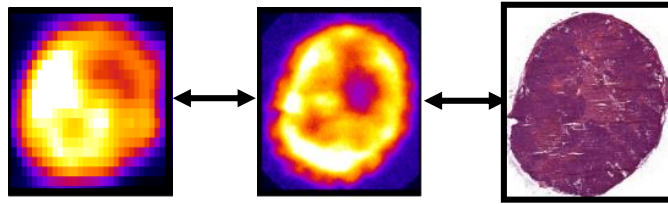
Méthodes  
statistiques  
spécifiques



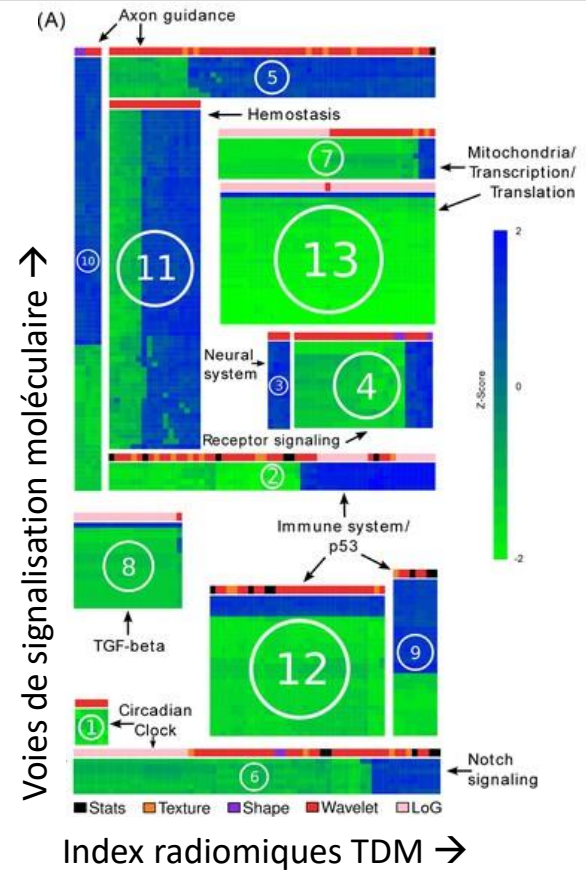
Signification biologique



- Comprendre le lien entre l'hétérogénéité sur les images et l'hétérogénéité biologique [Orlhac et al. *J Nucl Med* 2016]



- Associer les index radiomiques à la caractérisation moléculaire des lésions [Grossmann et al. *eLIFE* 2017]



Outils/codes/modèles  
à disposition et standardisés



Identification de phénotypes  
radiomiques spécifiques



Méthodes  
statistiques  
spécifiques



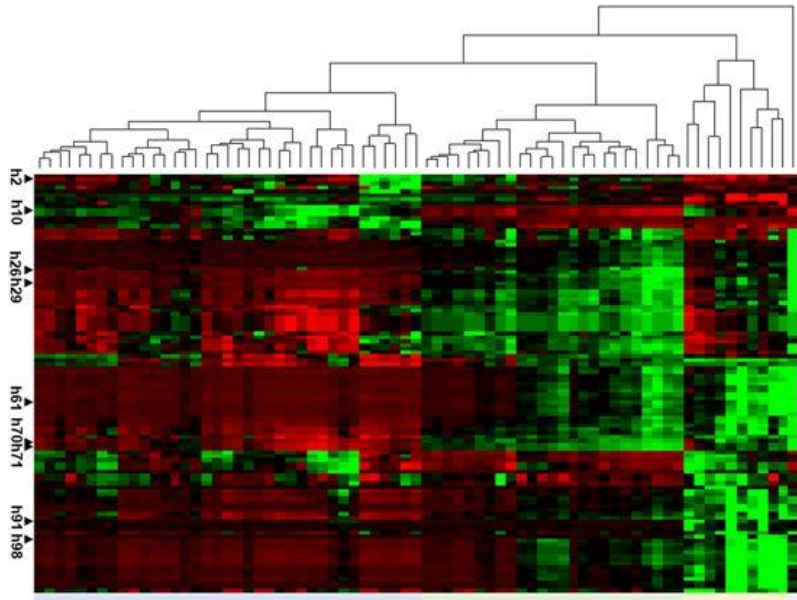
Signification biologique





Patients

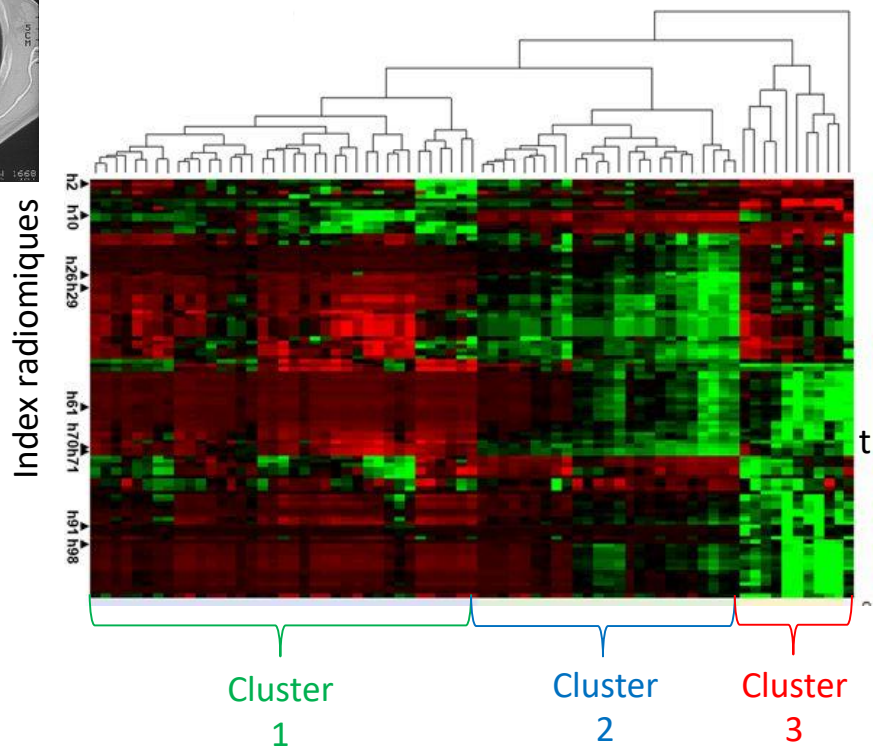
Index radiomiques



Séparation des patients suivant leur phénotype radiomique



Patients



Séparation des patients suivant leur phénotype radiomique



Identification de sous-groupes de tumeurs aux caractéristiques communes

Outils/codes/modèles  
à disposition et standardisés



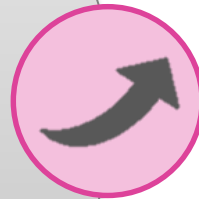
Identification de phénotypes  
radiomiques spécifiques



Méthodes  
statistiques  
spécifiques



Evolution des  
traitements et  
modalités d'imagerie



Signification biologique





Outils/codes/modèles  
à disposition et standardisés



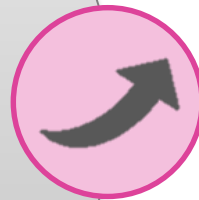
Identification de phénotypes  
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Méthodes  
statistiques  
spécifiques



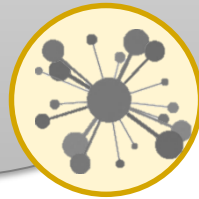
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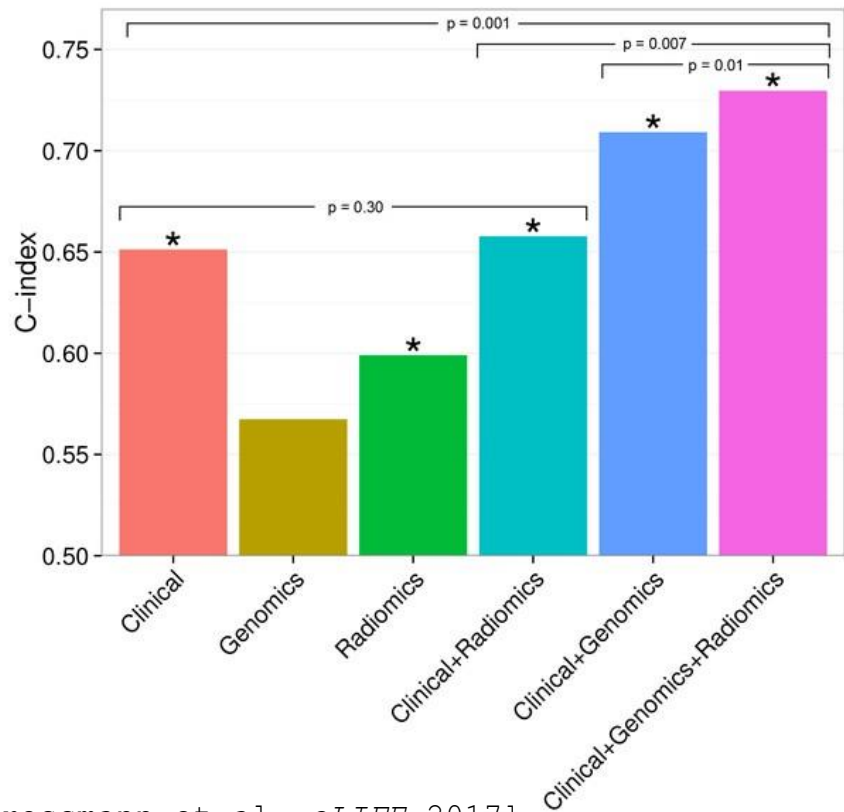


Signification biologique



Modèles multi-omiques





[Grossmann et al. *eLIFE* 2017]

Prédiction de la survie dans les cancers pulmonaires

→ Combinaison des données cliniques, génomiques et radiomiques

Outils/codes/modèles  
à disposition et standardisés



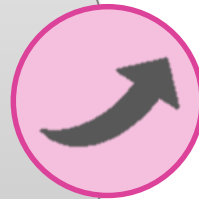
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Méthodes  
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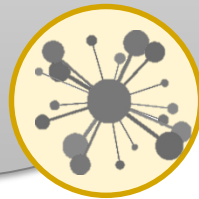
Evolution des  
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Signification biologique



Modèles multi-omiques

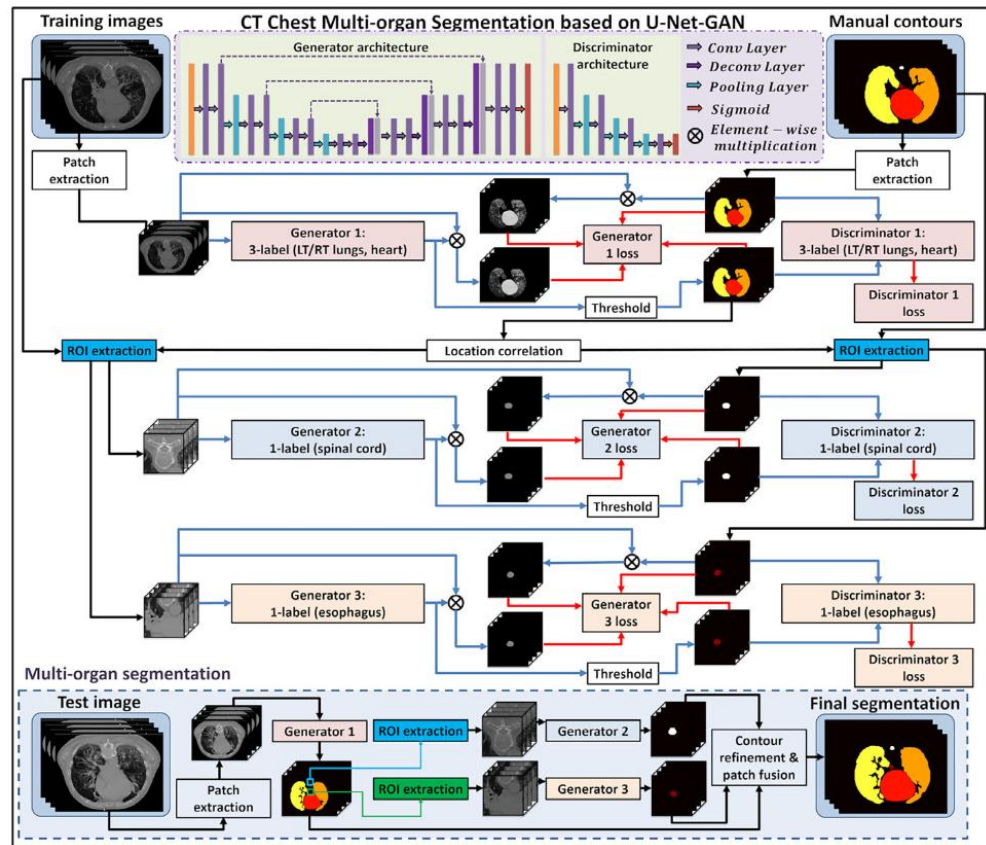
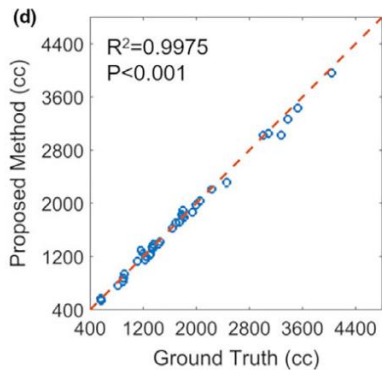
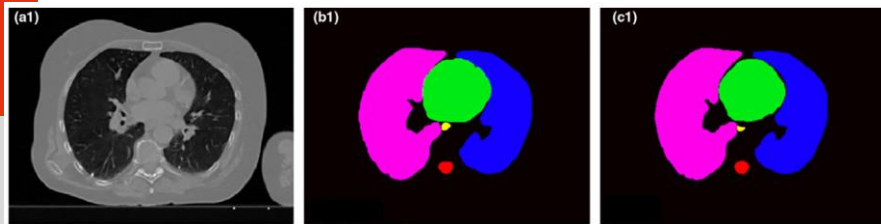


# Automatic multiorgan segmentation in thorax CT images using U-net-GAN.

Dong X<sup>1</sup>, Lei Y<sup>1</sup>, Wang T<sup>1</sup>, Thomas M<sup>1</sup>, Tang L<sup>2</sup>, Curran WJ<sup>1</sup>, Liu T<sup>1</sup>, Yang X<sup>1</sup>.

Segmentation  
manuelle

Segmentation  
automatique



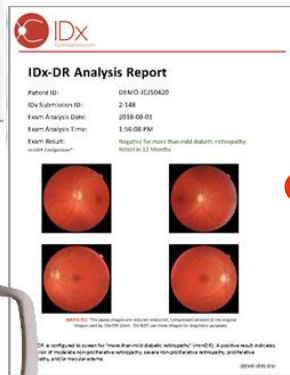
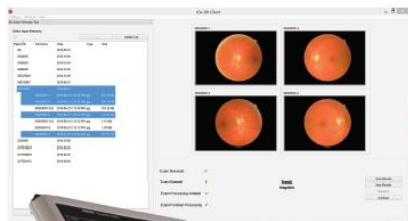
# Science

ARTIFICIAL INTELLIGENCE

## *In defense of the black box*

Black box algorithms can be useful in science and engineering

By Elizabeth A. Holm



Rétinopathie diabétique

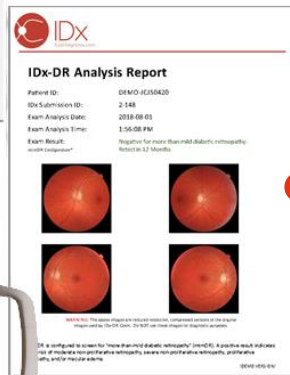
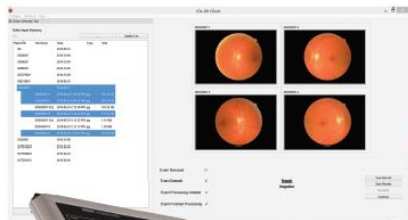
# Science

ARTIFICIAL INTELLIGENCE

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Black box algorithms can be useful in science and engineering

By Elizabeth A. Holm



Rétinopathie diabétique



Risque cardiovasculaire



Âge



Genre





institut**Curie**

Dr Alain Livartowski, PH  
Direction des Data  
Institut Curie

*Epione*  
e-patient / e-medicine

informatics mathematics  
*Inria*

Fanny Orlhac, PhD  
Equipe-projet Epione  
Inria Sophia Antipolis

