

Segmentation et radiomique en TEP/TDM : aspects méthodologiques

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Nantes, 18 Mai 2017



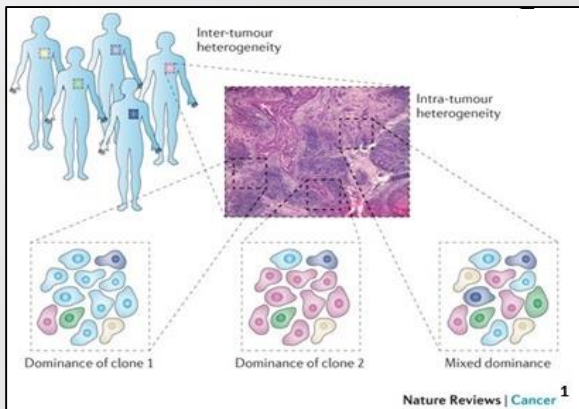
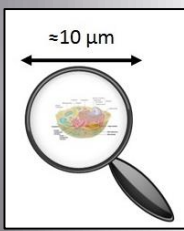
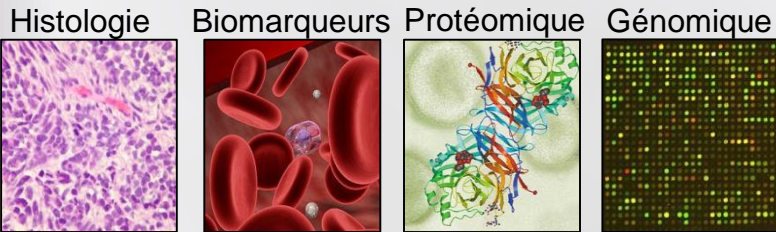
Radiomique : extraction “haut-debit” de données quantitatives des images médicales multimodales.

Principe : transformer les images (“*pictures*”) en données numériques dans lesquelles il devient possible de “fouiller” (*data mining*)

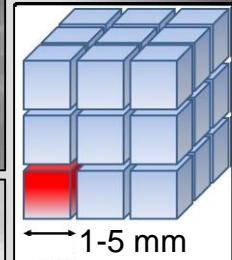
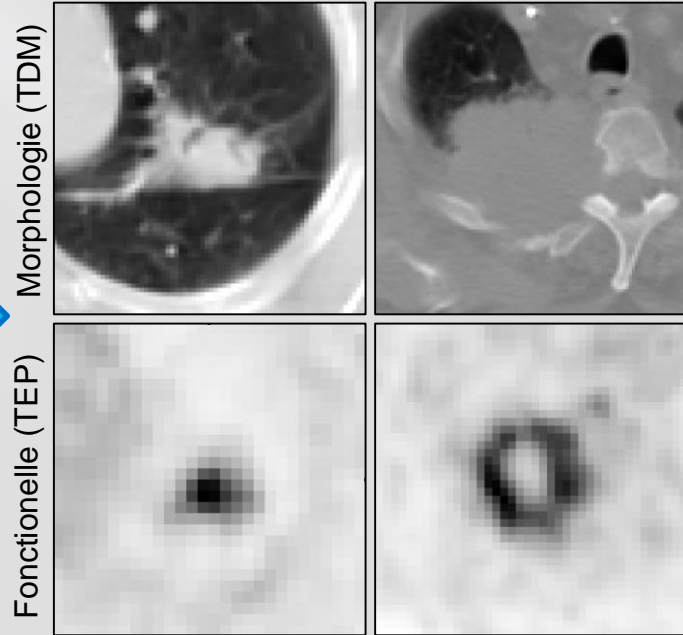


○ Hétérogénéité fonctionnelle et morphologique

- Les tumeurs sont hétérogènes [1] à toutes les échelles
 - Génétique, cellulaire, tissulaire (macroscopique)
 - Hypothèse : les caractéristiques des tumeurs dans les images médicales (échelle macro) reflètent (partiellement) les échelles inférieures y compris génétiques [2]

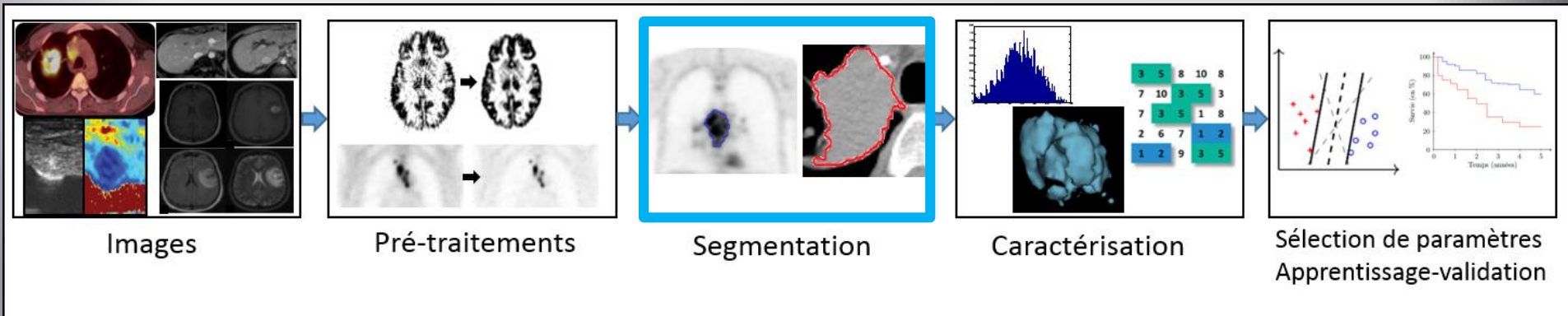


Nature Reviews | Cancer 1



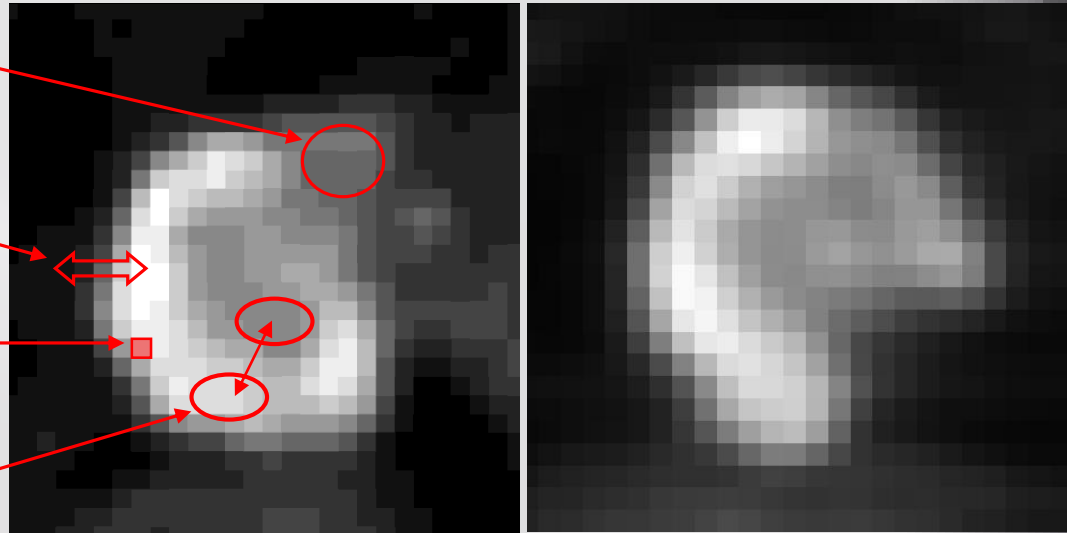
1. Gerlinger, *et al.* Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med.* 2012

2. Segal, *et al.* Decoding global gene expression programs in liver cancer by noninvasive imaging. *Nat Biotechnol.* 2007



➤ Défis en TEP

- ✓ Rapport signal à bruit limité
(sensibilité, durée d'acquisition...)
- ✓ Effets de volume partiel
(résolution spatiale ~ 5 mm FWHM)
- ✓ Echantillonnage spatial
(taille des voxels ~ 2 à 5 mm)
- ✓ Hétérogénéité
- ✓ Complexité des formes

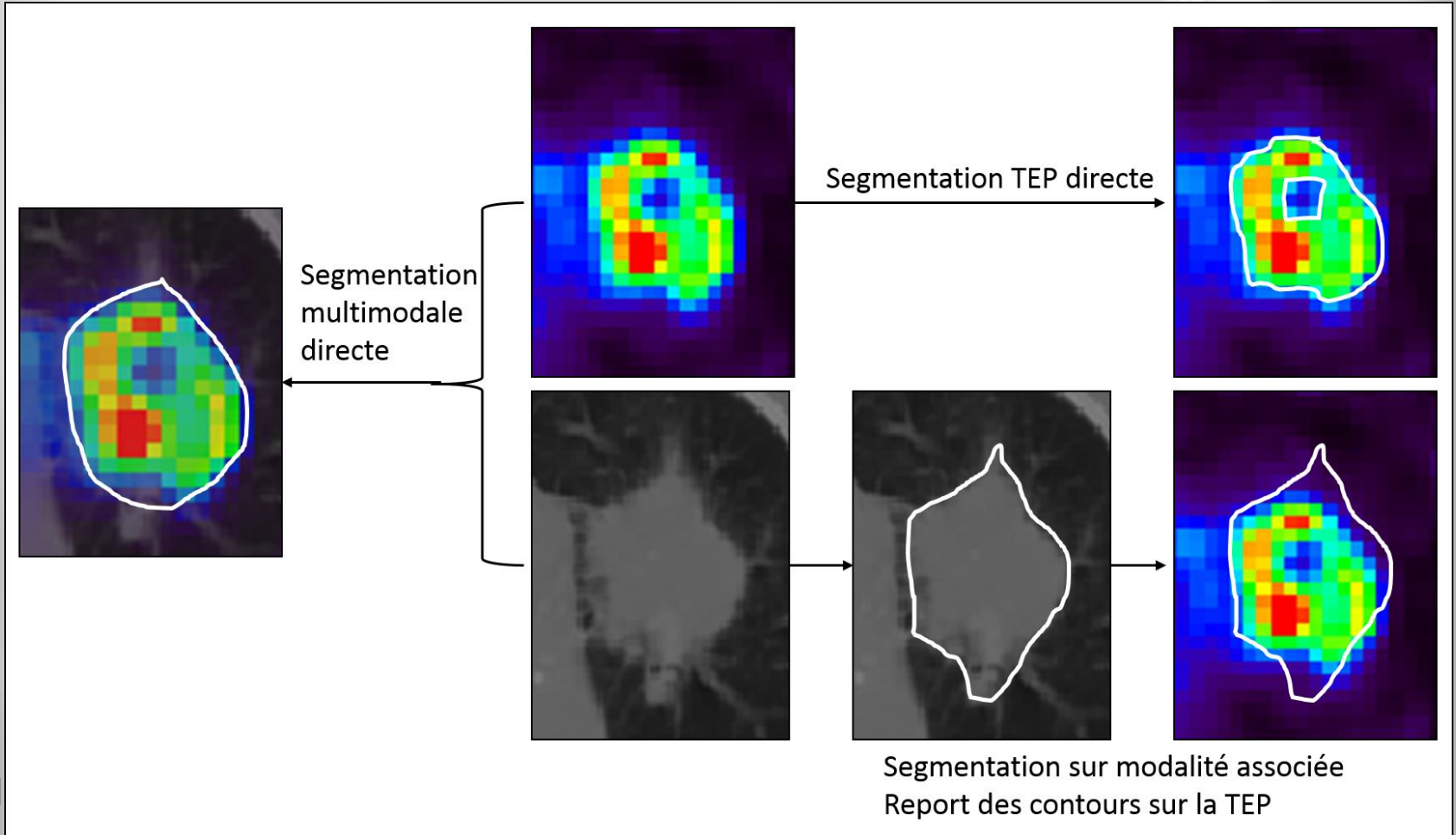


- Segmentation manuelle peu fiable (variabilité intra- & inter- experts)
- Il n'existe pas de seuil universel
- Une segmentation binaire n'est souvent pas appropriée

M. Hatt, *et al.* Metabolically active volumes automatic delineation methodologies in PET imaging: Review and perspectives. *Cancer Radiother* 2011

J.A. Lee. Segmentation of positron emission tomography images: some recommendations for target delineation in radiation oncology. *Radiother Oncol.* 2010

➤ Défis en TEP



- ◉ 1997-2007 : l'âge sombre
 - Un des premiers articles (conférence)
 - Suggestion d'un seuil fixe à 42% du maximum

Sixth Conference on Radioimmunodetection and
Radioimmunotherapy of Cancer

Supplement to Cancer

Segmentation of Lung Lesion Volume by Adaptive Positron Emission Tomography Image Thresholding

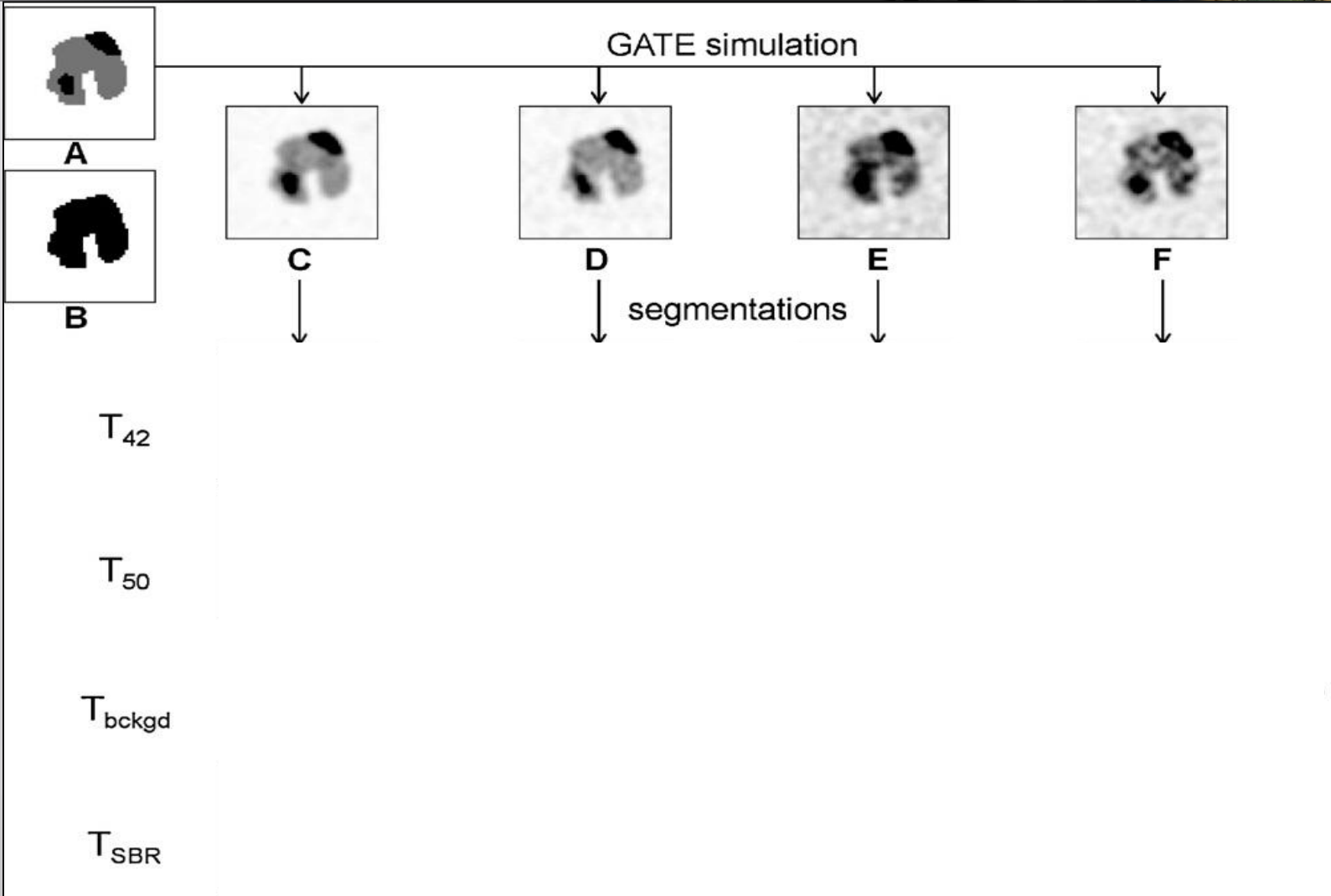
Yusuf E. Erdi, D.Sc.¹
 O. Mawlawi, M.Sc.²
 Steven M. Larson, M.D.²
 M. Imbriaco, M.D.²
 H. Yeung, M.D.²
 R. Finn, Ph.D.¹
 John L. Humm, Ph.D.¹

BACKGROUND. It is common protocol in radionuclide therapies to administer a tracer dose of a radiopharmaceutical, determine its lesion uptake and biodistribution by gamma imaging, and then use this information to determine the most effective therapeutic dose. This treatment planning approach can be used to quantify accurately the activity and volume of lesions and organs with positron emission tomography (PET). In this article, the authors focus on the specification of appropriate volumes of interest (VoI) using PET in association with computed tomography (CT).

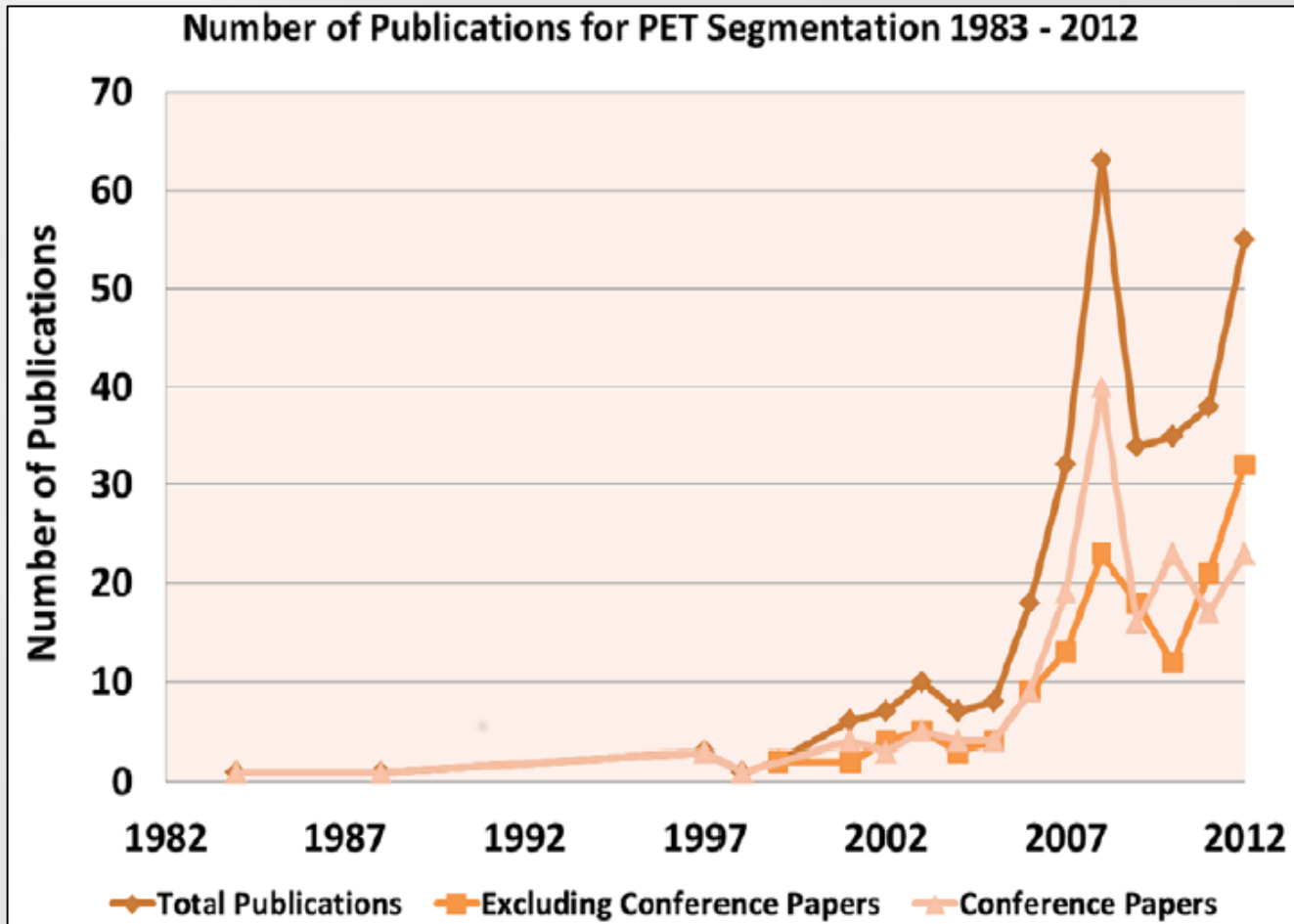
A.-S. Dewalle-Vignion, *et al.* Les méthodes de seuillage en
TEP : un état de l'art. *Médecine Nucléaire* 2010

Radiomique en TEP/TDM

Segmentation



2007 : l'ère de la segmentation d'images





- Task Group No. 211 - Classification, Advantages and Limitations of the Auto-Segmentation Approaches for PET
- 2011-2016
- Objectifs :
 - Recenser l'état de l'art
 - Evaluer de façon critique les différentes approches
 - Proposer une méthodologie d'évaluation des méthodes
 - Données (synthétiques, simulées, fantômes physiques, cliniques)
 - Métriques de performance (précision, robustesse, reproductibilité)

- Conclusions :
 - Des dizaines de méthodes publiées, niveau de validation très variable (et le plus souvent médiocre)
 - Pas de comparaisons à grande échelle, donc pas de consensus scientifique (à part concernant les seuillages)
 - *A fortiori* pas de consensus industriel et donc implémentation limitée d'outils pour les cliniciens
 - Besoin important de standardisation

Medical Physics
The International Journal of Medical Physics Research and Practice
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Task Group Report

Classification and evaluation strategies of auto-segmentation approaches for PET: Report of AAPM Task Group No. 211

Mathieu Hatt, John Lee, Charles R. Schmidtlein, Issam El Naqa, Curtis Caldwell, Elisabetta De Bernardi, Wei Lu, Shiva Das, Xavier Geets, Vincent Gregoire, Robert Jeraj, Michael P. MacManus, Osama R. Mawlawi, Ursula Nestle, Andrei B. Pugachev, Heiko Schöder, Tony Shepherd, Emiliano Spezi, Dimitris Visvikis, Habib Zaidi, Assen S. Kirov ✉

Medical Physics
The International Journal of Medical Physics Research and Practice
[Explore this journal >](#)

Research Article

Towards a standard for the evaluation of PET Auto-Segmentation methods: requirements and implementation

Beatrice Berthon, Emiliano Spezi ✉, Paulina Galavis, Tony Shepherd, Aditya Apte, Mathieu Hatt, Hadi Fayad, Elisabetta De Bernardi, Chiara Soffientini, Charles R. Schmidtlein, Issam El Naqa, Robert Jeraj, Wei Lu, Shiva Das, Habib Zaidi, Osama R. Mawlawi, Dimitris Visvikis, John A. Lee, Assen S. Kirov

1. M. Hatt, *et al.* Report of AAPM TG211: Classification and evaluation strategies of auto-segmentation approaches for PET. *Med Phys* 2017
2. B. Berthon, *et al.* Design and Implementation of PETASset: Benchmark Evaluation Software for PET Auto-Segmentation Methods. *Med Phys* 2017

⦿ Benchmark (« banc de test »)

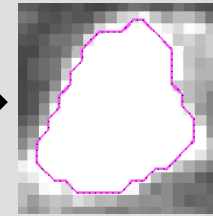
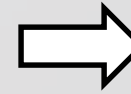
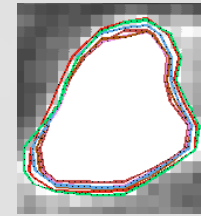
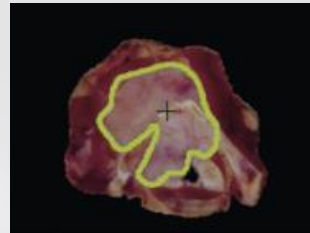
Fiabilité de la vérité terrain

Réalisme

❖ Images cliniques

Vérité approximative

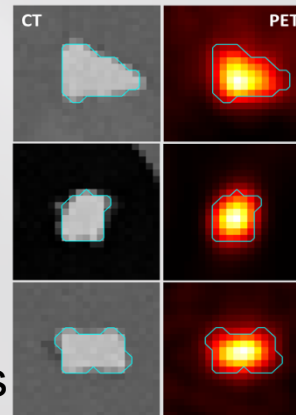
Cas réels



❖ Fantômes physiques

Vérité fiable (avec approximations)

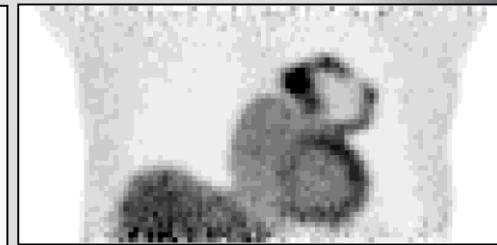
Acquisitions réelles mais objets simplifiés



❖ Simulations numériques

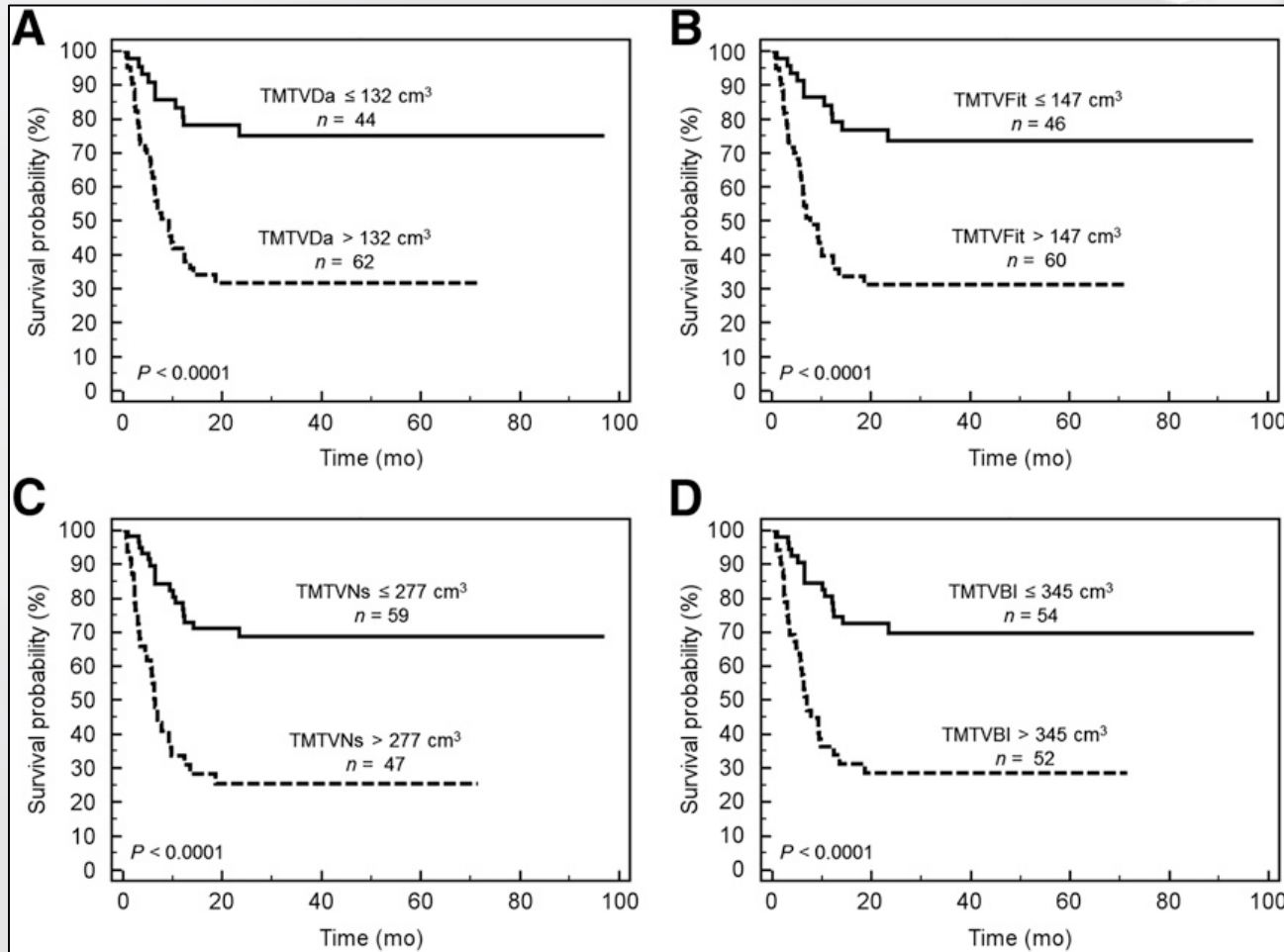
Vérité parfaitement fiable

Réalisme variable à la fois dans les caractéristiques d'images et dans les objets

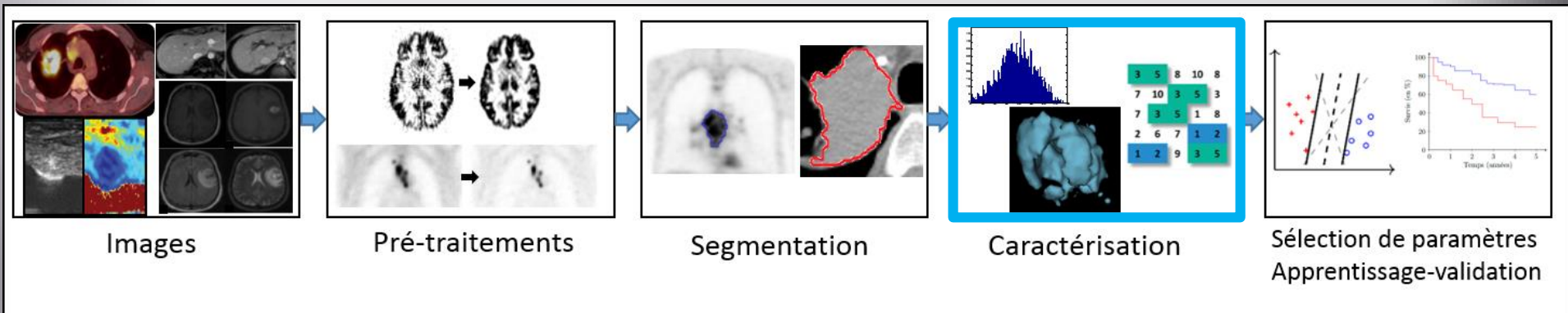


1. M. Hatt, *et al.* Report of AAPM TG211: Classification and evaluation strategies of auto-segmentation approaches for PET. *Med Phys* 2017
2. B. Berthon, *et al.* Design and Implementation of PETASset: Benchmark Evaluation Software for PET Auto-Segmentation Methods. *Med Phys* 2017

Variabilité due à la segmentation TEP

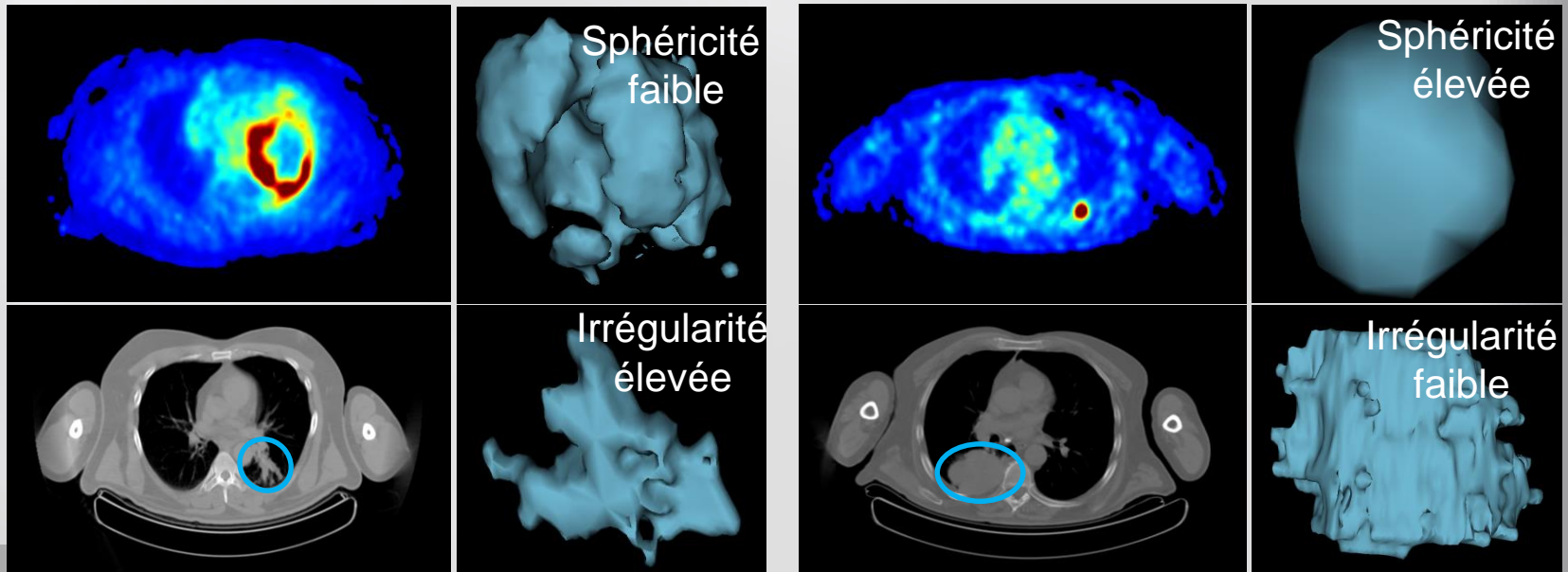


A-S. Cottreau, *et al.* Baseline Total Metabolic Tumor Volume Measured with Fixed or Different Adaptive Thresholding Methods Equally Predicts Outcome in Peripheral T Cell Lymphoma. *J Nucl Med* 2017



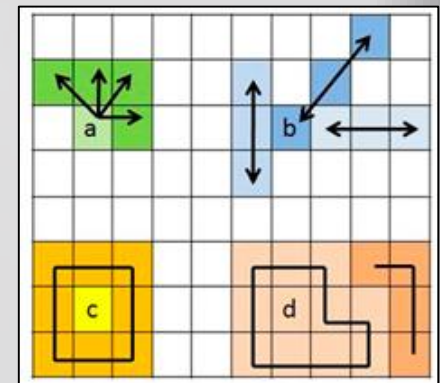
Forme 3D:

- Hypothèse : agressivité, potentiel métastatique...
 - Forme anatomique (TDM, IRM...)
 - Forme fonctionnelle (TEP)
 - Calculs simples avec descripteurs géométriques

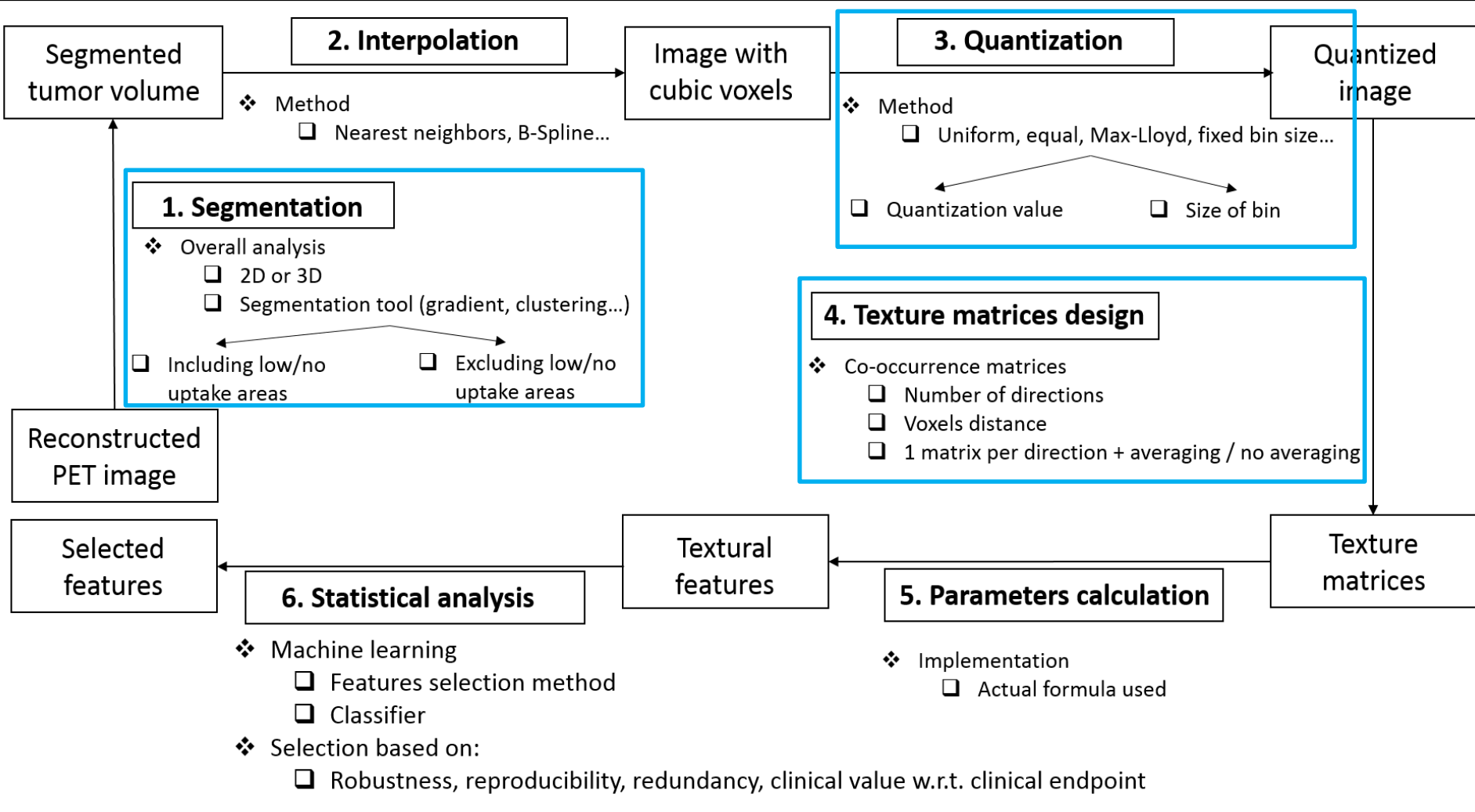


• Textures

- Technique utilisée depuis les années 70 dans tous les domaines du traitement d'image
- Quantification des motifs et les variations d'intensité et leur arrangement spatial
- Imagerie médicale (TDM IRM >1990^{1,2}, TEP >2009³)
 - Quantification d'organes/tissus/tumeurs
 - Segmentation
 - Détection
 - Classification d'images
 - Radiomics (>2012)



1. Schad LR, et al. MR tissue characterization of intracranial tumors by means of texture analysis. *Magn Reson Imaging* 1993.
 2. Mir AH, et al. Texture analysis of CT-images for early detection of liver malignancy. *Biomed Sci Instrum*. 1995.
 3. El Naqa I, et al. Exploring feature-based approaches in PET images for predicting cancer treatment outcomes. *Pattern Recognit*. 2009

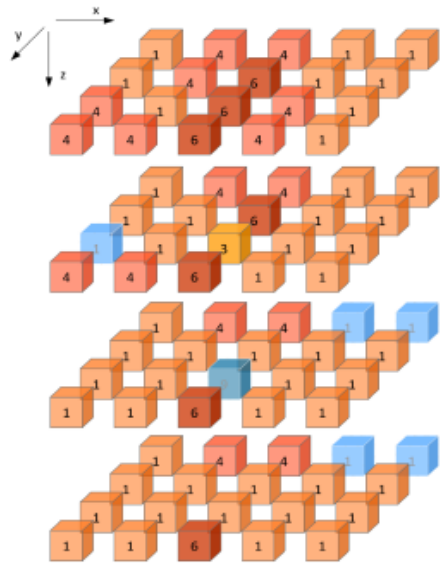


Initiative de standardisation



Participants

- Study leader: Alex Zwanenburg
- Cardiff University
 - Philip Whybra, Emiliano Spezi
 - Dana Farber Cancer Institute and Brigham and Women's Hospital, Harvard University
 - Andriy Fedorov, Hugo Aerts
 - Gemelli ART, Università Cattolica del Sacro Cuore
 - Jacopo Lenkovicz, Luca Boldrini, Nicola Dinapoli, Vincenzo Valentini
 - German Cancer Research Center (DKFZ)
 - Michael Götz, Nils Gählerl, Fabian Isensee, Klaus H. Maier-Hein
 - INSERM Brest, University of Brest
 - Marie-Charlotte Desseroit, Taman Upadaya, Mathieu Hatt
 - Leiden University Medical Center
 - Floris H.P. van Velden
 - MAASTRO clinic, Maastricht University
 - Ralph T.H. Leijenaar, Philippe Lambin
 - McGill University
 - Martin Vallières, Issam El Naqa
 - Memorial Sloan Kettering Cancer Center
 - Aditya Apte
 - Moffitt Cancer Center
 - Mahmoud A. Abdalah, Robert Gillies
 - OncoRay – National Center for Radiation Research in Oncology and NCT Dresden
 - Alex Zwanenburg, Stefan Leger, Esther Troost, Christian Richter, Steffen Löck
 - The Netherlands Cancer Institute (NKI)
 - Joost van Griethuysen, Cuong Viet Dinh, Uulke van der Heide
 - Universitätsklinikum Tübingen, Eberhard Karls University Tübingen
 - Jairo Socarras Fernandez, Daniela Thorwarth
 - University Hospital Zürich, University of Zürich
 - Marta Bogowicz, Stephanie Tanadini-Lang, Matthias Guckenberger
 - University of Bergen
 - Are Losnegård
 - University of California, San Francisco
 - Olivier Morin
 - University of Groningen, University Medical Center Groningen
 - Lisanne V. van Dijk, Jom Beukinga, Nanna M. Sijtsma, Roel J.H.M. Steenbakkers, Ronald Boellaard



Digital phantom. Blue voxels lie outside of the region of interest.



Standardisation progress. Height indicates the number of features per family. LI: Local intensity; IH: intensity histogram; IVH: intensity-volume histogram; CM: co-occurrence matrix; RLM: run length matrix; SZM: size zone matrix; NGTDM: neighbourhood grey tone difference matrix; DZM: distance zone matrix; NGLDM: neighbouring grey level difference matrix

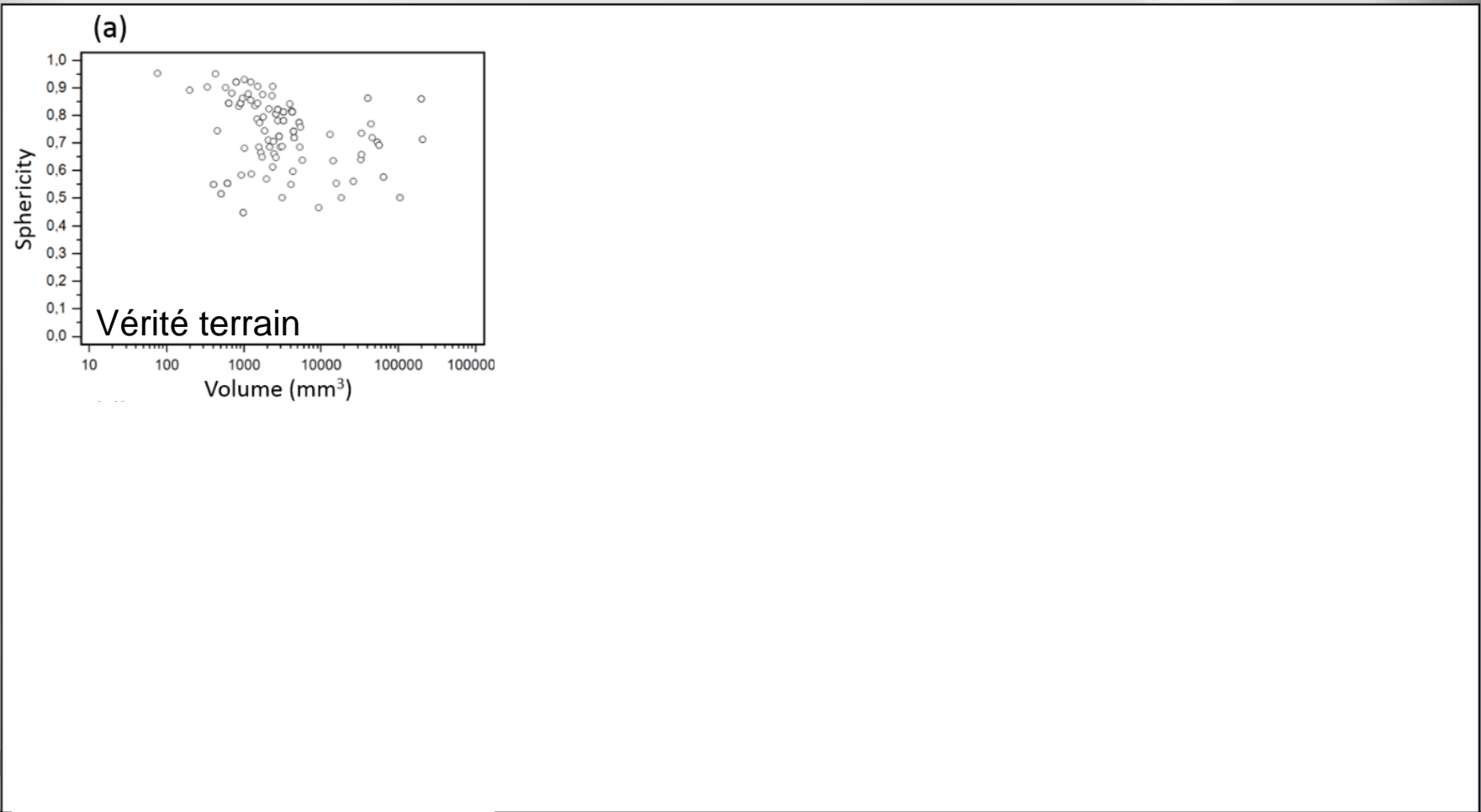
Current status:

	current	09-10-16
• no agreement (< 3 institutions or < 50% identical)	52	192
• agreement (> 50% identical)	59	85
• standardised (> 80% identical)	240	25

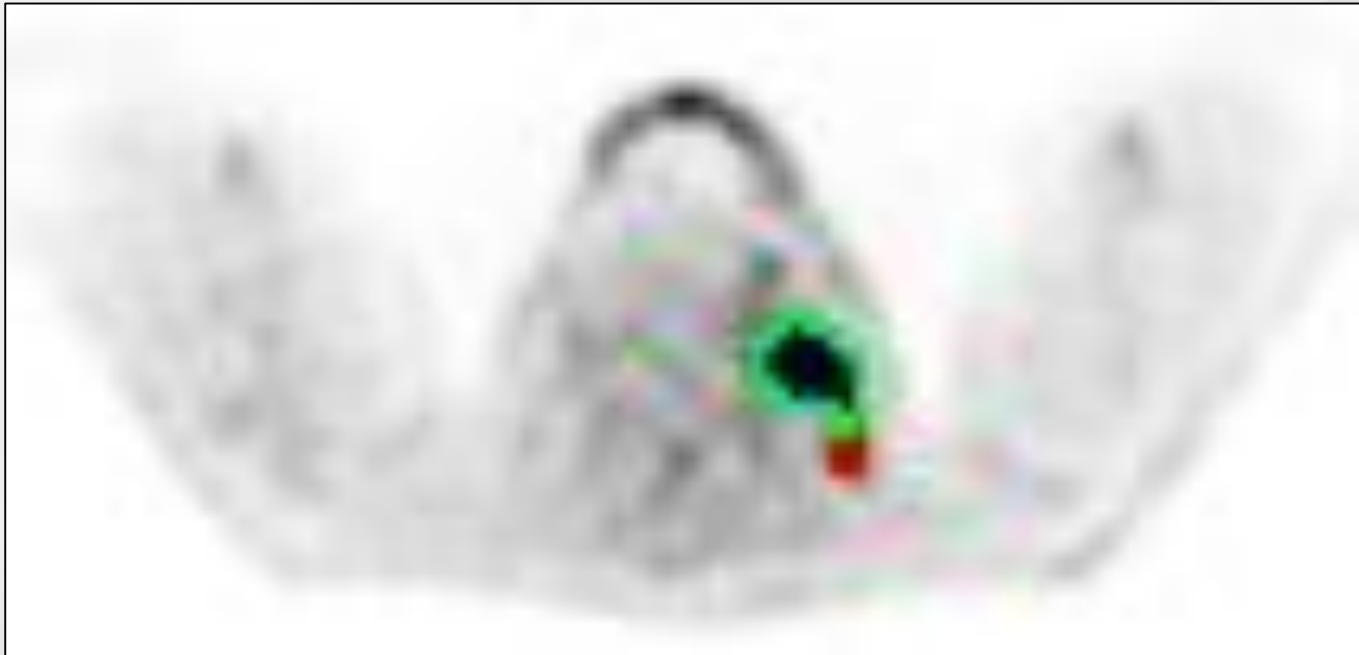
Conclusions:

- Benchmarking of features is recommended: high initial differences
- Standard values found for most features

➤ Dépendence à la segmentation



- **Dépendence à la segmentation**

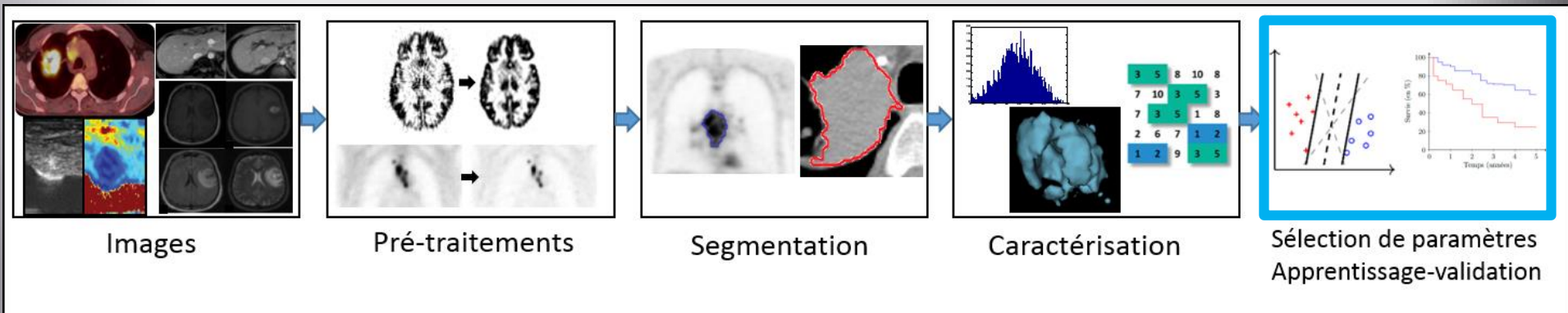


Lésion jugulocarotidienne gauche d'un lymphome du manteau

Rouge : FLAB

Bleu : 40%

Vert : SUV 2.5



Problèmes dans les analyses statistiques

Table 1. Statistical characteristics of the selected studies divided in three categories: A) Studies with multiple hypotheses testing only, B) studies employing both multiple hypothesis testing and the optimum cut-off approach and C) studies with multiple hypothesis testing, with or without the optimum cut-off approach, but with validation analysis.

Category	Study	Multivariate analysis included	volume	Optimum cut-off	Type I error adjustment	Validation dataset	cross correlation reported	Sample size	Hypotheses tested
A	Willaime [19]	Not applicable		No/Mean	No	No	Yes	12	68
	El Naqa [31]	NI*		Not clear	No	No	No	14/9	19
	Tixier [33]	NI		Not clear	No	No	Yes	41	54
	Yip [41]	No		No/Median	Yes [#]	No	No	36	90
B	Miles [30]	No		Yes	No	No	No	48	10
	Goh [32]	No		Yes	No	No	No	39	24
	Cook [29]	No		Yes	No	No	Yes	53	30
	Ganeshan [28]	No		Yes	No	No	Yes	21	15
	Ganeshan [34]	No		Yes	No	No	No	54	8
	Ng [36]	No		Yes	No	No	Yes	55	25
	Zhang [40]	Yes		Yes	No	No	No	72	40
	Cheng [39]	Yes		Yes	No	No	Yes	70	59 [†]
	C	Vaidya [35]	Yes		No	No	LOOCV [†]	No	27
Win [37]		No		Yes	No	Yes	No	66	12
Ravanelli [38]		No		No/Median	No	LOOCV	No	53	16

* No information provided

[#]For multiple hypotheses tested

[†]Leave one out cross validation

[‡] Number is a conservative approximation due to the difficulty establishing the exact number of hypotheses tested

➤ Segmentation TEP

- Beaucoup de progrès en 10 ans
- Très nombreuses méthodes, validation médiocre
- Peu d'outils performants disponibles en clinique
- Benchmark et standardisation en cours
- Besoin de précision / robustesse dépendant de l'application et des objectifs

➤ Segmentation TEP/TDM

- De nombreuses méthodes déjà publiées
- Efforts de validation/standardisation pas au niveau de la TEP seule

➤ Radiomique

- Domaine très dynamique
- Enormément de difficultés méthodologiques, en particulier sur les textures
- Pas de standardisation
- Validation statistique difficile (machine learning)

➤ Evolutions futures

- Standardisation (en cours)
- Grandes études multicentriques prospectives
- Apprentissage automatique (profond)



Merci pour votre attention





Diapos supplémentaires



2007 : l'ère de la segmentation d'images

Eur J Nucl Med Mol Imaging (2007) 34:1427–1438
DOI 10.1007/s00259-006-0363-4

ORIGINAL ARTICLE

A gradient-based method for segmenting FDG-PET images: methodology and validation

Xavier Geets • John A. Lee • Anne Bol • Max Lonneux •
Vincent Grégoire

IOP PUBLISHING

PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. 52 (2007) 3467–3491

[doi:10.1088/0031-9155/52/12/010](https://doi.org/10.1088/0031-9155/52/12/010)

Fuzzy hidden Markov chains segmentation for volume determination and quantitation in PET

M Hatt¹, F Lamare¹, N Boussion¹, A Turzo^{1,2}, C Collet³, F Salzenstein⁴,
C Roux^{1,5}, P Jarritt⁶, K Carson⁶, C Cheze-Le Rest^{1,2} and D Visvikis¹

► Potentiel discriminant

1^{er} ordre
(histogrammes)

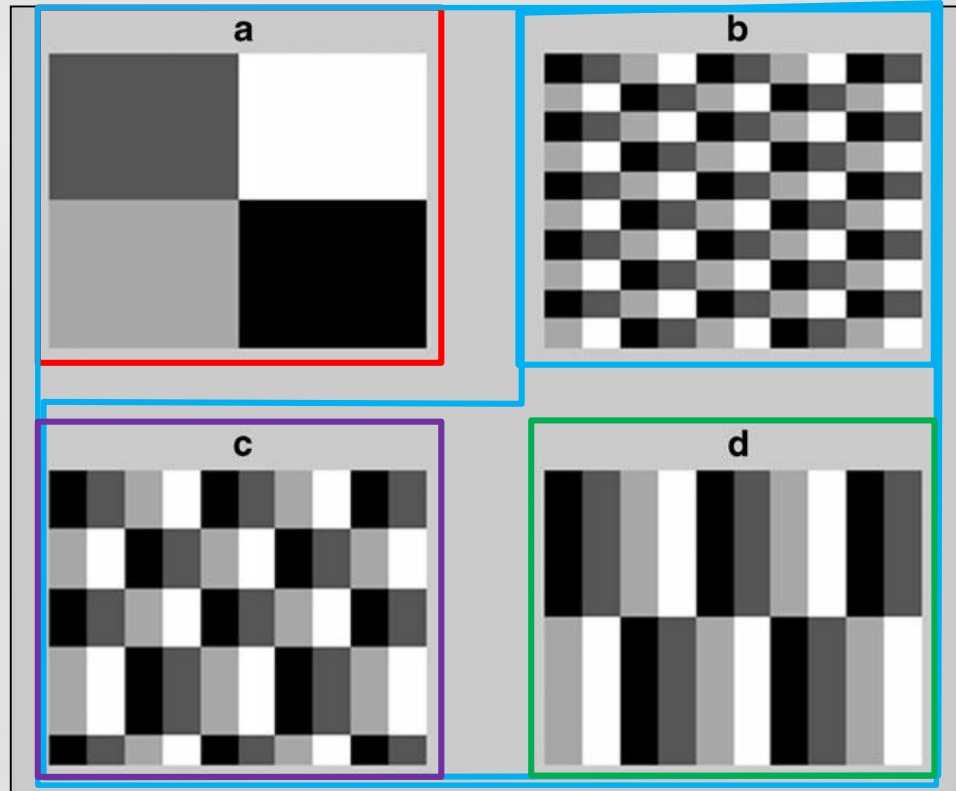
$$a = b = c = d$$

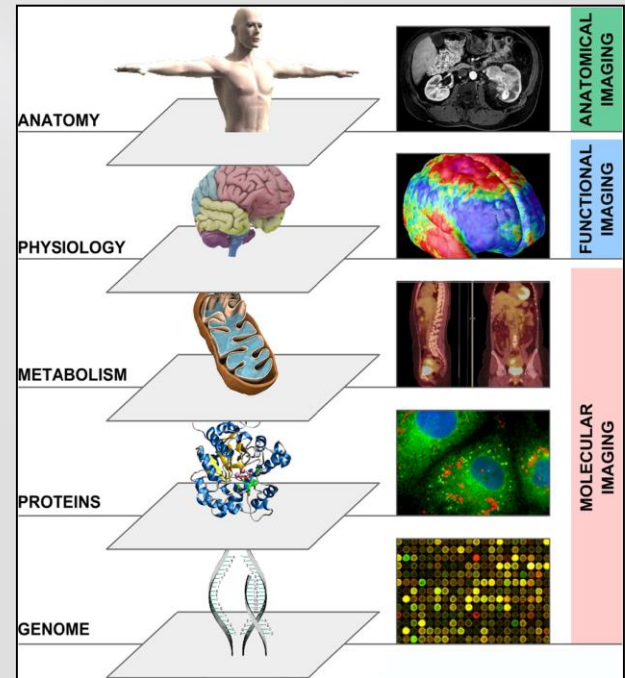
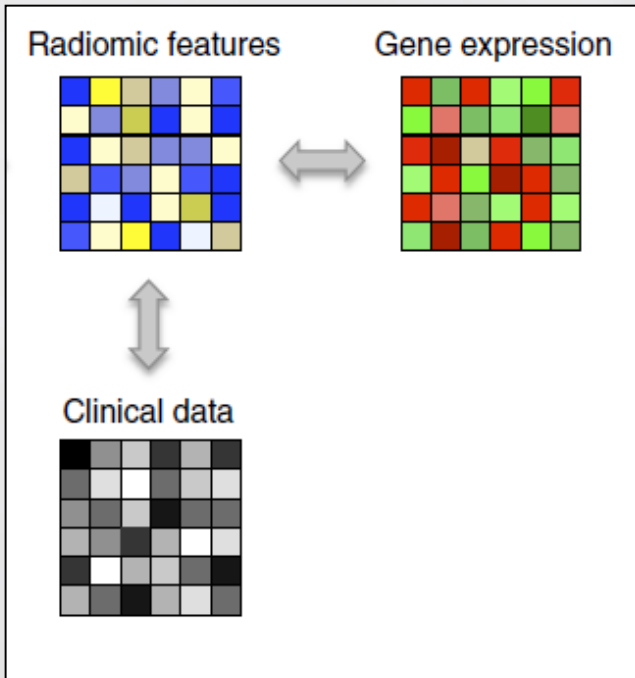
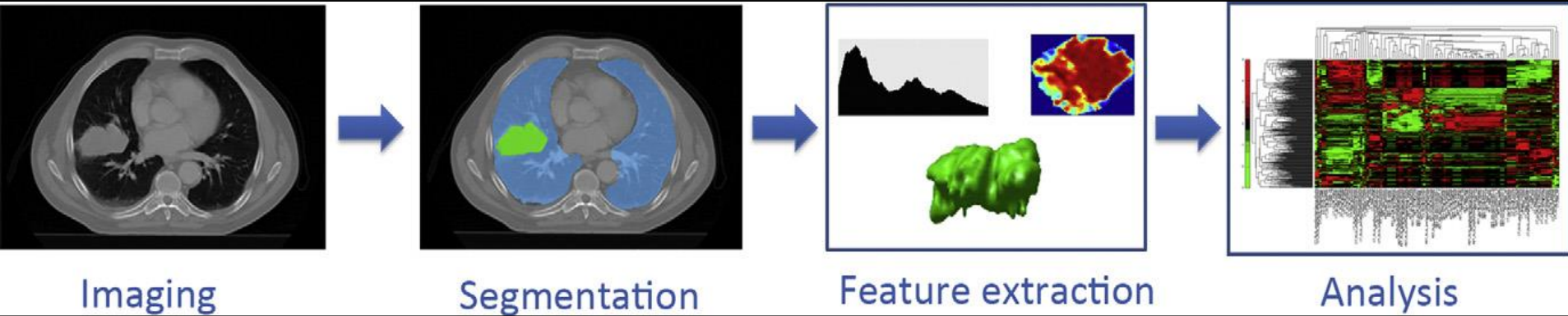
2^{ème} ordre
(voisinages)

$$a \# (b = c = d)$$

3^{ème} ordre
(groupes de pixels)

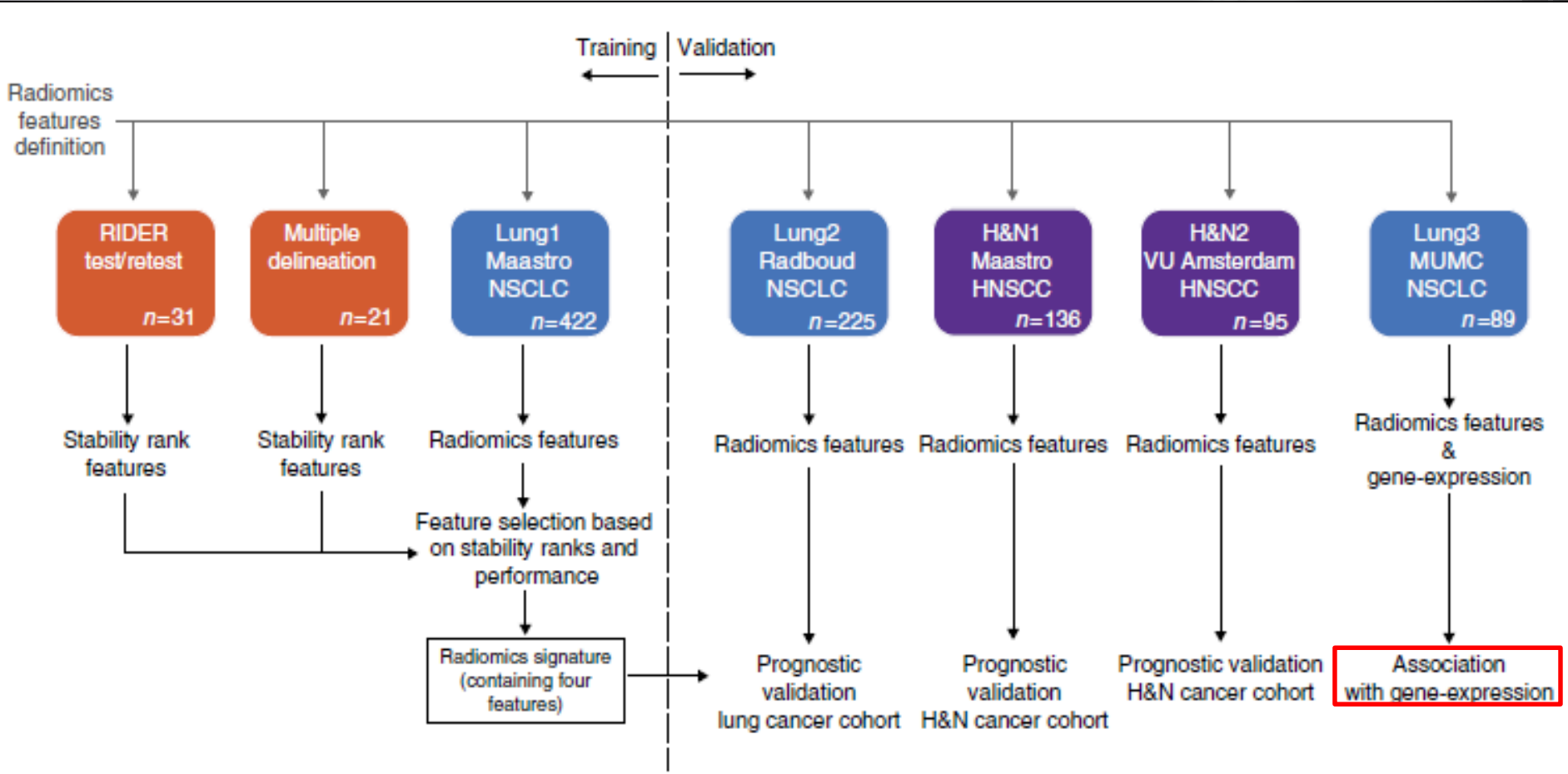
$$a \# b \# c \# d$$

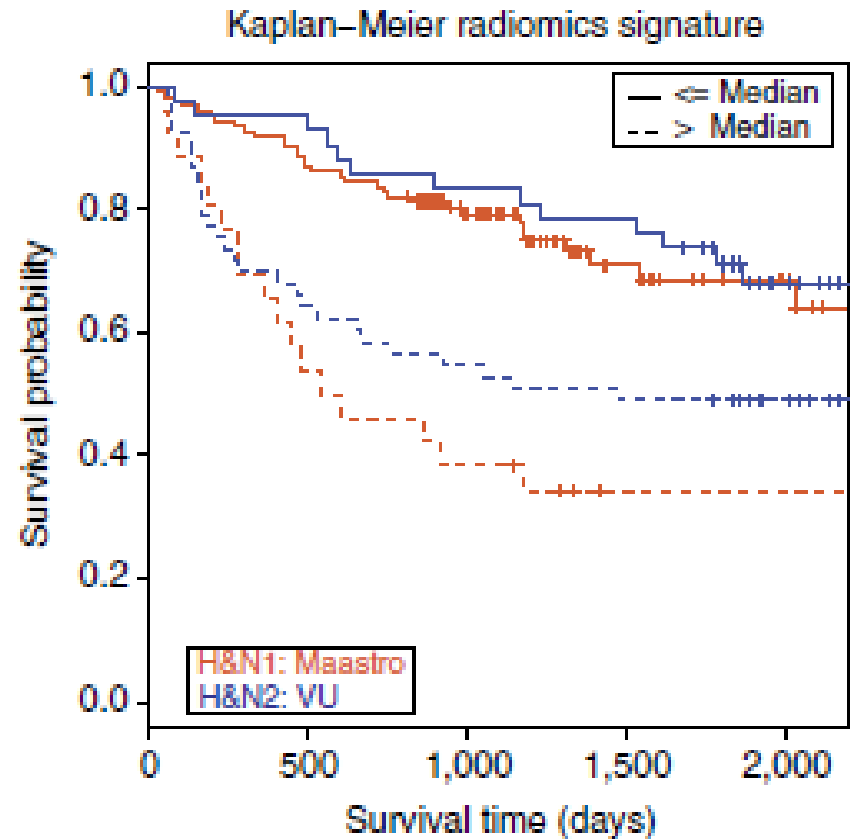
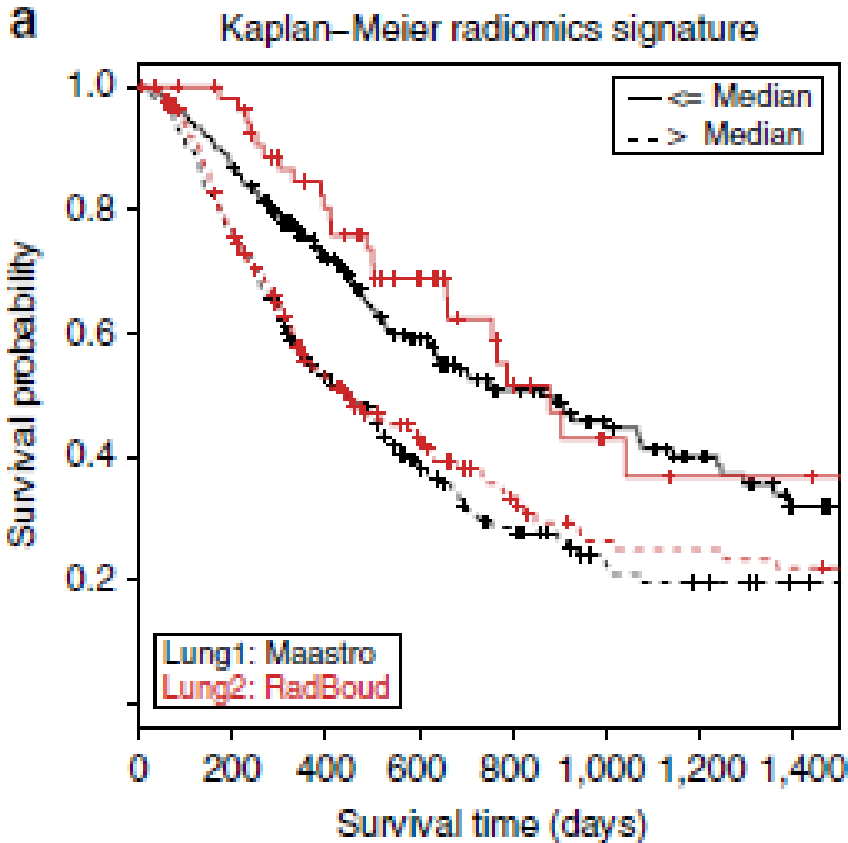


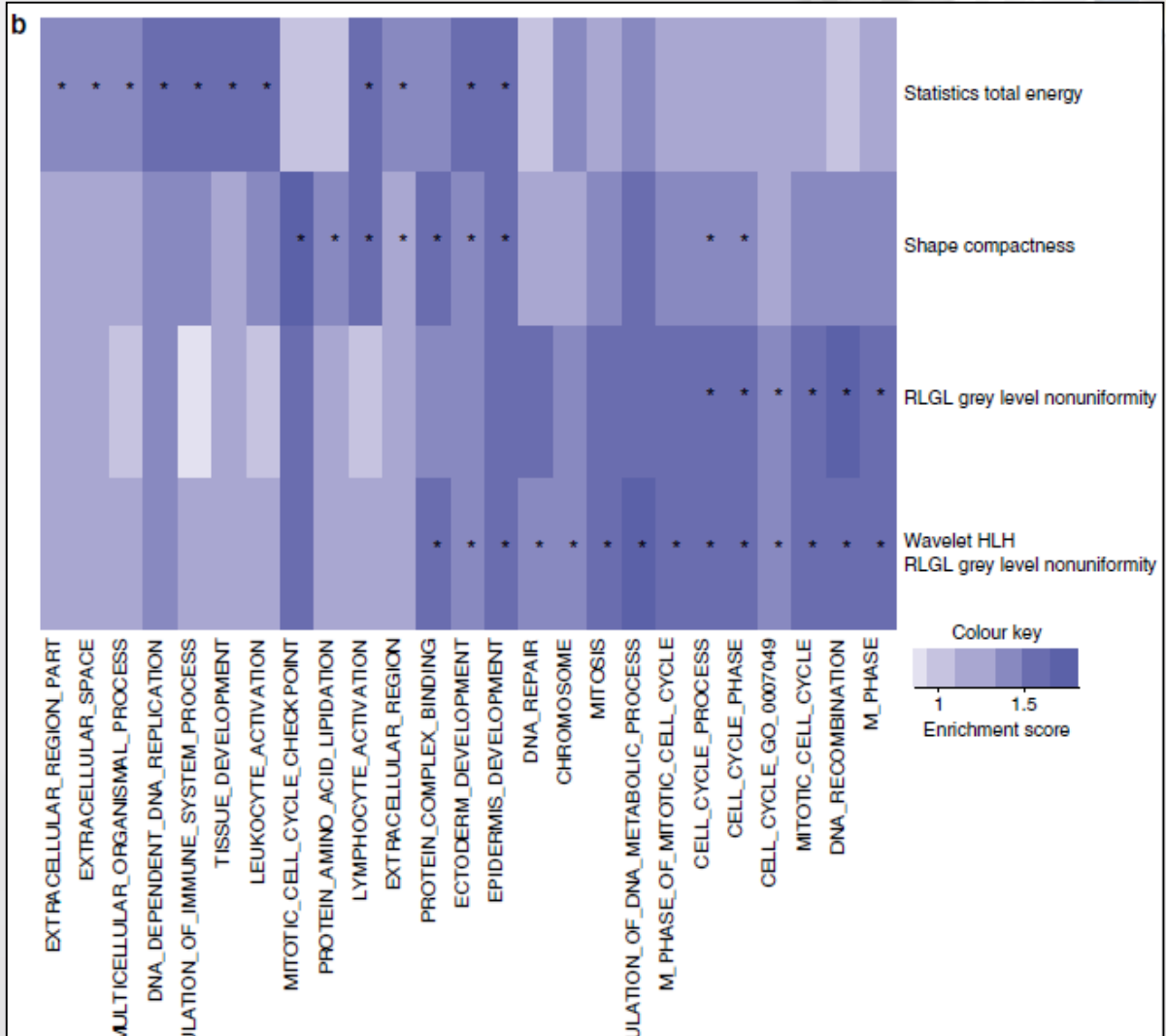


P Lambin, *et al.* Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012

HJ. Aerts, *et al.* Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun.* 2014



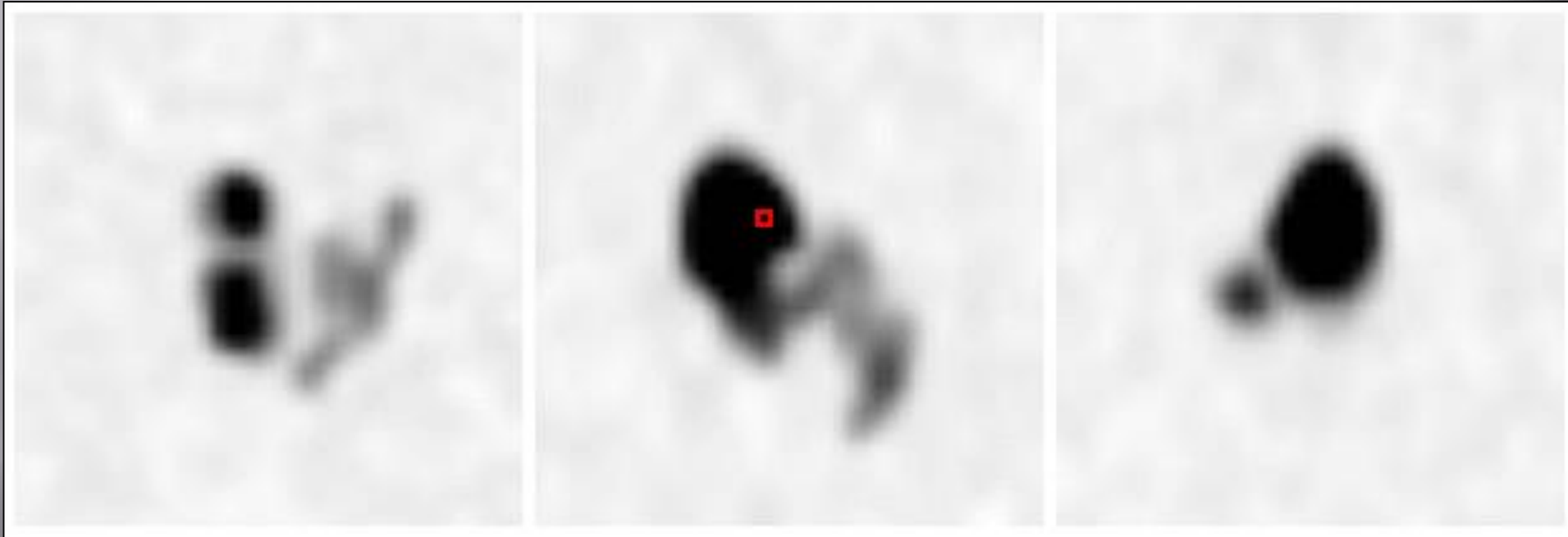




HJ. Aerts, *et al.* Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun.* 2014



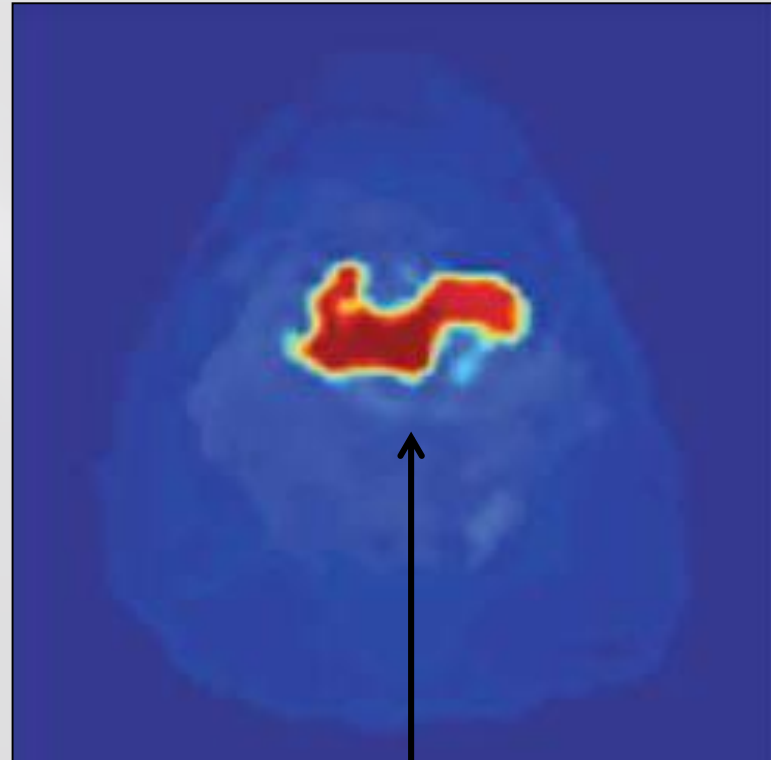
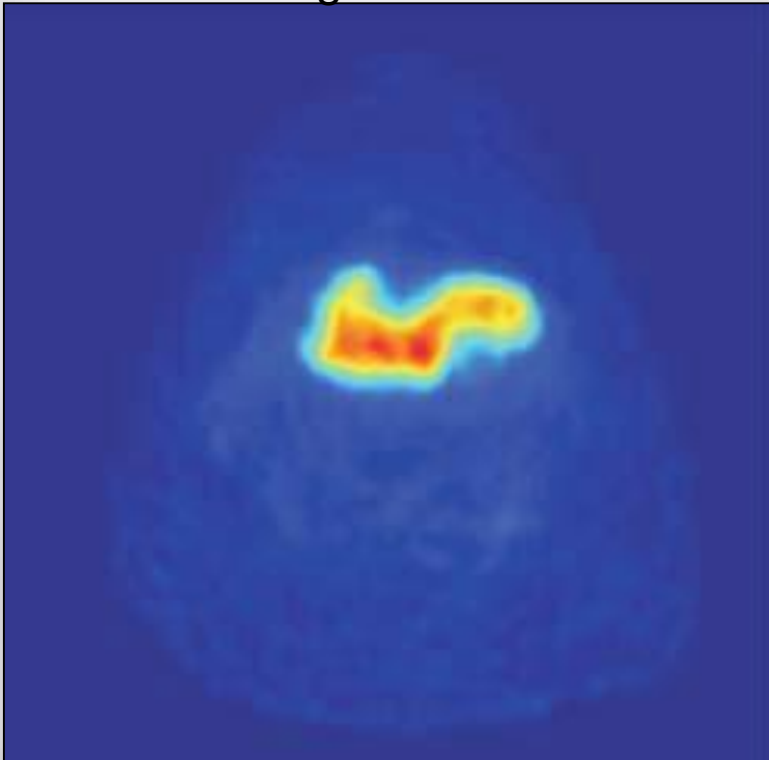
- Examples: ROVER method



► **Examples: gradient-based**

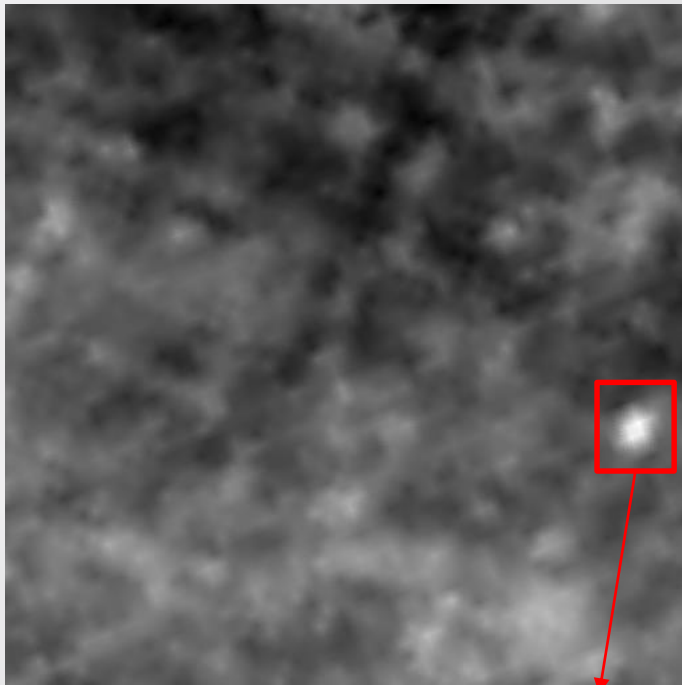
+ bilateral filtering
+ iterative deconvolution

Original PET



Contours detection

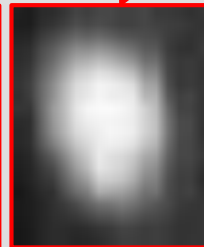
Examples: FLAB



Nebula



¹⁸F-FDG PET



Hatt, *et al.* A fuzzy locally adaptive Bayesian segmentation approach for volume determination in PET. *IEEE Trans Med Imaging*. 2009

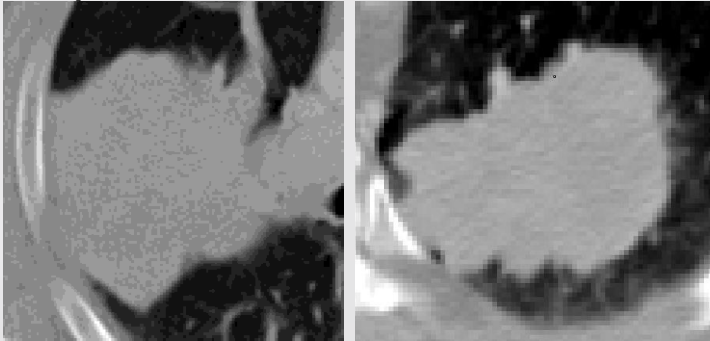
Hatt, *et al.* Accurate automatic delineation of heterogeneous functional volumes in positron emission tomography for oncology applications. *Int J Radiat Oncol Biol Phys*. 2010

Examples: FLAB

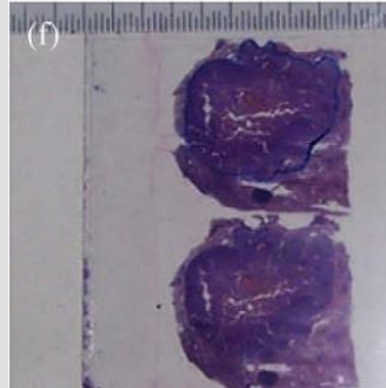
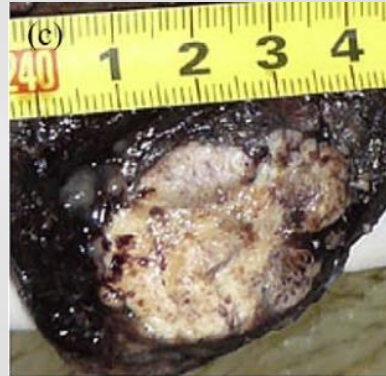
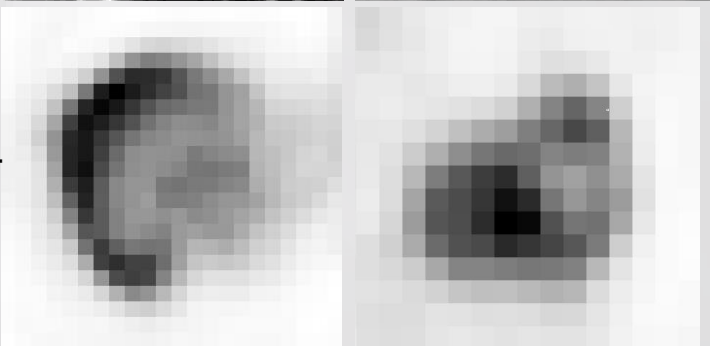
18 clinical NSCLC tumors with histopathology

- ✓ max diameter: 12-90 mm
- ✓ Heterogeneity: variable
- ✓ Shapes: variable

CT



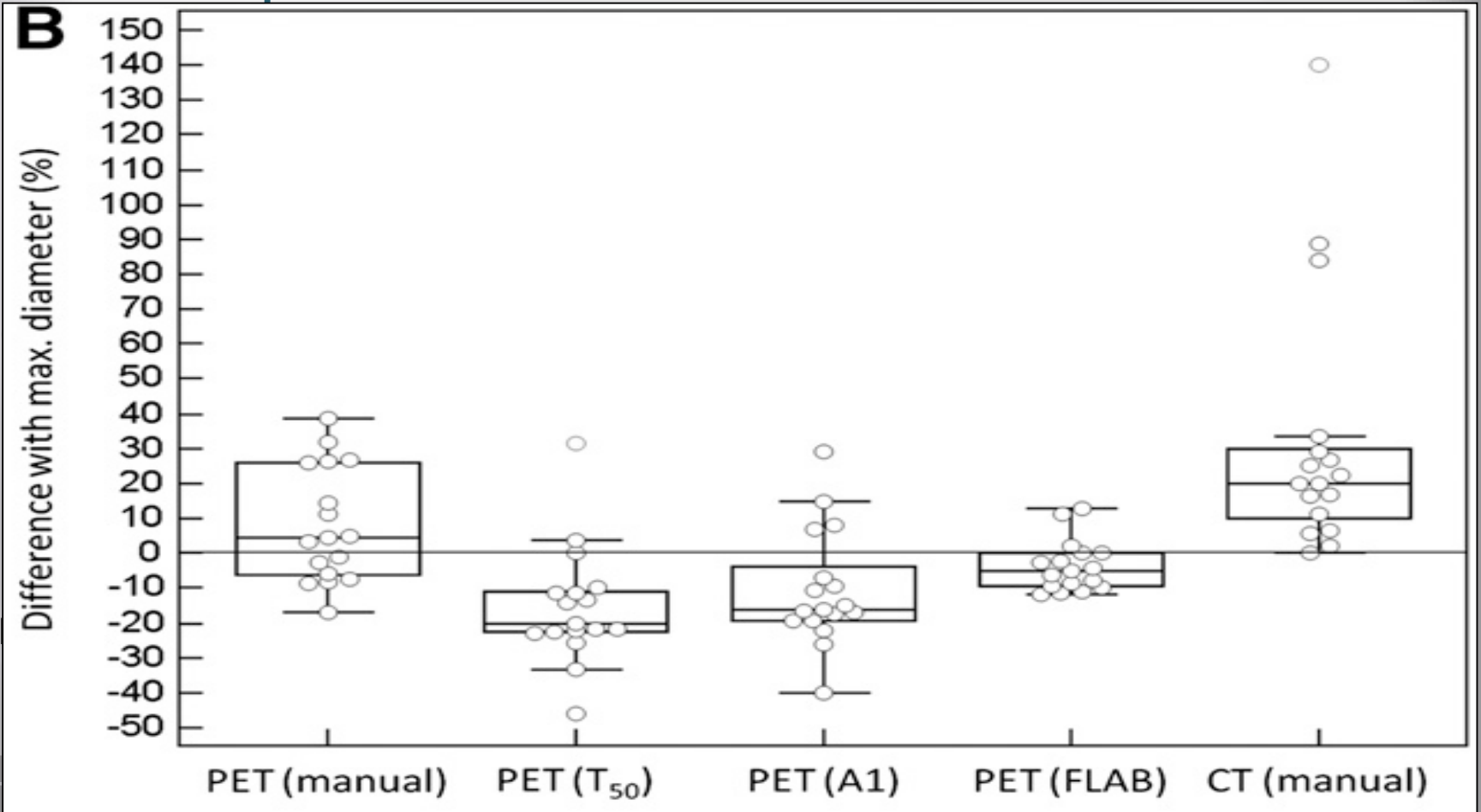
PET



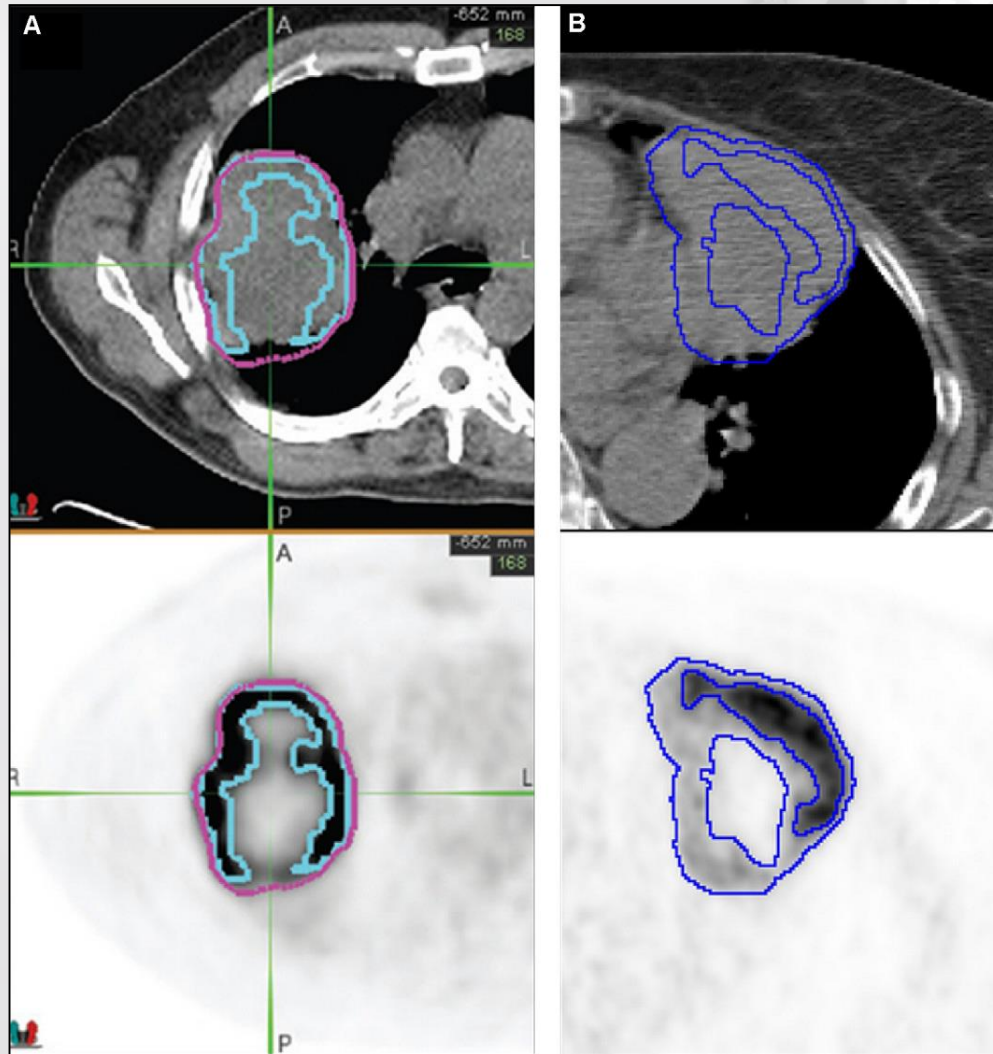
van Baardwijk et al,
*International Journal of
Radiation Oncology Biology
Physics*, 2007



Examples: FLAB



Comparison between FLAB and gradient-based



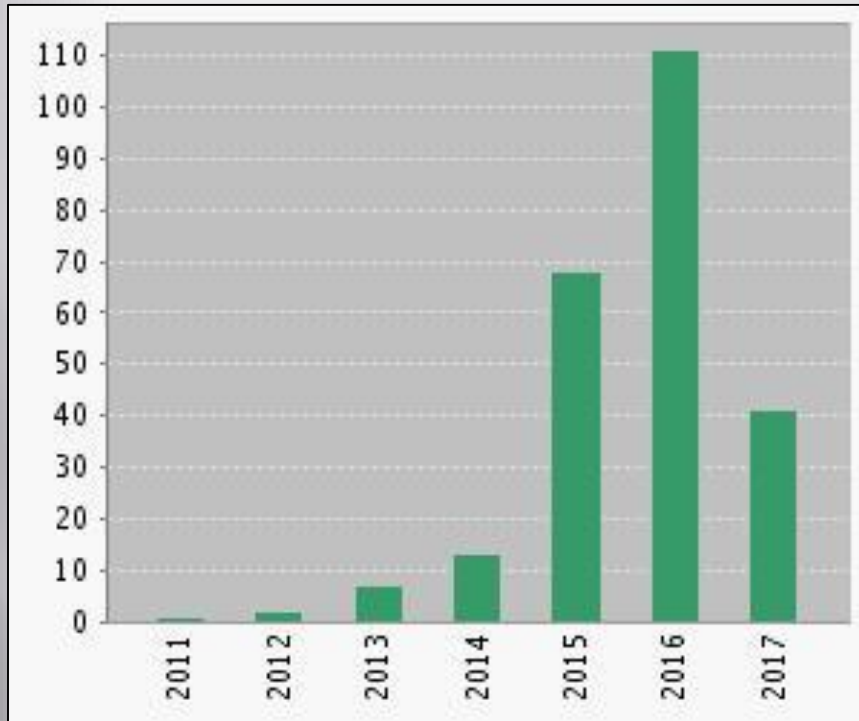
Hatt, *et al.* Metabolically active volumes automatic delineation methodologies in PET imaging: Review and perspectives. *Cancer Radiother* 2011

➤ Problèmes de nomenclature

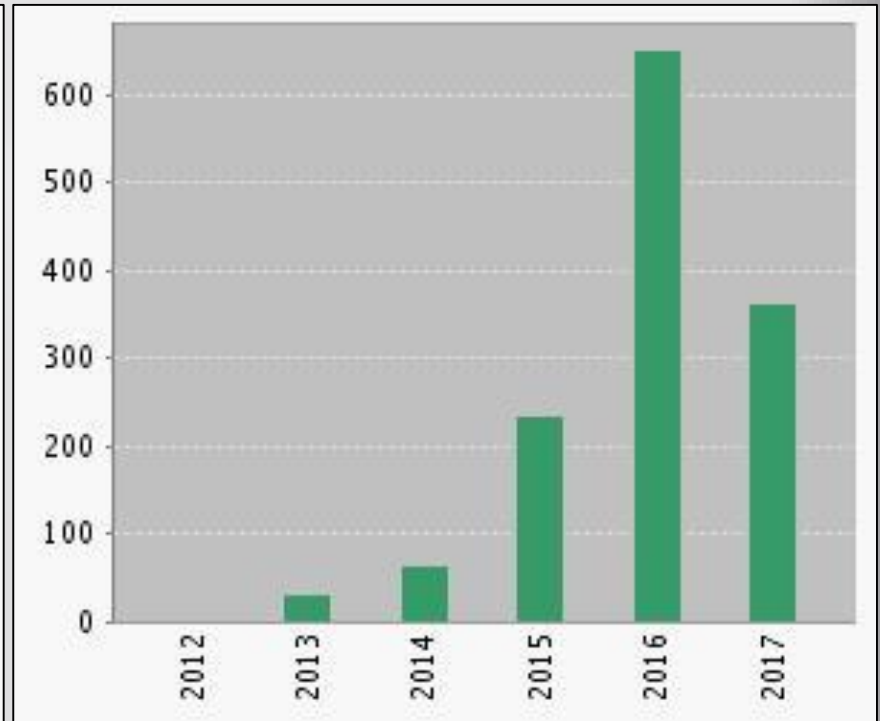
Parameter	AUC	95% confidence interval
SUV _{max}	0.52	0.32–0.71
Skewness	0.55	0.33–0.75
Kurtosis	0.61	0.39–0.81
SUV _{mean}	0.68	0.48–0.85
Diameter	0.68	0.48–0.85
COV	0.73	0.53–0.88
Volume	0.75	0.55–0.90
TLG	0.79	0.59–0.92

Radiomics : 243 publications recensées au 16/05/2017

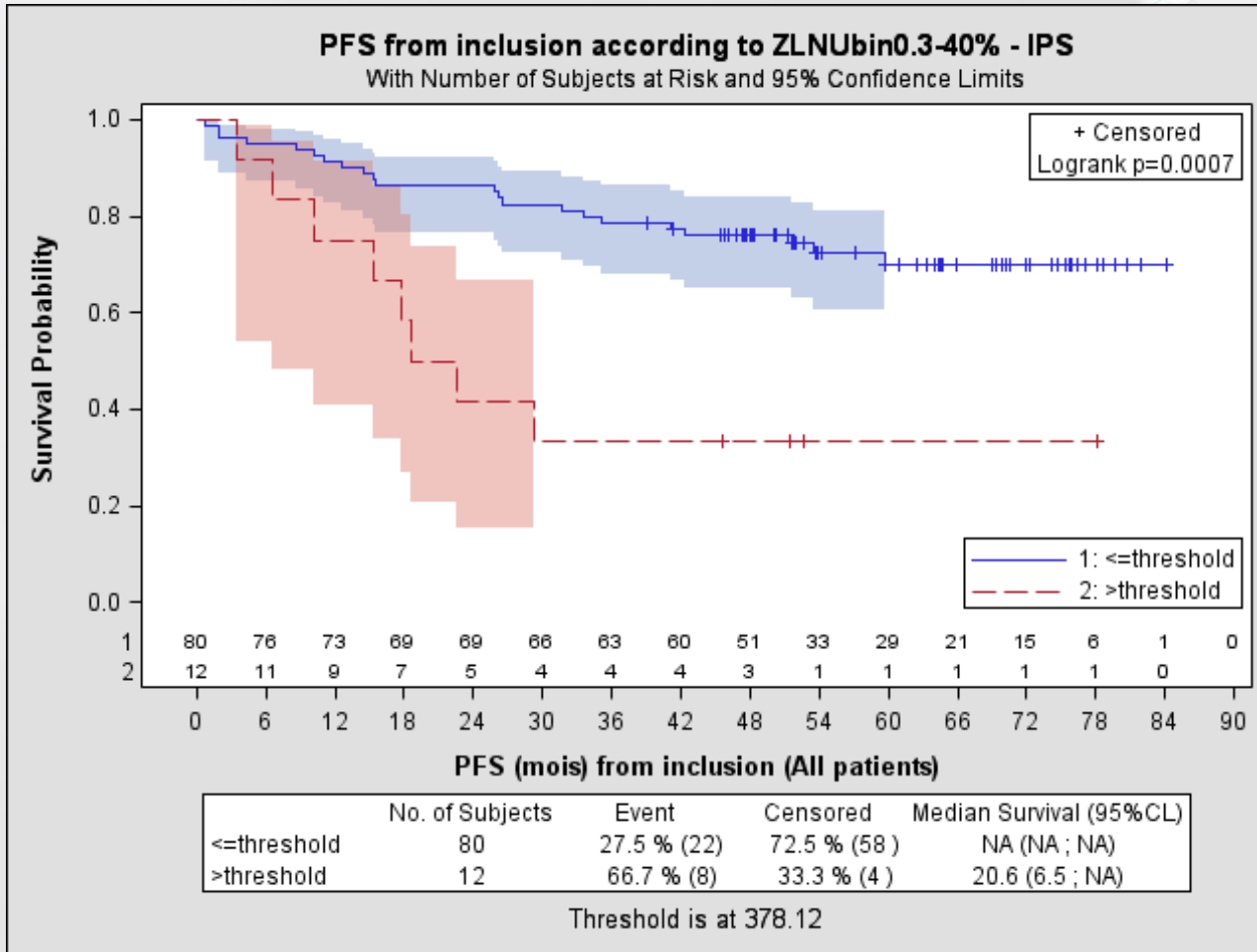
Nombre de publications



Nombre de citations



Texture TEP et survie



3D geometrical shape:

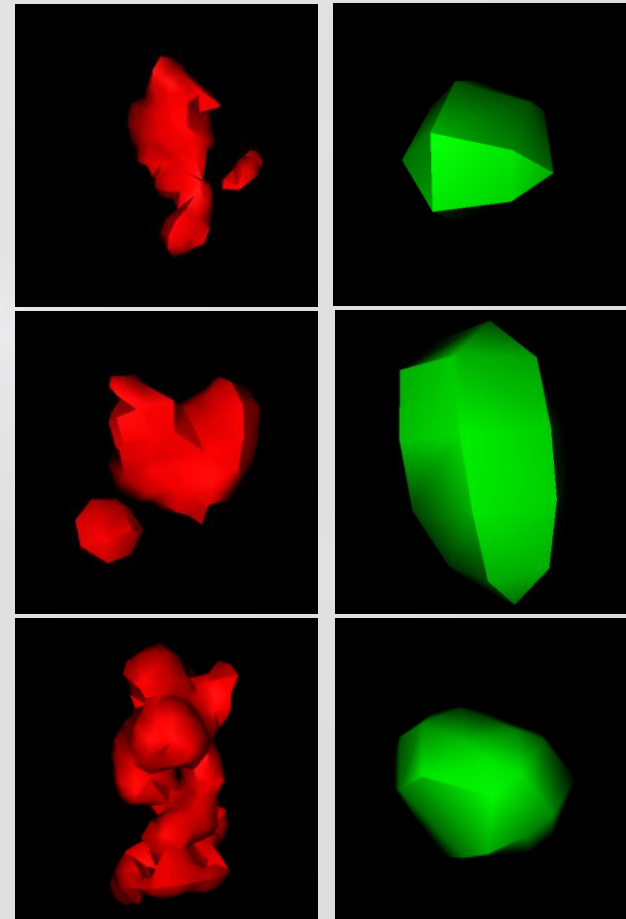
$$\text{Solidity} = \frac{\text{Volume}}{\text{Convex Hull volume}}$$

$$\text{Rectangularity} = \frac{\text{Volume}}{\text{Min bounding box volume}}$$

$$\text{Sphericity} = \frac{\sqrt[3]{36 \pi \text{Volume}^2}}{\text{Surface}}$$

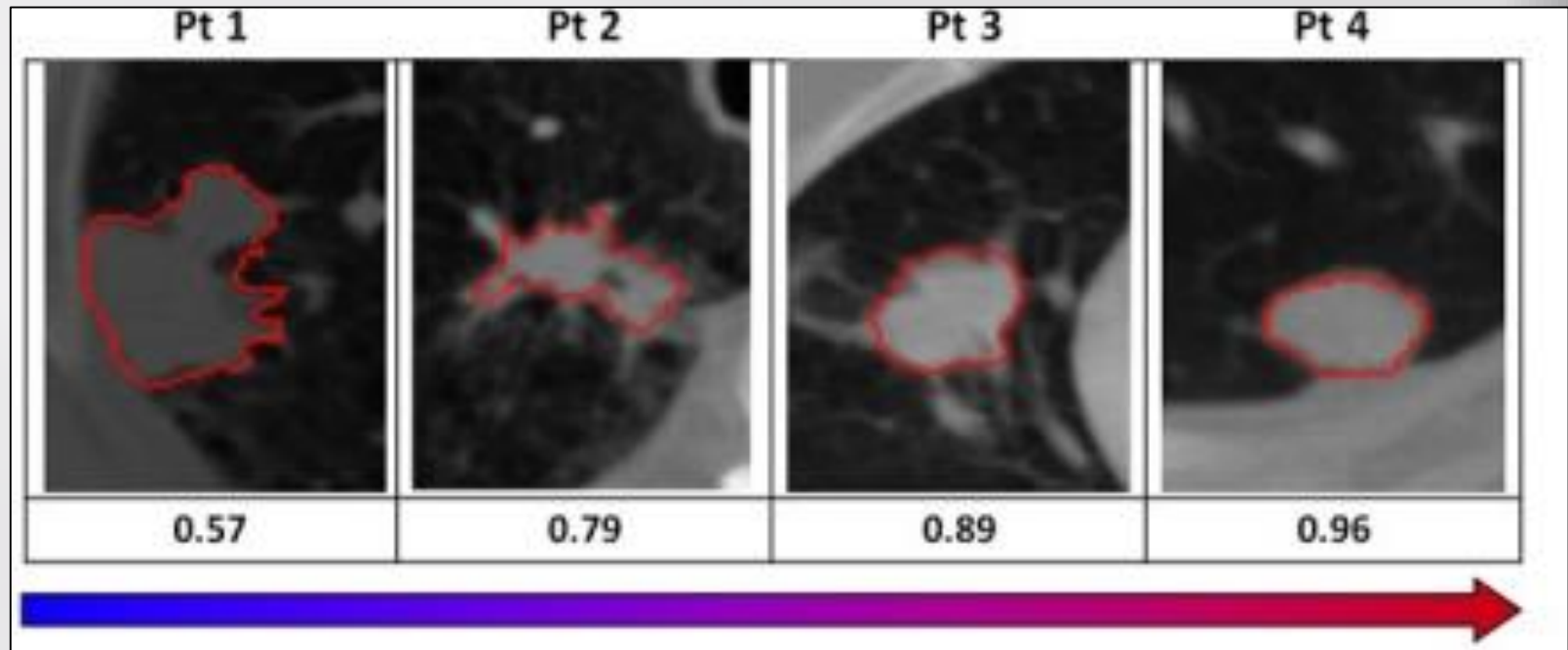
Low

High



- 3D geometrical shape:

Images TDM



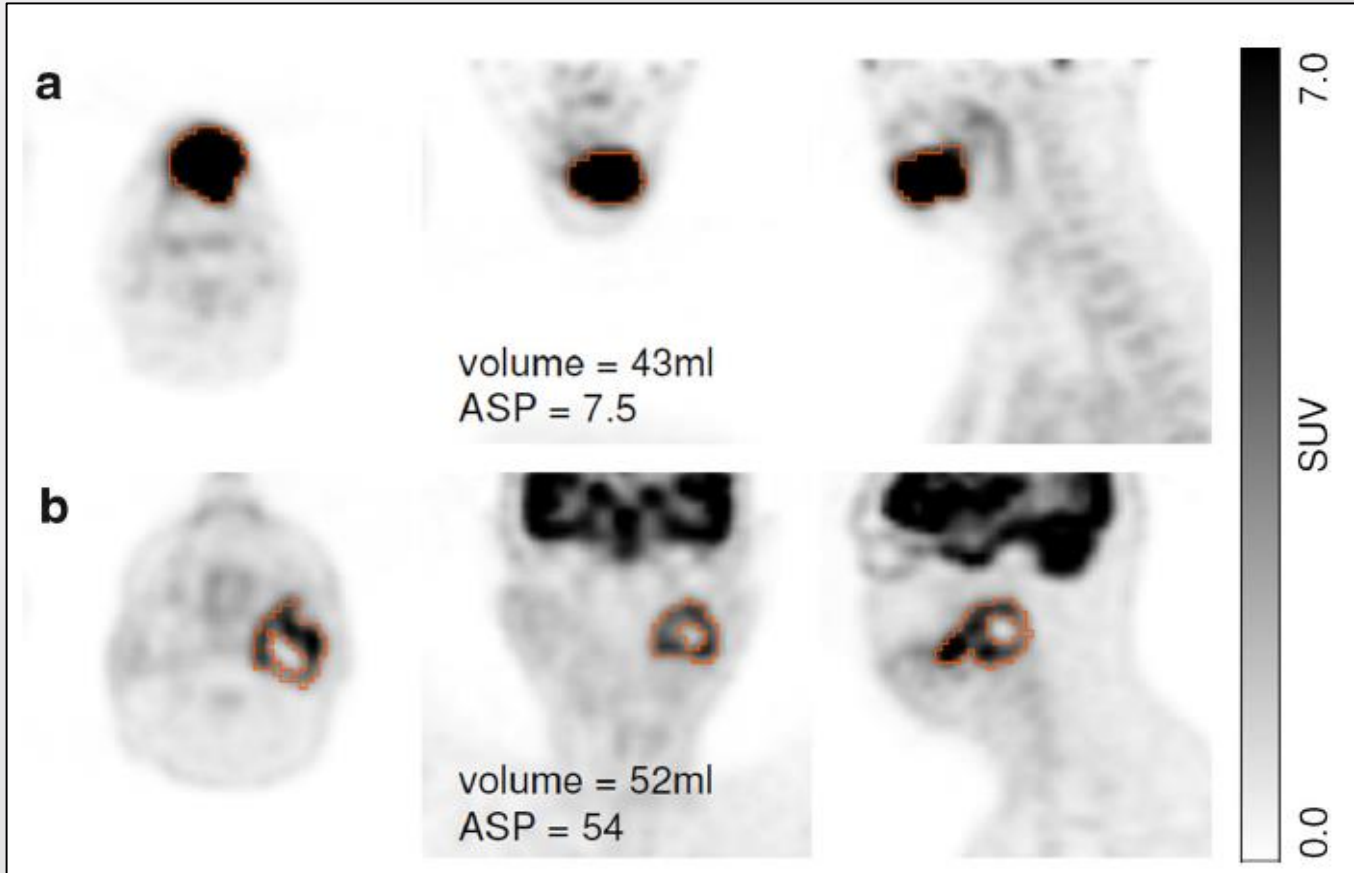
Convexity

O. Grove, *et al.* Quantitative computed tomographic descriptors associate tumor shape complexity and intratumor heterogeneity with prognosis in lung adenocarcinoma.

PLOS ONE 2015

Forme 3D

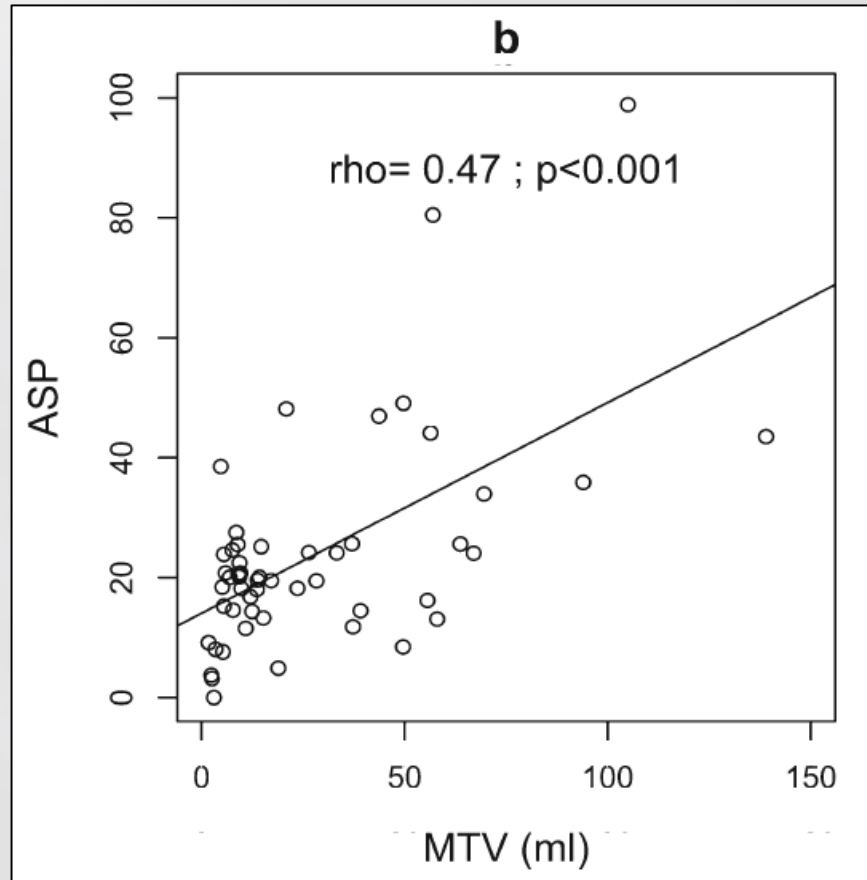
- Sphéricité



I. Apostolova, *et al.* Asphericity of pretherapeutic tumour FDG uptake provides independent prognostic value in head-and-neck cancer. *Eur Radiol.* 2014

► Forme 3D

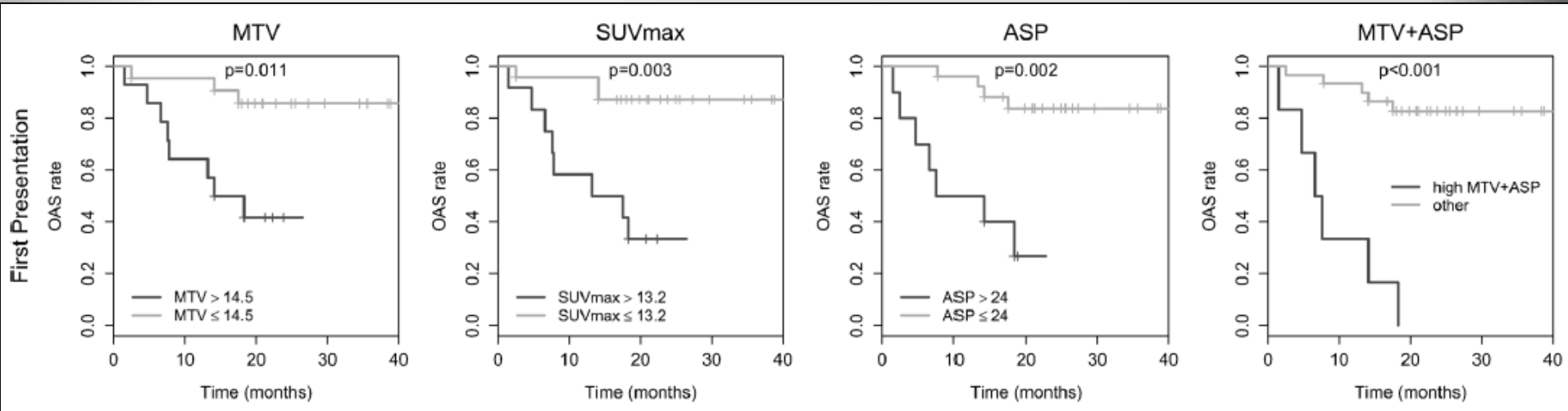
- Sphéricité



I. Apostolova, *et al.* Asphericity of pretherapeutic tumour FDG uptake provides independent prognostic value in head-and-neck cancer. *Eur Radiol.* 2014

► **Forme 3D**

- Sphéricité

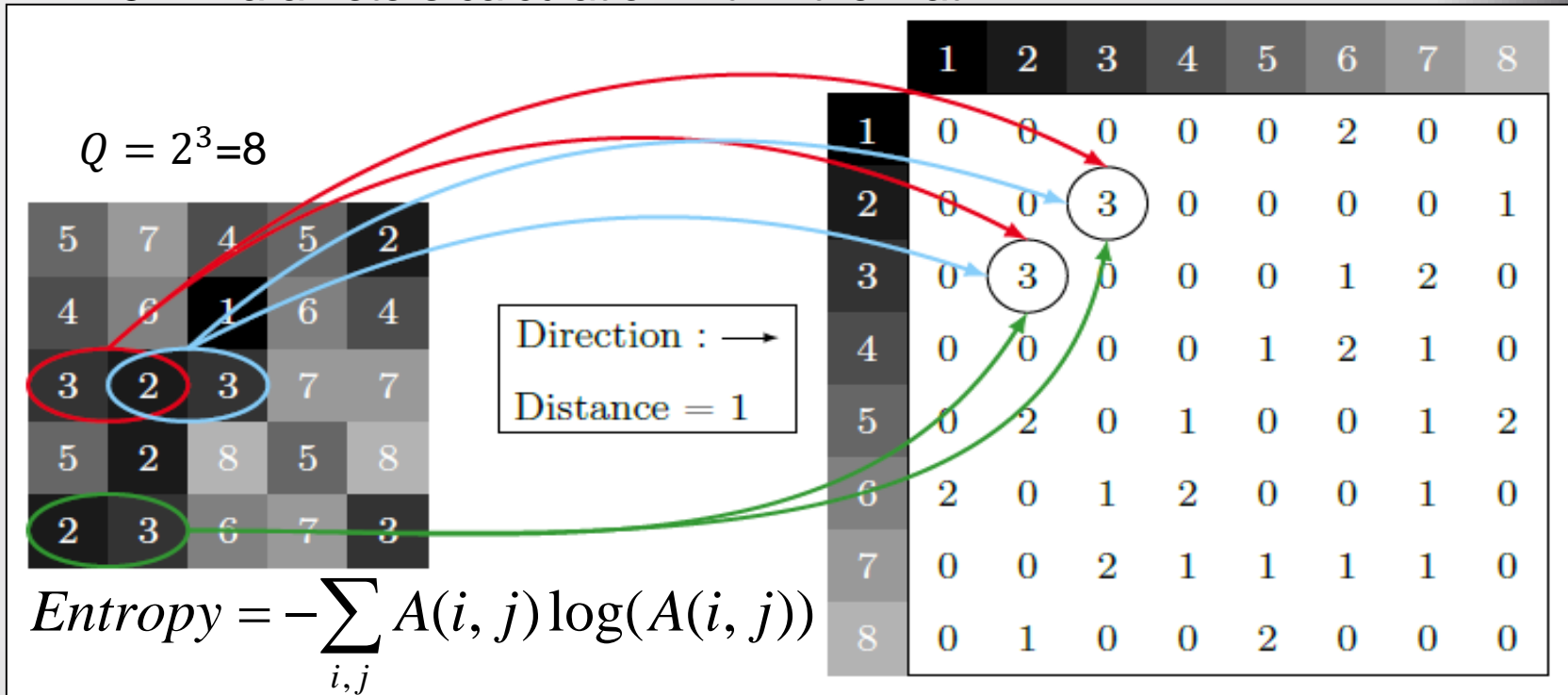


I. Apostolova, *et al.* Asphericity of pretherapeutic tumour FDG uptake provides independent prognostic value in head-and-neck cancer. *Eur Radiol.* 2014

◉ Numerous types of features exist

2nd order example: co-occurrence matrix

1. Necessary quantization ($Q = 2^n, n = 3,4,5,6,7$)
2. Matrix design and building (direction(s), distance...)
3. Parameters calculation within the matrix



➤ Numerous types of features exist

Increasing complexity and difficulty of interpretation

Versatility and potential

Order of textural feature	Description		Examples
First	Grey level frequency distribution from histogram analysis	Global	Minimum, mean and maximum intensity Standard deviation Skewness Kurtosis
Second	From spatial grey level dependence matrices	Local	Entropy Energy Contrast Homogeneity Dissimilarity Uniformity Correlation
Higher	From neighbourhood grey-tone difference matrices	Local	Coarseness Contrast Busyness Complexity
	From voxel alignment matrices	Regional	Run-length and emphasis Run-length variability
	From grey level size zone matrices	Regional	Zone emphasis Size-zone variability

Histogram analysis
No spatial info

Co-occurrence matrix
Local spatial info

Size-zone matrix
Regional spatial info

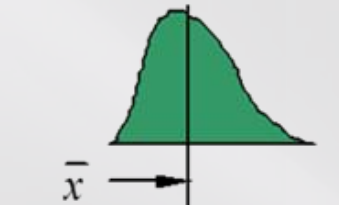


- Numerous types of features exist

1st order: histogram analysis

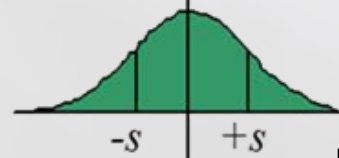
First Moment:

mean - measure of location



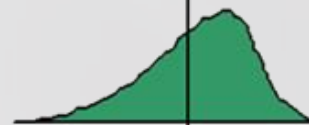
Second Moment:

Standard deviation - measure of spread



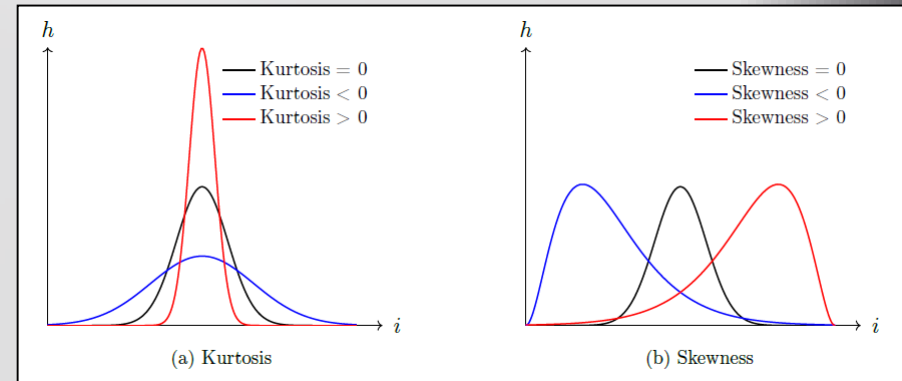
Third Moment:

skewness - measure of symmetry

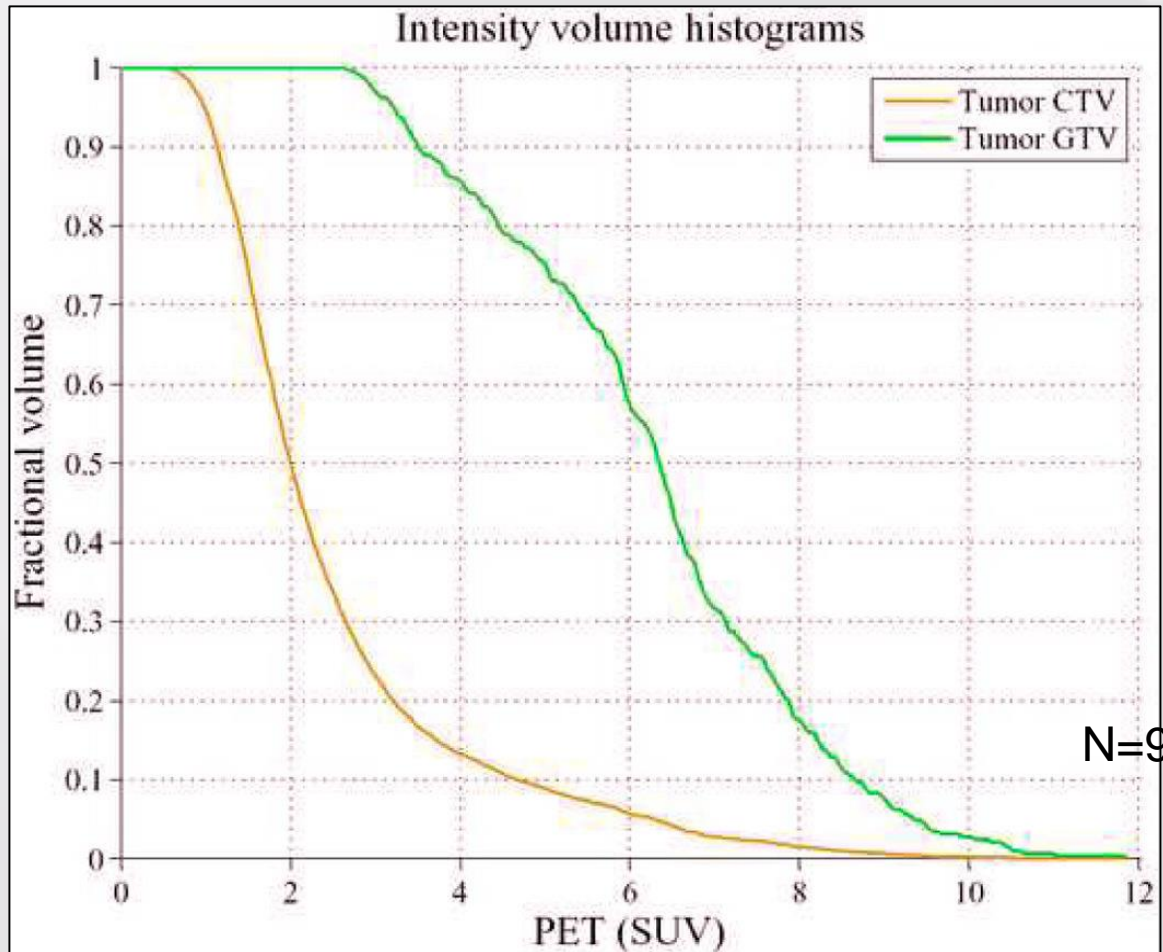


Fourth Moment:

kurtosis - measure of peakedness

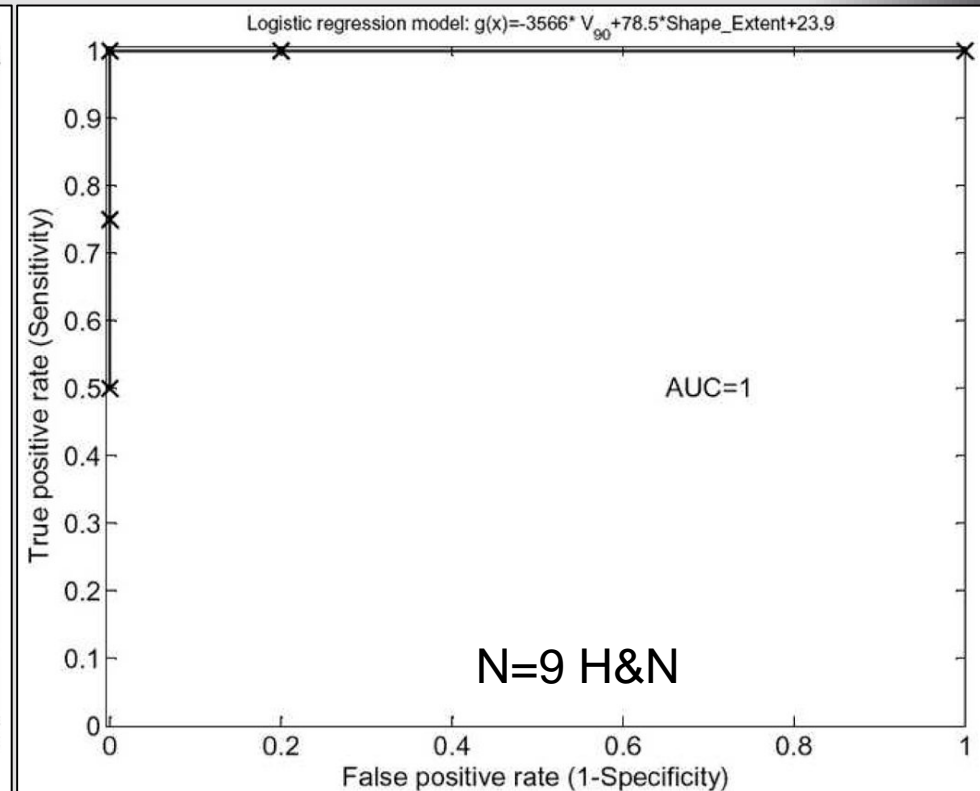
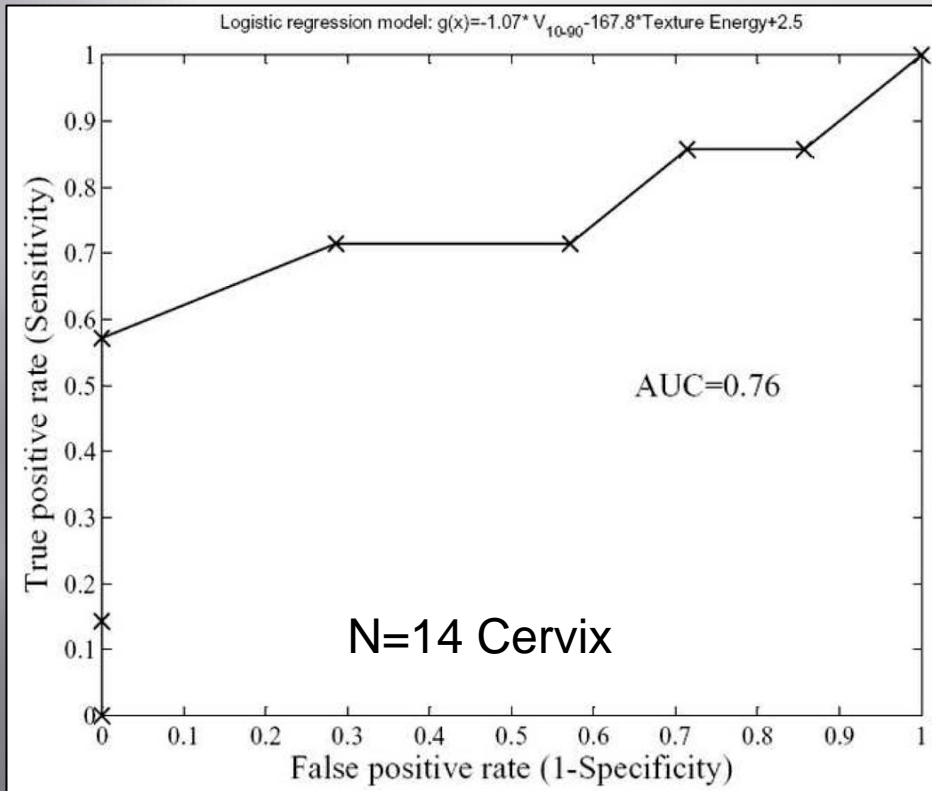


First papers





First papers

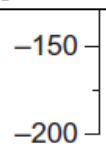




➤ First papers

Image #	Acq. Mode	Grid-Size	Recon. Alg	Iter. number	Post-filter width (mm)	Legend
1	2D	128×128	OSEM	2	3	2D-128-OSEM2-3mm
2	2D	128×128	OSEM	2	5	2D-128-OSEM2-5mm
3	2D	128×128	OSEM	4	5	2D-128-OSEM4-5mm
4	2D	256×256	OSEM	2	3	2D-256-OSEM2-3mm
5	2D	256×256	OSEM	2	5	2D-256-OSEM2-5mm
6	3D	128×128	ITER	2	3	3D-128-ITER2-3mm
7	3D	128×128	ITER	2	6	3D-128-ITER2-6mm
8	3D	128×128	ITER	4	6	3D-128-ITER4-6mm
9	3D	256×256	ITER	2	3	3D-256-ITER2-3mm
10	3D	256×256	ITER	2	6	3D-256-ITER2-6mm

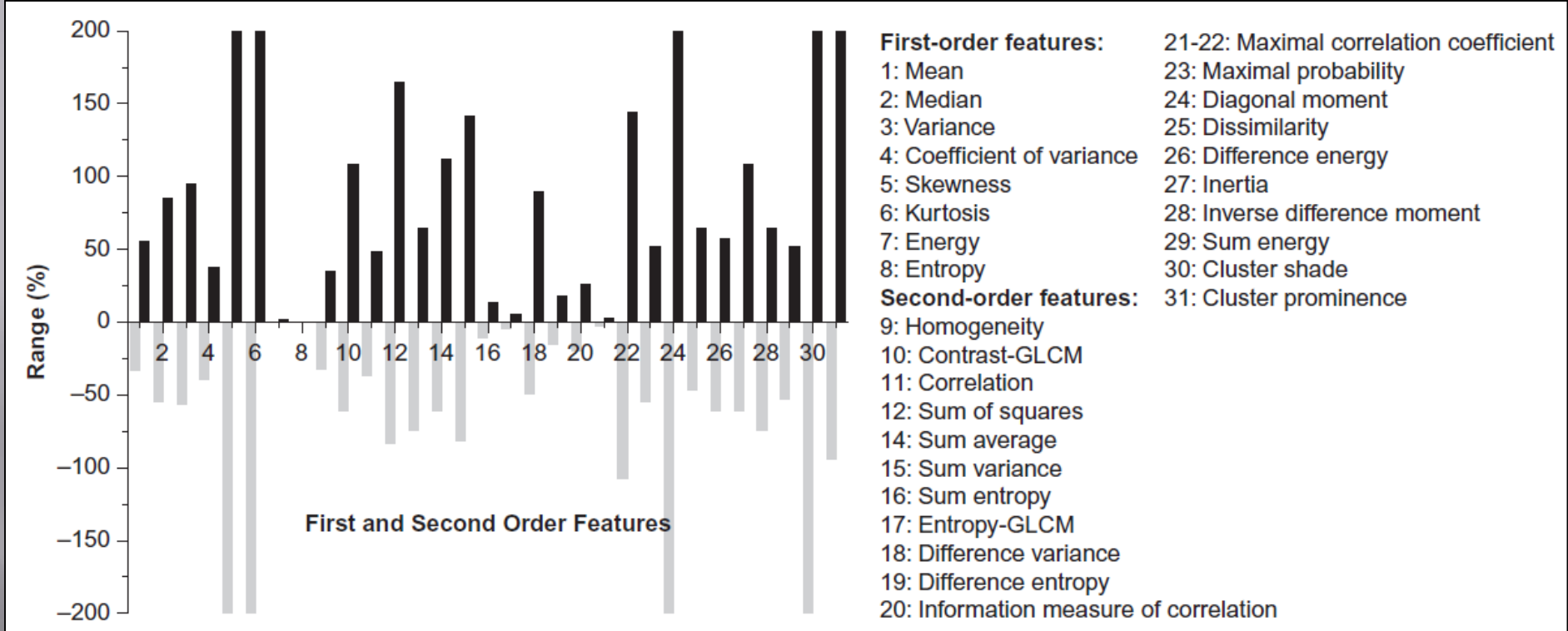
Acq. Mode = acquisition mode; Recon. Alg = reconstruction algorithm; Iter = iteration.



- 47: Entropy-NGL
- High Order Features (NGTD)
- 48: Coarseness
- 49: Contrast-NGL
- 50: Busyness

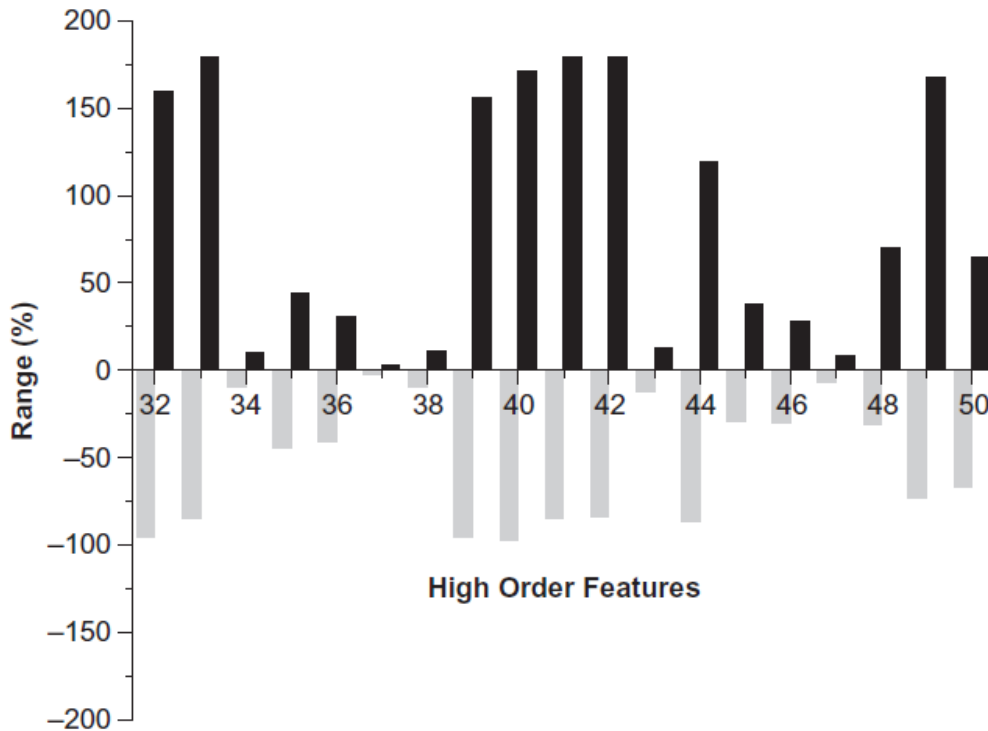


First papers





First papers



High Order Features (GLRL)

- 32: Short run emphasis
- 33: Long run emphasis
- 34: Gray-level nonuniformity
- 35: Run length nonuniformity
- 36: Run Percent
- 37: Low gray-level run emphasis
- 38: High gray-level run emphasis
- 39: Short run low gray-level emphasis
- 40: Short run high gray-level emphasis
- 41: Long run low gray-level emphasis
- 42: Long run high gray-level emphasis

High Order Features (NGL)

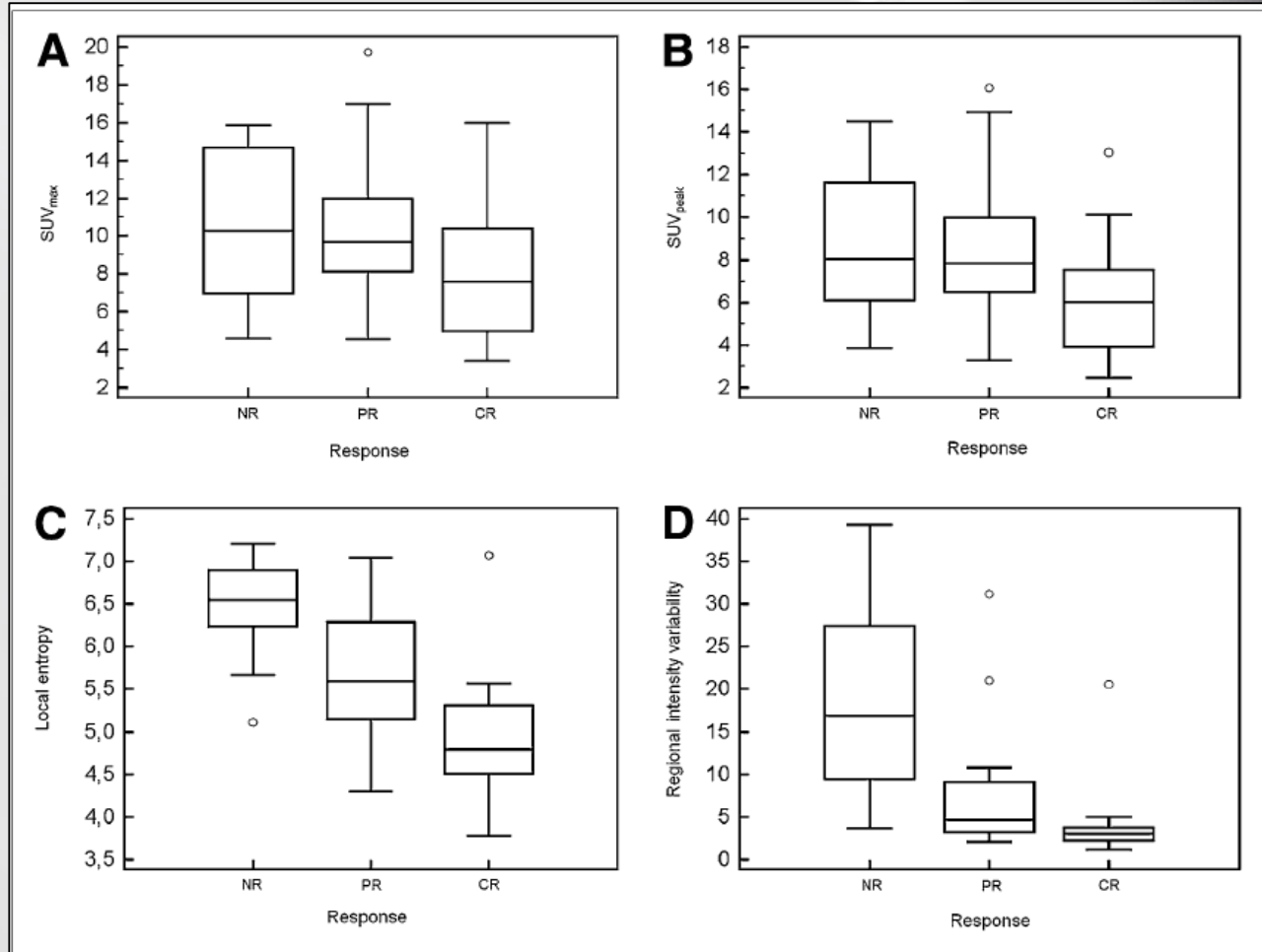
- 43: Small number emphasis
- 44: Large number emphasis
- 45: Number nonuniformity
- 46: Second moment
- 47: Entropy-NGL

High Order Features (NGTD)

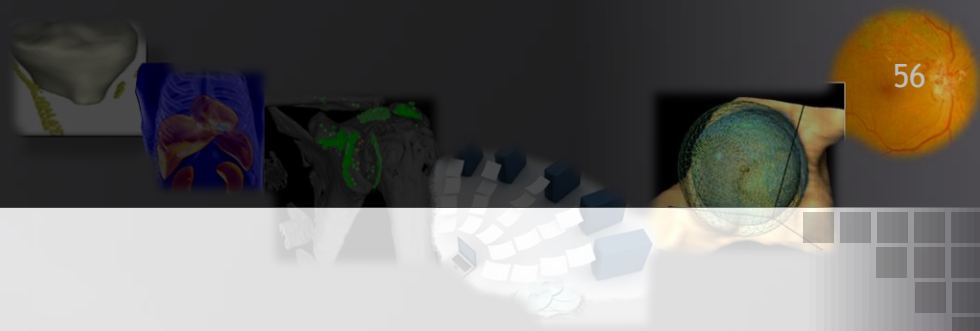
- 48: Coarseness
- 49: Contrast-NGL
- 50: Busyness

First papers

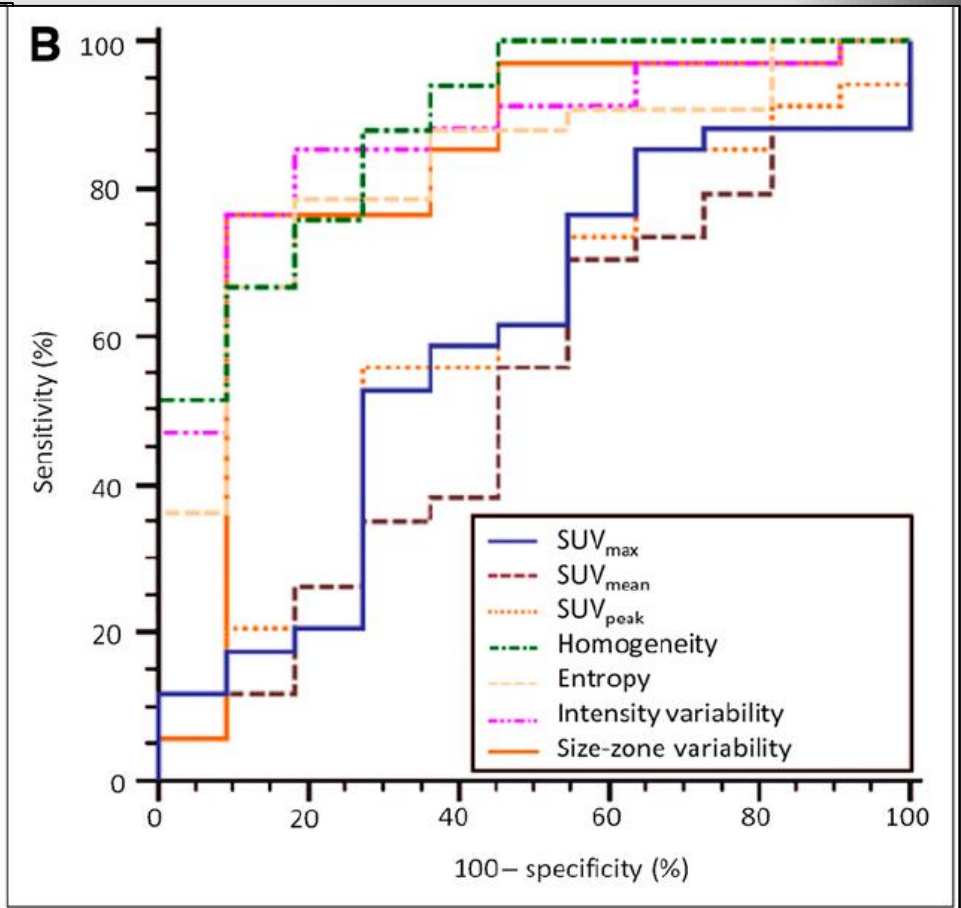
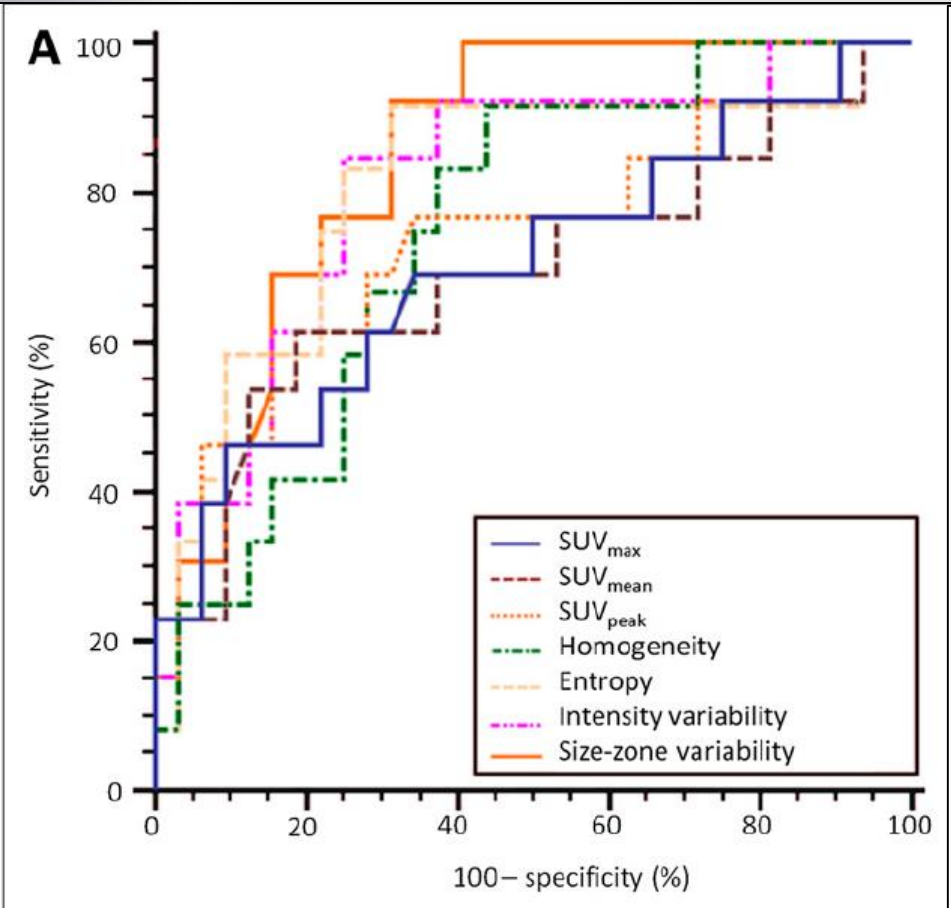
N=41 esophageal cancer



F. Tixier, *et al.* Intratumor heterogeneity characterized by textural features on baseline 18F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer. *J Nucl Med.* 2011 [Highly cited (>200), top 1%]



First papers



► >2011: numerous other papers

- Dozens, in several pathologies
 - Breast, Lung, Head and neck, rectum, sarcoma, lymphoma...
- Use of textural features or different quantification approaches
 - Different types of textural features
 - Area under the curve of the cumulative histogram
 - Simpler metrics (heterogeneity factor, SUV_{COV} or SUV_{SD})
- As many issues as there are papers...
 - Small cohorts, no external validation
 - Use of unreliable/unreproducible features
 - Lack of rigorous statistical analysis
 - Lack of redundancy analysis
 - ...

- ◉ Did we go too fast? ^{1,2}
 - No thorough technical validation
 - Little to no consideration of volume interaction, and redundancy among features
 - (Very) small cohorts
 - Loose statistical analysis, only surrogate of endpoints/outcome, no gold-standard
 - Use of unreliable features, no acknowledgment of previous publications
 - ...

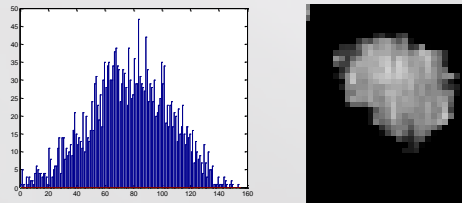
1. Cheng NM, *et al.* The promise and limits of PET texture analysis. *Ann Nucl Med.* 2013

2. Brooks FJ. On some misconceptions about tumor heterogeneity quantification. *Eur J*

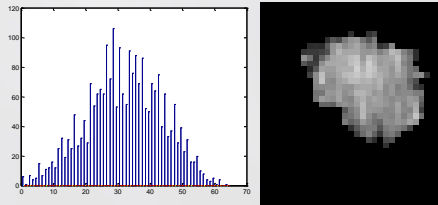
Nucl Med Mol Imaging. 2013

Quantization

- A largely ignored and underestimated problem before 2014
- Required for 2nd and 3rd order features calculations
- Huge impact on resulting features

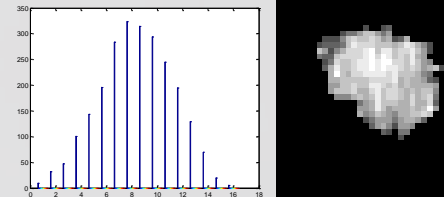


Linear transform¹



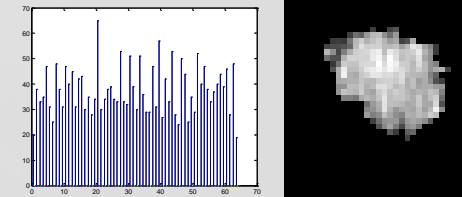
$$I_L(p) = 1 + (N - 1) * \frac{I(p) - I_{min}}{I_{max} - I_{min}}$$

Regular bins²



$$I_F(p) = 1 + E \left[\frac{I(p) - I_{min}}{F} \right]$$

Histogram equalization



$$I_E(p) = 1 + (N - 1) * hic(p)$$

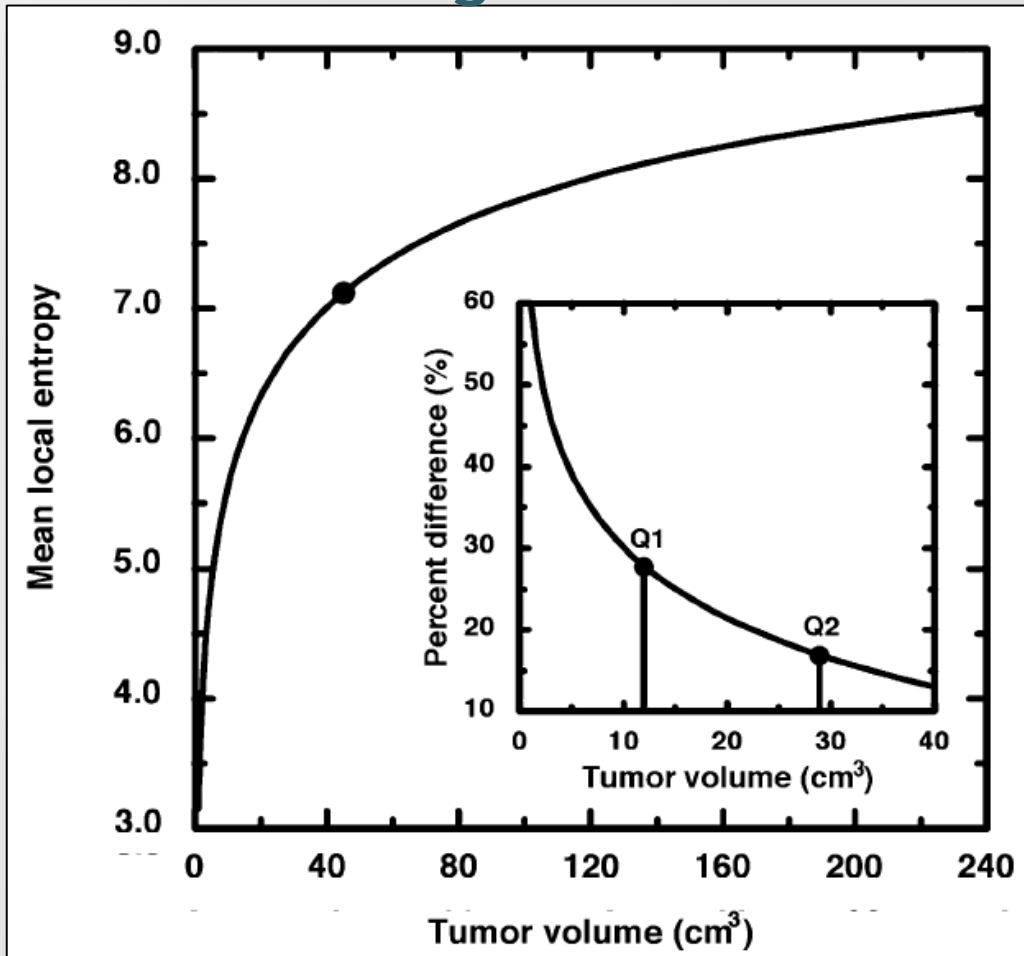
1. Tixier F, et al. Reproducibility of tumor uptake heterogeneity characterization through textural feature analysis in 18

FDG PET. *J Nucl Med* 2012

2. Leijenaar RTH, et al. The effect of SUV discretization in quantitative FDG-PET Radiomics: the need for standardized

methodology in tumor texture analysis. *Acta Oncol* 2013

Volume confounding effect



FJ. Brooks, *et al.* The effect of small tumor volumes on studies of intratumoral heterogeneity of tracer uptake. *J Nucl Med.* 2014

Volume confounding effect

Example Heterogeneity Statistic

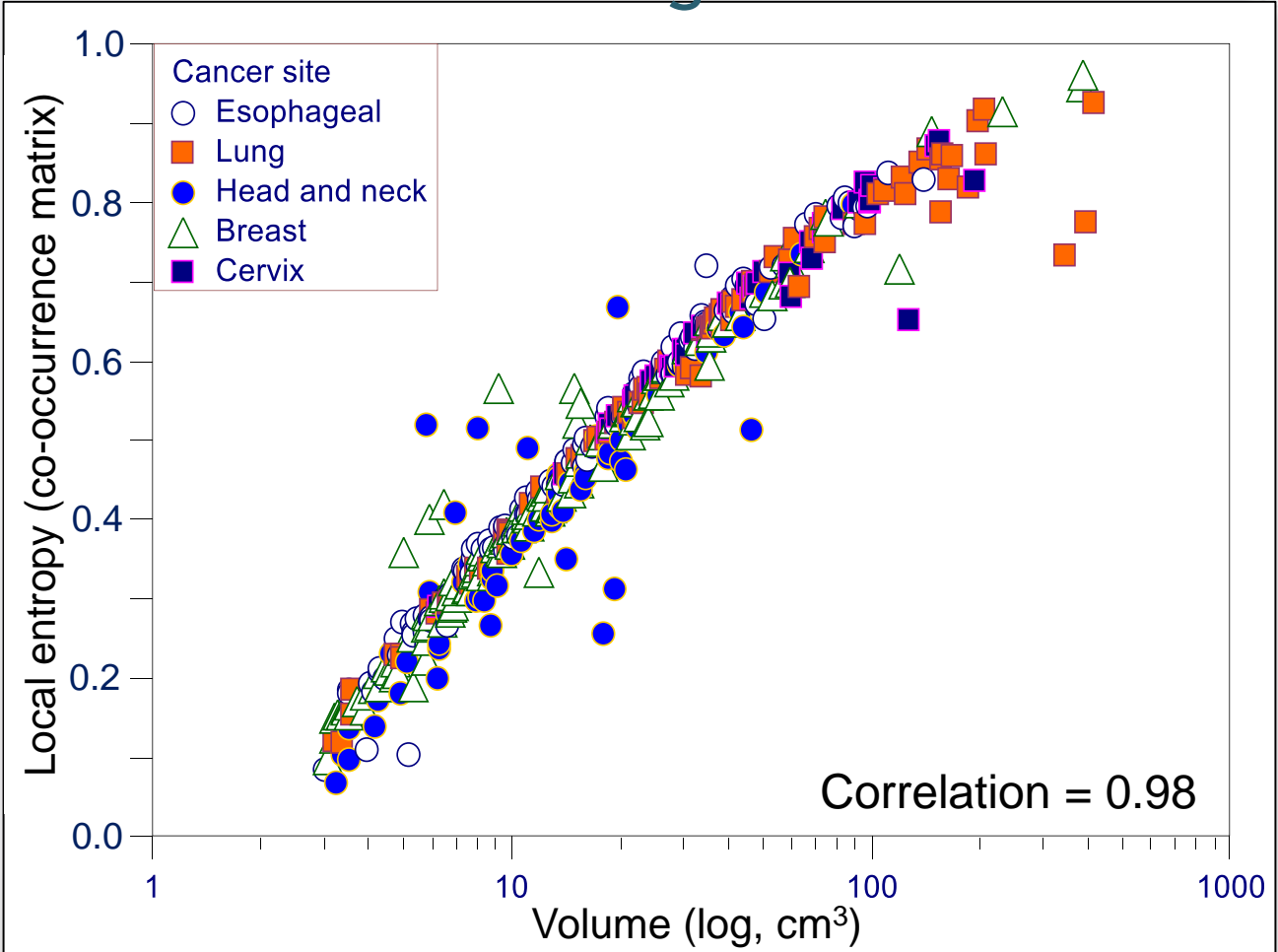
We computed the local information entropy of a 2-dimensional image as described by Haralick et al. (13). In brief, the cooccurrence matrix describes the probability p that a pixel of a shade i occurs next to a pixel of shade j . This matrix can be computed for various directions, pixel separations, and bit depths. We computed the horizontal and vertical cooccurrence matrices for the nearest pixel neighbors of 8-bit gray-scale images. From each of these matrices, the local entropy

$$h = - \sum_{j=103}^{255} \sum_{i=103}^{255} p(i,j) \ln p(i,j) \quad \text{Eq. 1}$$

was computed for each direction and then root-mean-square-averaged to obtain a single local entropy value. The limits on the summations reflect the 40% clinical threshold within the 8-bit (0–255) color scale.

FJ. Brooks, *et al.* The effect of small tumor volumes on studies of intratumoral heterogeneity of tracer uptake. *J Nucl Med.* 2014

Volume confounding effect



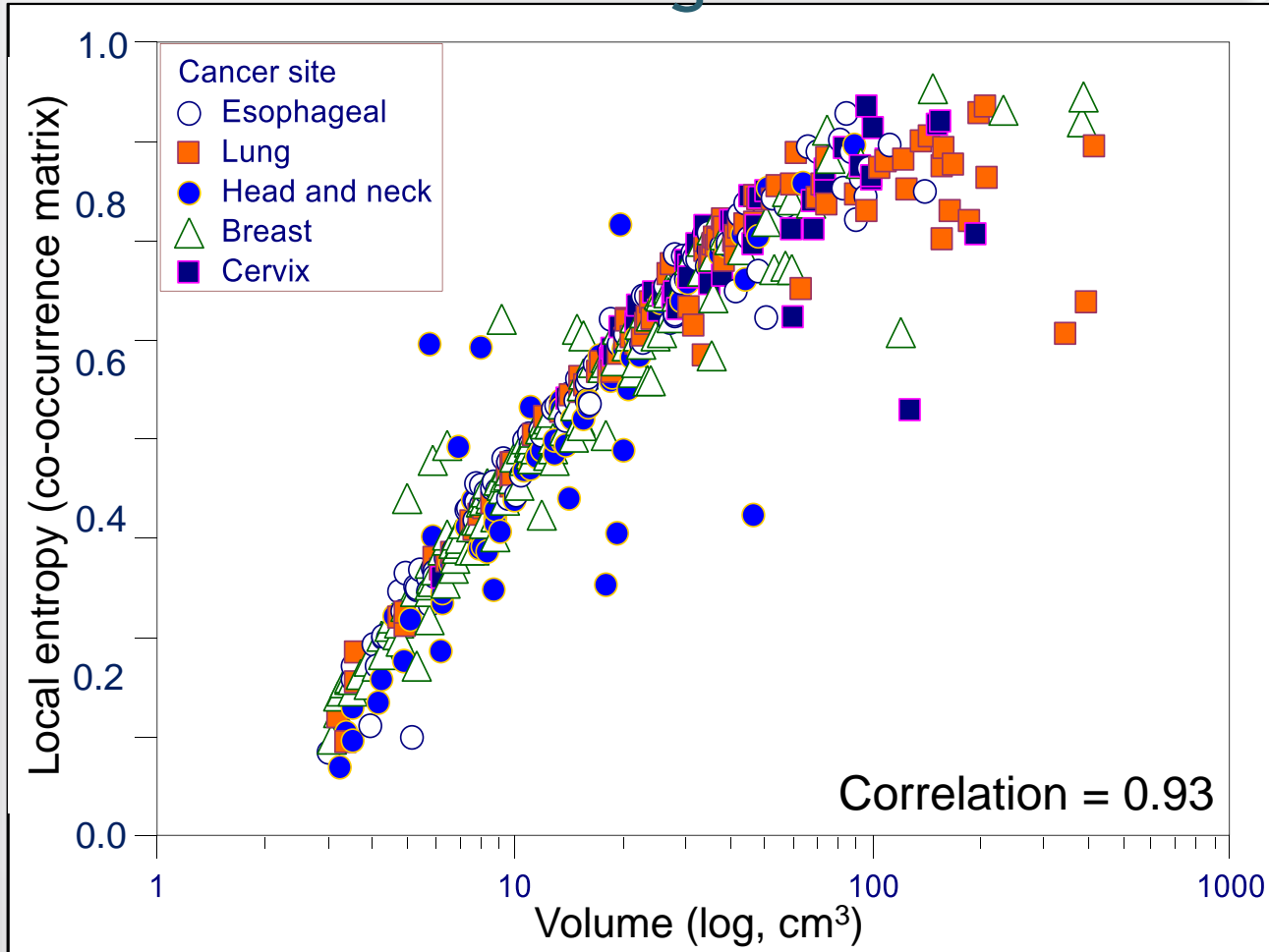
Quantization = 128

13 matrices + averaging

Radiomics in PET/CT

The present: criticism and doubts

Volume confounding effect



Quantization
= 64

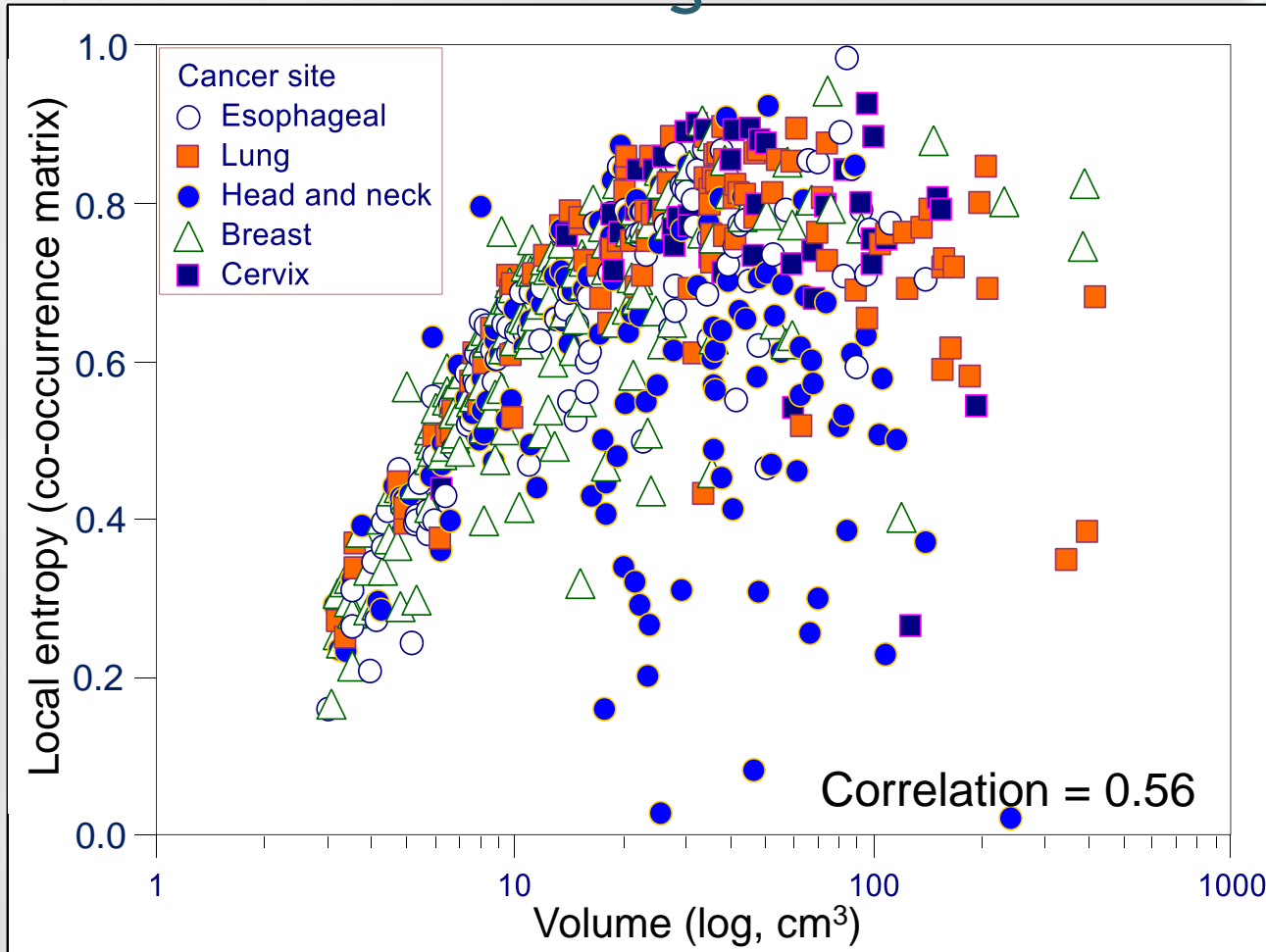
13 matrices
+ averaging

M. Hatt, *et al.* 18F-FDG PET uptake characterization through texture analysis: investigating the complementary nature of heterogeneity and functional tumor volume in a multi-cancer site patient cohort. *J Nucl Med* 2015

Radiomics in PET/CT

The present: criticism and doubts

Volume confounding effect

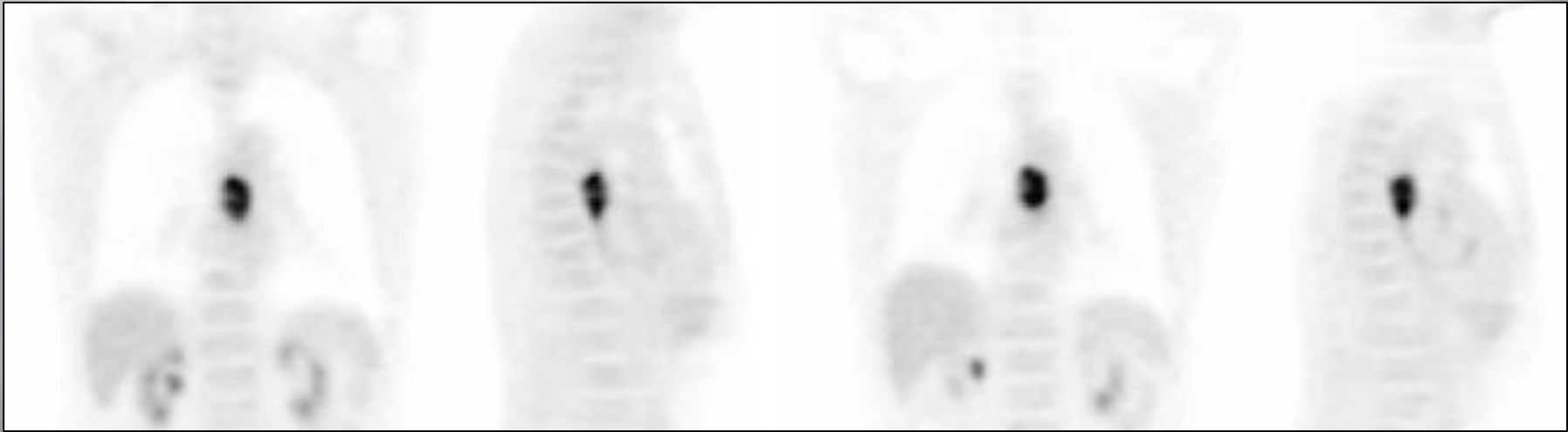


Quantization
= 64

1 matrix

M. Hatt, *et al.* 18F-FDG PET uptake characterization through texture analysis: investigating the complementary nature of heterogeneity and functional tumor volume in a multi-cancer site patient cohort. *J Nucl Med* 2015

- Selection and validation of parameters
 - Before investigating any potential clinical value
 - Evaluate their repeatability
 - Test-retest (double baseline) images^{1,2,3}

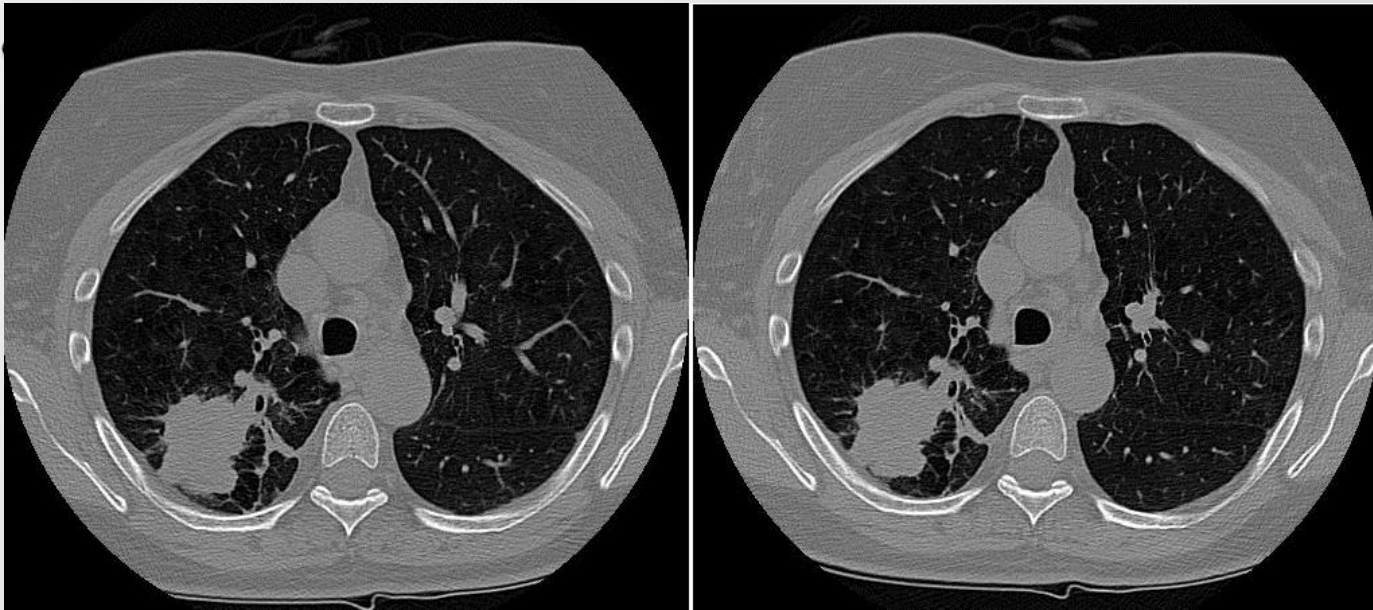


1. Tixier F, et al. Reproducibility of Glucuronide Uptake Heterogeneity of Glucuronide Uptake in Three FDG PET/CT Tracers: A Comparative Analysis of Different FDG Acquisition Modes and Integrated Analysis of Test-Retest and Inter-Observer Variability. *Acta Oncol* 2014

2. Seljenar RT, et al. Stability of FDG PET Radiomics Parameters: An Integrated Analysis of Test-Retest and Inter-Observer Variability. *Acta Oncol* 2014

3. Fried DV, et al. Prognostic Value and Reproducibility of Pre-treatment CT-based FDG PET Stage-like Parameters on Overall Survival of Cancer Patients: A Radiomics Study. *Eur J Nuc Med* 2013

- ▶ **Selection and validation of parameters**
 - Before investigating any potential clinical value
 - Evaluate their repeatability
 - Test-retest (double baseline) images^{1,2,3}



1. Tixier F, et al. Reproducibility of Glucuronide Uptake Heterogeneity of Glucuronide Uptake in Liver Lesions: A PET/CT Study. *Acta Oncol* 2014

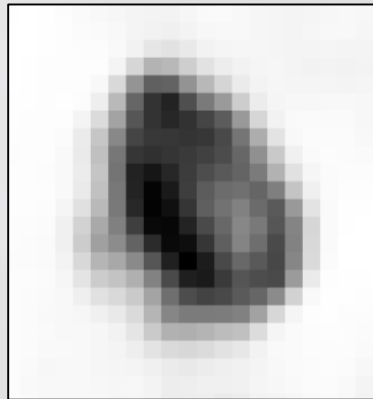
2. Tixier F, et al. Stability of FDG PET Radiomic Parameters: An Integrated Analysis of Test-Retest and Inter-Observer Variability. *Acta Oncol* 2014

3. Fried DV, et al. Prognostic value and reproducibility of pretreatment CT texture features for FDG PET stage take on overall survival in pancreatic cancer: a pilot study. *Biol Phys* 2014

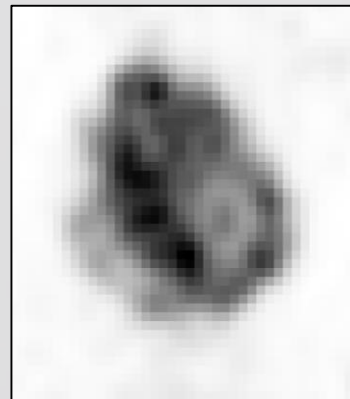
response prediction in esophageal carcinoma. *Eur J Nuc Med* 2013

- ▶ Selection and validation of parameters
 - Before investigating any potential clinical value
 - Evaluate their repeatability
 - Test-retest (double baseline) images^{1,2,3}
 - Evaluate their robustness
 - Reconstruction algorithms and parameters⁴
 - Processing and analysis workflow⁵

4x4x4 mm³



2x2x2 mm³



1. Tixier F, et al. Reproducibility of Glucose Uptake Heterogeneity of Ovarian Cancer Lesions: A PET/CT Radiomics Study. *Acta Oncol* 2014
 2. Tixier F, et al. Stability of FDG PET Radiomics Parameters: An Integrated Analysis of Test-Retest and Inter-Observer Variability. *Acta Oncol* 2014
 3. Fried DV, et al. Prognostic Value and Reproducibility of Pre-treatment CT Texture Features for Predicting Response Prediction in Esophageal Carcinoma. *Eur J Nuc Med* 2013

- ▶ **Selection and validation of parameters**
 - Before investigating any potential clinical value
 - Evaluate their repeatability
 - Test-retest (double baseline) images^{1,2,3}
 - Evaluate their robustness
 - Reconstruction algorithms and parameters⁴
 - Processing and analysis workflow⁵
 - Features very sensitive to small intensity variations
 - Features quantifying regions of small size and/or low intensity
 - Not robust / reproducible
- Among dozens of parameters, only a handful are sufficiently reliable (robust+reproducible)

1. Tixier F, et al. Reproducibility of Glucagon Receptor-1 Receptor (GR1) PET/CT in the characterization of metastatic disease. *Eur J Nucl Med Mol Imaging* 2014

2. Leijenar RT, et al. Stability of FDG PET Radiomics features as a function of test-retest and inter-observer variability. *Acta Oncol* 2014

3. Fried DV, et al. Prognostic value and reproducibility of pretreatment CT texture features for PET stage prediction in esophageal carcinoma. *Eur J Nuc Med* 2013

▶ Repeatability & robustness

TABLE 3
Reproducibility Results for All Image-Derived Parameters, Including SUVs and Textural Features
(Calculated Using Downsampling Range of 64 Values)

Texture	Feature	Mean ± SD	95% CI	LRL	95% CI for LRL	URL	95% CI for URL
Global	Minimum SUV	6.3 ± 26.5	-7.8 to 20.4	-45.6	-70.2 to -20.9	58.2	33.6 to 82.8
	SUV _{max}	4.7 ± 19.5	-5.7 to 15.0	-33.5	-51.7 to -15.4	42.9	24.7 to 61.0
	SUV _{mean}	5.5 ± 21.2	-5.8 to 16.8	-36.1	-55.8 to 16.4	47.1	27.3 to 66.8
	SD	1.2 ± 23.2	-11.1 to 13.6	-44.18	-65.7 to -22.6	46.6	25.1 to 68.2
	Skewness	-0.3 ± 27.5	-15.0 to 14.3	-54.2	-79.8 to -28.6	53.6	28.0 to 79.2
	Kurtosis	2.1 ± 18.0	-7.4 to 11.7	-33.1	-49.8 to -16.4	37.3	20.6 to 54.0
	Mean/SD	4.1 ± 24.1	-8.8 to 16.9	-43.2	-65.6 to -20.7	51.3	28.9 to 73.7
Local	Second angular moment	10.9 ± 26.4	-3.2 to 25.0	-40.9	-65.5 to -16.3	62.7	38.1 to 87.3
	Contrast (inertia)	5.4 ± 24.0	-18.1 to 7.4	-52.3	-74.6 to -30.0	41.6	19.3 to 63.9
	Entropy	-2.0 ± 5.4	-4.9 to 0.9	-12.6	-17.7 to -7.6	8.7	3.6 to 13.8
	Correlation	-0.6 ± 27.7	-15.3 to 14.1	-54.8	-15.3 to 14.1	53.6	27.9 to 79.3
	Homogeneity	1.8 ± 11.5	-4.4 to 7.9	-20.8	-31.5 to -10.1	24.4	13.6 to 35.1
	Dissimilarity	-2.1 ± 13.0	-9.0 to 4.9	-27.6	-39.7 to -15.5	23.5	11.4 to 35.6
Regional	Small-area emphasis	-6.0 ± 54.3	-35.0 to 22.9	-112.5	-163.0 to -62.0	100.4	49.9 to 150.9
	Large-area emphasis	3.6 ± 30.0	-12.4 to 19.6	-55.2	-83.1 to -27.3	62.4	34.5 to 90.3
	Intensity variability	-9.7 ± 24.0	-22.5 to 3.1	-56.7	-79.0 to -34.4	37.3	15.0 to 59.6
	Size-zone variability	11.2 ± 23.1	-1.1 to 23.5	-34.1	-55.6 to -12.6	56.5	35.0 to 78.0
	Zone percentage	-2.7 ± 16.9	-11.7 to 6.2	-35.8	-51.5 to -20.1	30.3	14.6 to 46.0
	Low-intensity emphasis	-4.0 ± 55.3	-33.5 to 25.4	-112.4	-163.9 to -61.0	104.4	52.9 to 155.8
	High-intensity emphasis	3.9 ± 20.4	-7.0 to 14.8	-36.1	-55.1 to -17.1	44.0	24.9 to 63.0
	Low-intensity small-area emphasis	-7.0 ± 67.6	-43.1 to 29.0	-139.5	-202.4 to -76.6	125.4	62.5 to 188.3
	High-intensity small-area emphasis	1.0 ± 31.2	-15.6 to 17.6	-60.1	-89.1 to -31.1	62.0	33.0 to 91.0
	Low-intensity large-area emphasis	1.8 ± 28.9	-13.6 to 17.2	-54.9	-81.8 to 28.0	58.5	31.6 to 85.4
High-intensity large-area emphasis	3.5 ± 35.8	-15.6 to 22.6	-66.7	-100.1 to -33.4	73.7	40.4 to 107.1	

LRL and URL = lower and upper reproducibility limits, respectively.

F. Tixier, *et al.* Reproducibility of tumor uptake heterogeneity characterization through textural feature analysis in 18F-FDG PET. *J Nucl Med* 2012

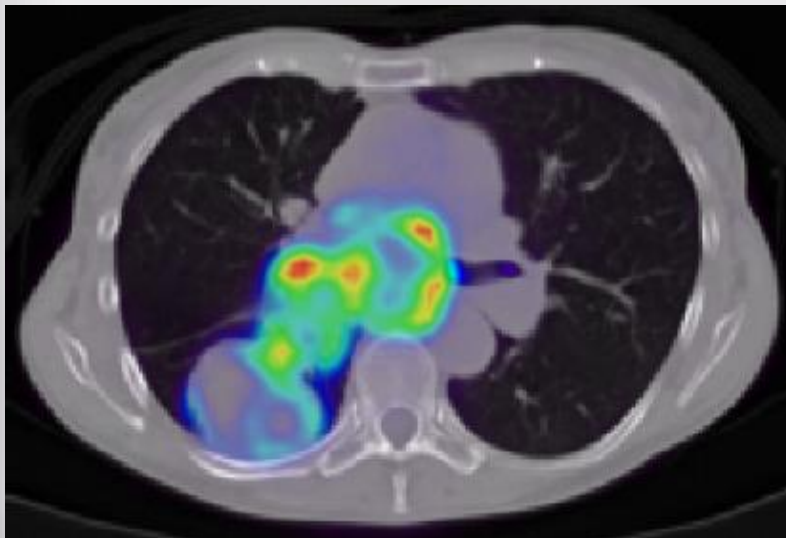
Repeatability & robustness

Study	Modality	# of patients	Features evaluated
Tixier, <i>J Nucl Med</i> 2012	FDG PET	16	1st-order, textural
Leijenaar, <i>Acta Oncol</i> 2013	FDG PET	11	Shape, 1st-order, textural
Willaime, <i>Phys Med Biol</i> 2013	FLT PET	11	1st-order, textural
Fried, <i>Int J Radiat Oncol Biol Phys</i> 2014	CT + CE-CT	20, 13	1st-order, textural
Aerts, <i>Nat Commun</i> 2014	CT	31	Shape, 1st-order, textural
Yang, <i>Comput Med Imaging Graph</i> 2015	CE-CT	8	Shape, 1st-order, textural
Fave, <i>Med Phys</i> 2015	CBCT	10	1st-order, textural
Desseroit, <i>Eur J Nucl Med Mol Imaging</i> 2016	CT	31	1st-order, textural
Van Velden, <i>Mol Imaging Biol</i> 2016	FDG PET	11	Shape, 1st-order, textural

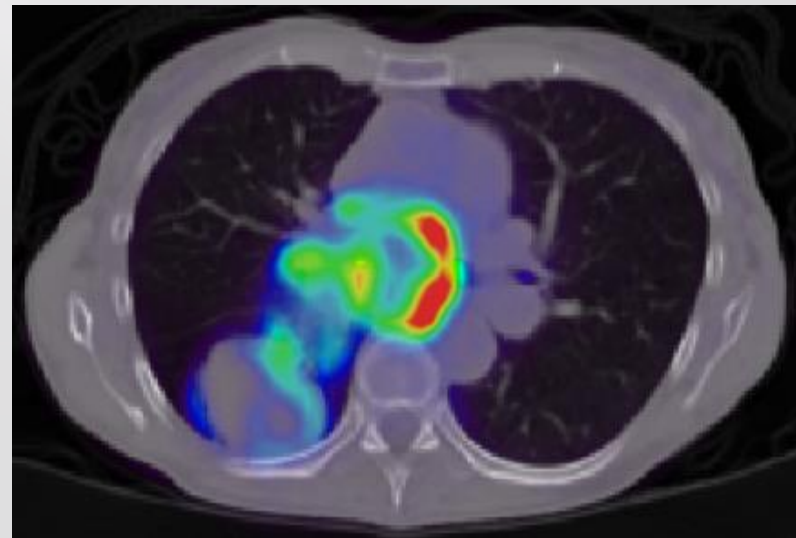
M-C. Desseroit, *et al.* Reliability of PET/CT shape and heterogeneity features in functional and morphological components of Non-Small Cell Lung Cancer tumors: a repeatability analysis in a prospective multi-center cohort. *J Nucl Med* 2017

Repeatability & robustness

- N = 74 NSCLC stage III-IV, prospective inclusion in 31 sites
 - Merck (n = 40, 17 sites Europe + Asia)
 - American College of Radiology Imaging Network (ACRIN) 6678 (n = 34, 14 sites USA)
 - Test and re-test acquisitions performed within 1 week

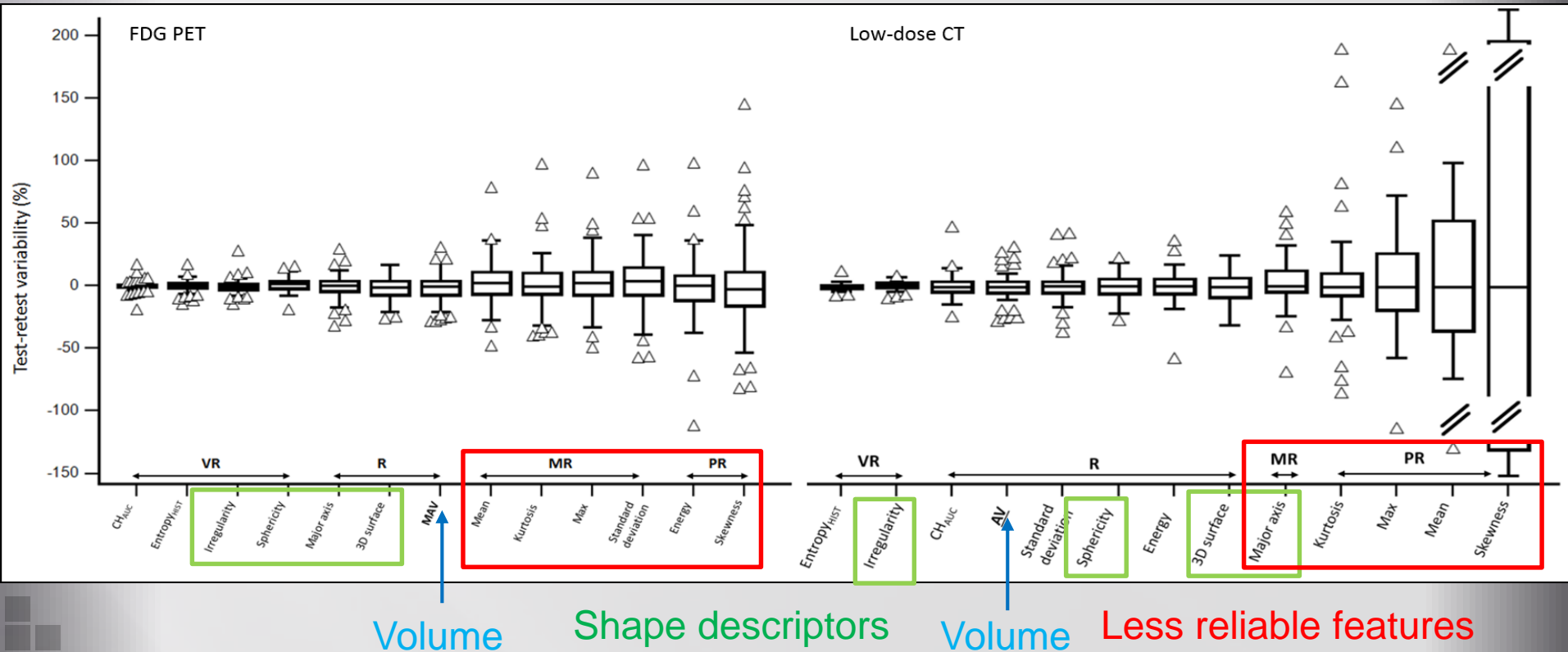


Test PET/CT



Re-test PET/CT

Repeatability & robustness



Volume

Shape descriptors

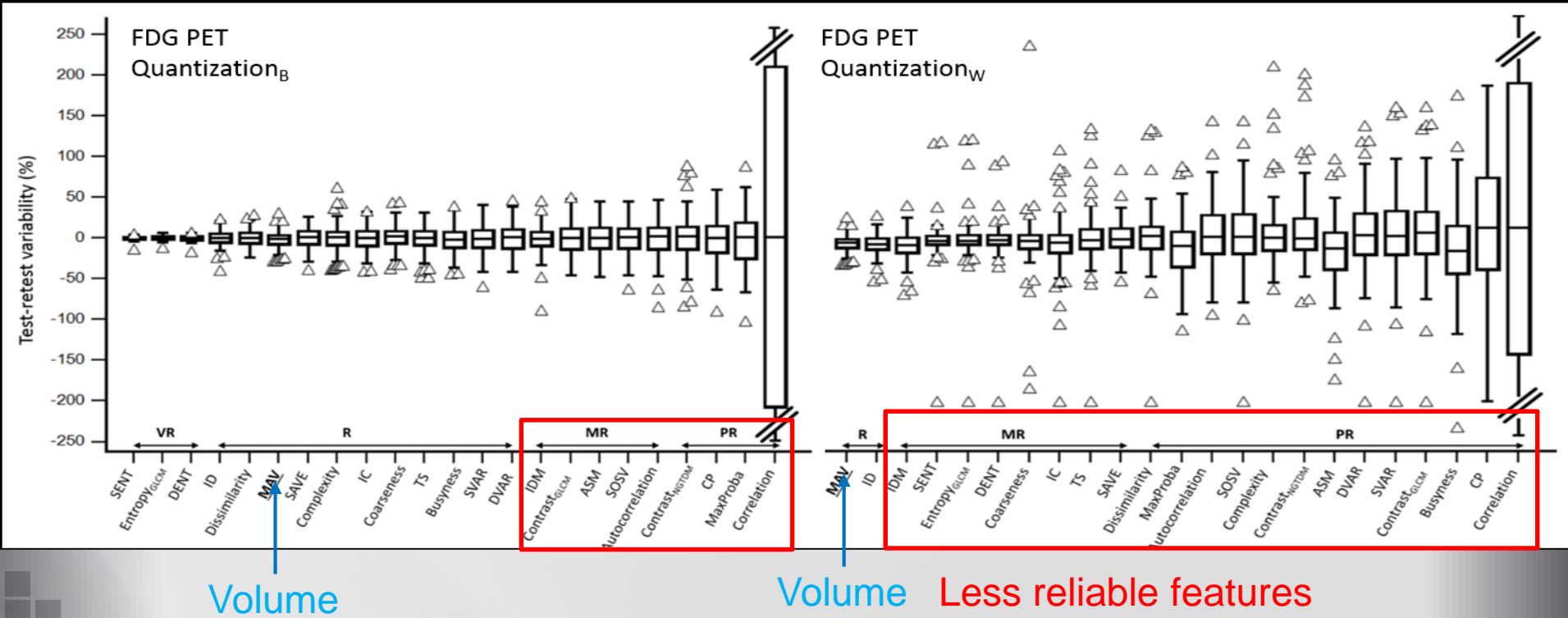
Volume

Less reliable features

▶ Repeatability & robustness

Set number of bins (64)

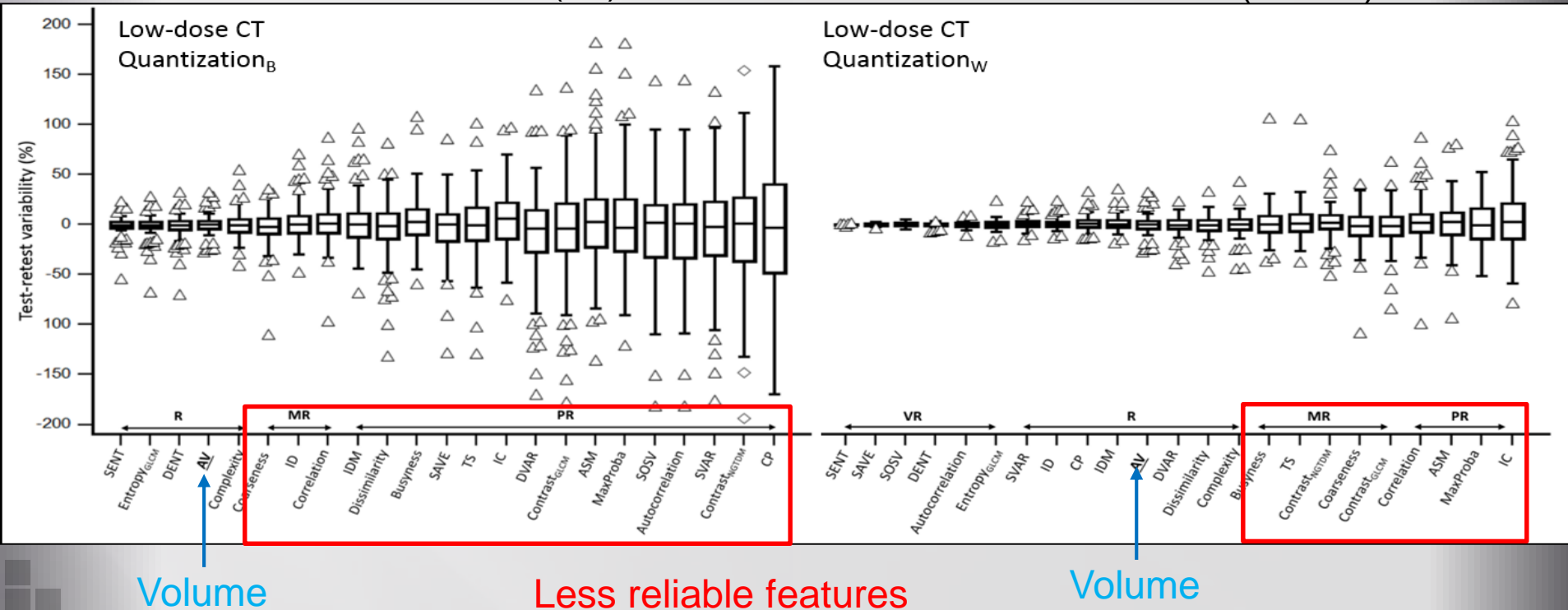
Bins of set width (0.5 SUV)



Repeatability & robustness

Set number of bins (64)

Bins of set width (10 HU)



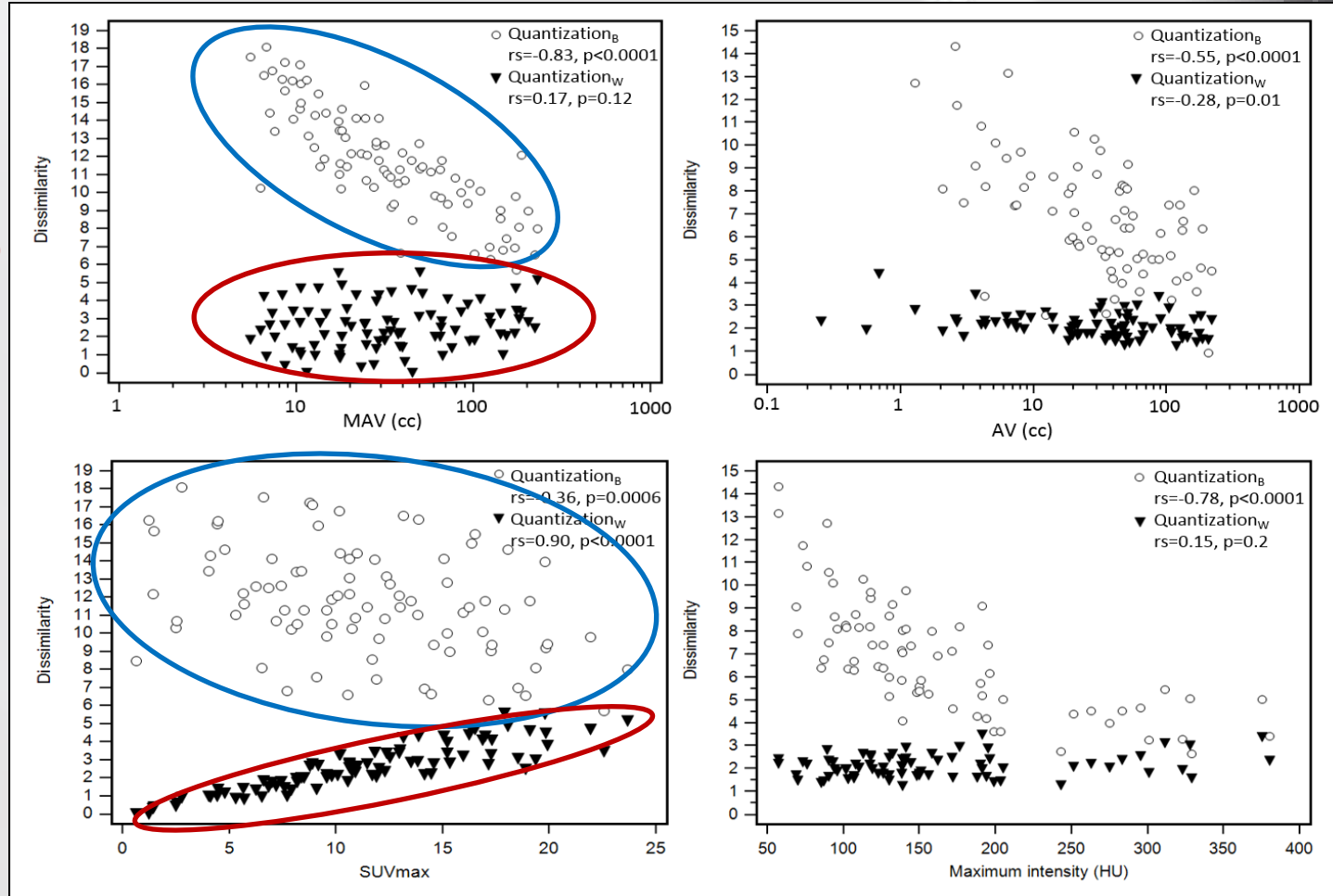
Repeatability & robustness

Set number of bins (64)

Quantization_B

Bins of set width (0.5 SUV)

Quantization_W



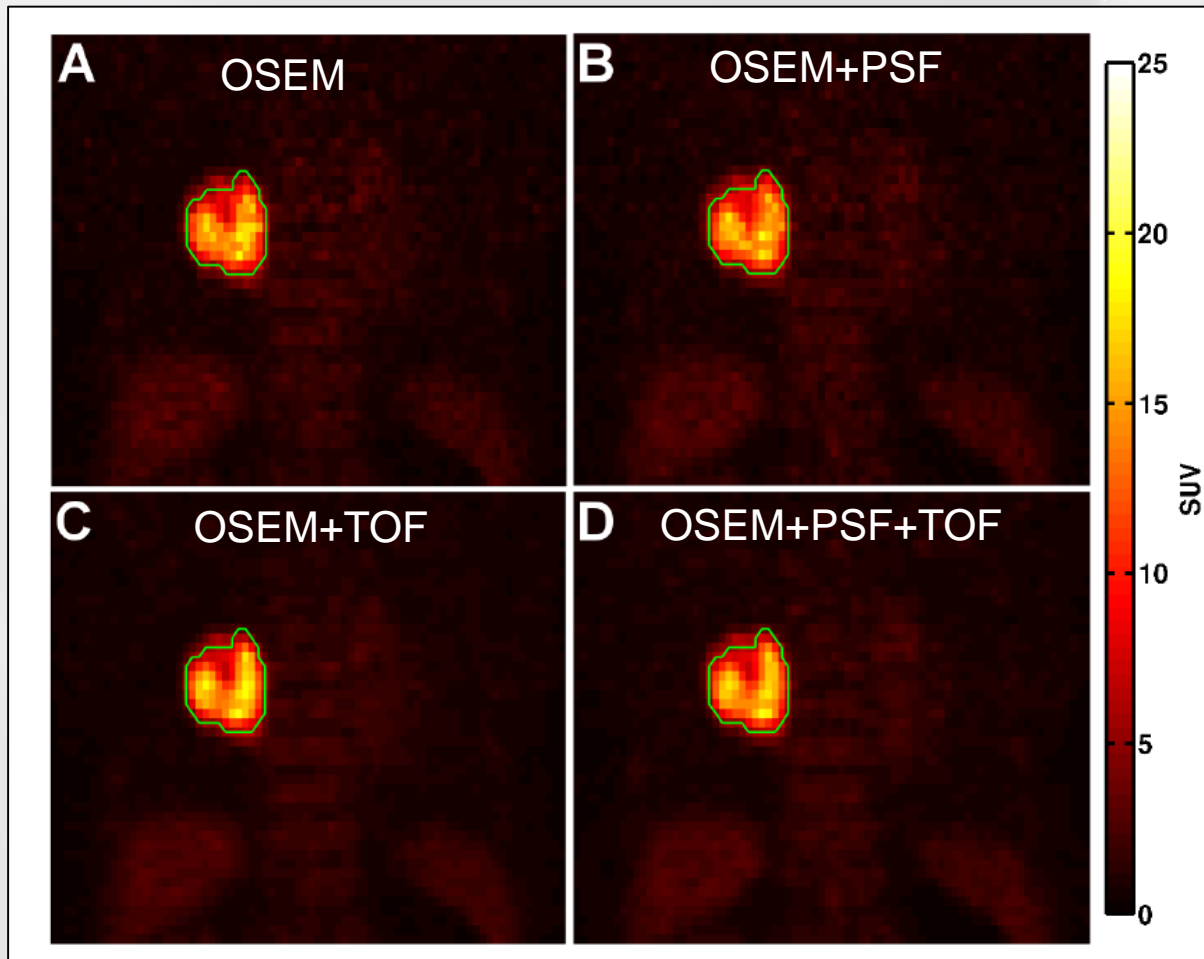
M-C. Desseroit, *et al.* Reliability of PET/CT shape and heterogeneity features in functional and morphological components of Non-Small Cell Lung Cancer tumors: a repeatability analysis in a prospective multi-center cohort. *J Nucl Med* 2017

Reproducibility/variability/robustness

TABLE 1
List of reconstruction settings

Reconstruction algorithm	Variation over the default reconstruction settings	Impact of iteration number on image features	Impact of FWHM on image features	Impact of grid size on image features
		<u>FWHM: 2.5 mm;</u> <u>Grid size: 256 × 256</u>	<u>iteration: 2;</u> <u>Grid size: 256 × 256</u>	<u>iteration: 2;</u> <u>FWHM: 2.5mm</u>
OSEM	iteration: 2 FWHM: 2.5 mm; Grid size: 256 × 256	iteration: 1, 2, 3	FWHM: 2.5, 3.5, 4.5, 5.5 mm;	Grid size: 256 × 256 128 × 128
OSEM+PSF	iteration: 2 FWHM: 2.5 mm; Grid size: 256 × 256	iteration: 1, 2, 3	FWHM: 2.5, 3.5, 4.5, 5.5 mm;	Grid size: 256 × 256 128 × 128
OSEM+TOF	iteration: 2 FWHM: 2.5 mm; Grid size: 256 × 256	iteration: 1, 2, 3	FWHM: 2.5, 3.5, 4.5, 5.5 mm;	Grid size: 256 × 256 128 × 128
OSEM+PSF+TOF	iteration: 2 FWHM: 2.5 mm; Grid size: 256 × 256	iteration: 1, 2, 3	FWHM: 2.5, 3.5, 4.5, 5.5 mm;	Grid size: 256 × 256 128 × 128

- Reproducibility/variability/robustness



J. Yan, *et al.* Impact of Image Reconstruction Settings on Texture Features in 18F-FDG PET. *J Nucl Med* 2015

Reproducibility/variability/robustness

TABLE 2

Change of image features over the default reconstruction settings

	COV≤5%	5%<COV≤10%	10%<COV≤20%	COV>20%
SUV	SUVmean, SUVpeak	SUVmax		
FOS	Entropy	COV, Kurtosis, Energy	Variance	Skewness
GLCM	Dissimilarity, Energy, Entropy, ID, SE, DE, IMC, IDM, IDMN, DM, SDN	Contrast, Correlation, Homogeneity, MP, SA, DV	Autocorrelation, SOS, SV	CS
GLRLM	GLNr, RP, LGRE, HGRE		SRE, LRE, RLN, SRLGE, SRHGE, LRLGE, LRHGE	
GLSZM	GLNz, LGZE	ZLN, HGZE, WVGLZ_S	SZE, LZE, SZLGE, SZHGE, LZLGE, LZHGE, WVGLZ_N	ZP
NGLDM	Entropy	SNE, NN, SM	LNE	
NGTDM		Coarseness, Busyness, Complexity, TS	Contrast	
				Busyness, Complexity, TS

Reproducibility/variability/robustness

TABLE 5

Impact of grid size on image features

	COV≤5%	5%<COV≤10%	10%<COV≤20%	COV>20%
SUV		SUVmean, SUVpeak	SUVmax	
FOS	Entropy		Kurtosis, Variance, COV, Energy	Skewness
GLCM	DE, IDM, IDMN	SA, SE	Autocorrelation, Entropy, ID, SOS, SV	Contrast, Correlation, CS, Dissimilarity, Energy, Homogeneity, MP, DV, IMC, DM, SDN
GLRLM	LGRE, HGRE			LRE, SRE, GLNr, RLN, RP, SRLGE, SRHGE, LRLGE, LRHGE
GLSZM	LGZE		SZE, LZE, LZLGE, HGZE, SZLGE, LZHG	GLNz, ZLN, ZP, SZHG, WVGLZ_N, WVGLZ_S
NGLDM			SNE	LNE, NN, SM, Entropy
NGTDM				Coarseness, Contrast, Busyness, Complexity, TS

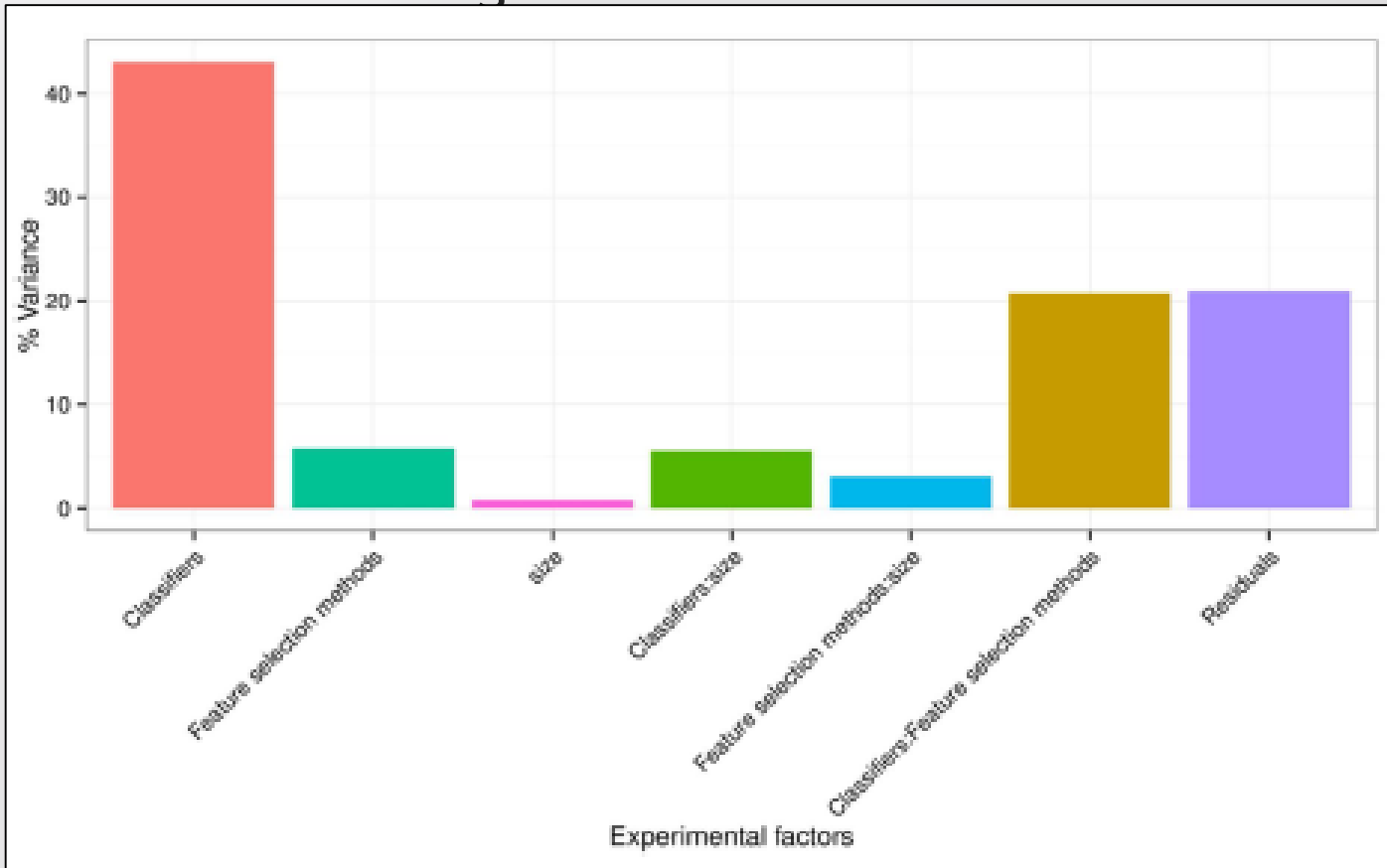
Challenges

- Machine learning

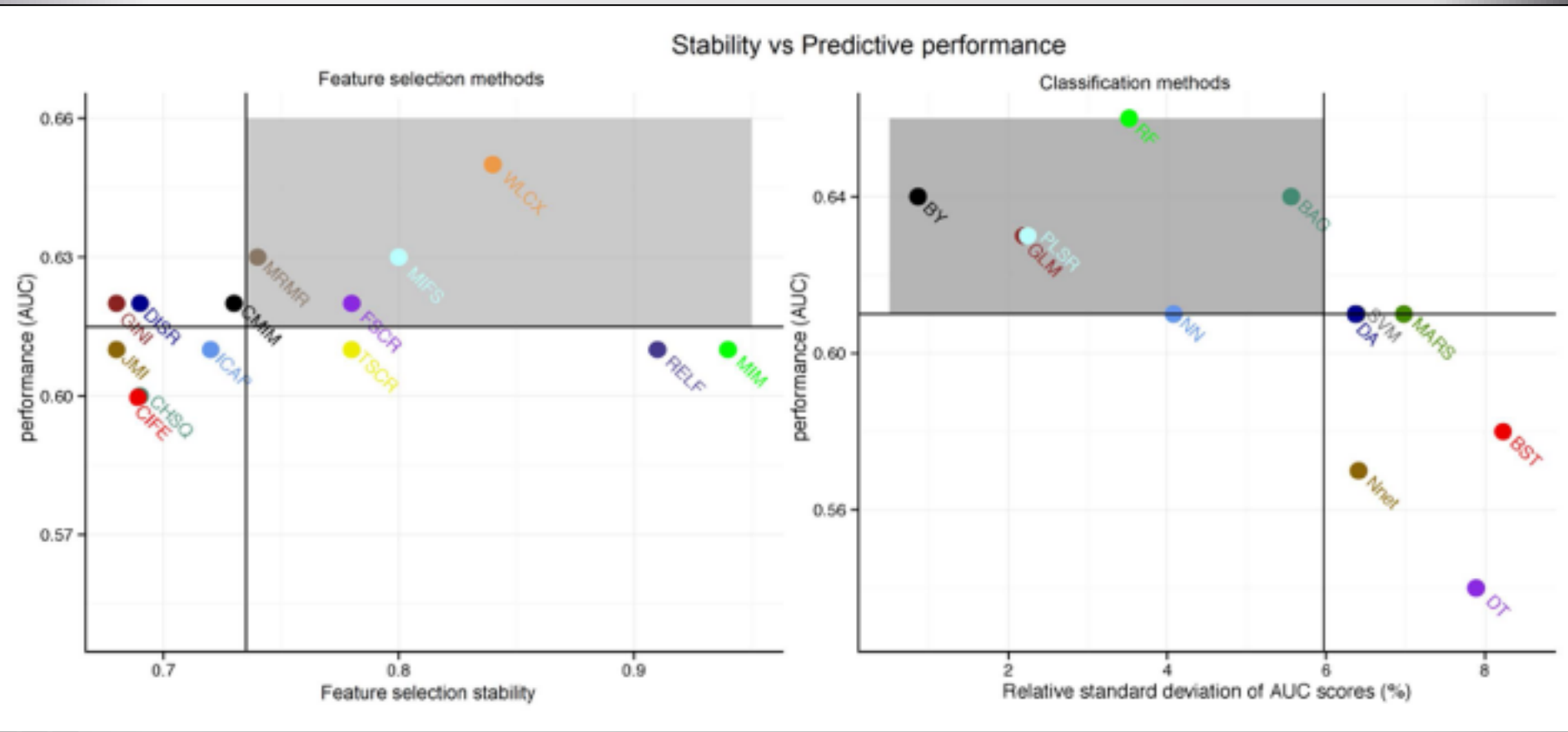
Classification method acronym	Classification method name	Feature Selection method acronym	Feature selection method name
Nnet	Neural network	RELF	Relief
DT	Decision Tree	FSCR	Fisher score
BST	Boosting	GINI	Gini index
BY	Bayesian	CHSQ	Chi-square score
BAG	Bagging	JMI	Joint mutual information
RF	Random Forset	CIFE	Conditional infomax feature extraction
MARS	Multi adaptive regression splines	DISR	Double input symmetric relevance
SVM	Support vector machines	MIM	Mutual information maximization
DA	Discriminant analysis	CMIM	Conditional mutual information maximization
NN	Neirest neighbour	ICAP	Interaction capping
GLM	Generalized linear models	TSCR	T-test score
PLSR	Partial least squares and principal componenet regression	MRMR	Minimum redundancy maximum relevance
—	—	MIFS	Mutual information feature selection
—	—	WLCX	Wilcoxon

Challenges

- Machine learning

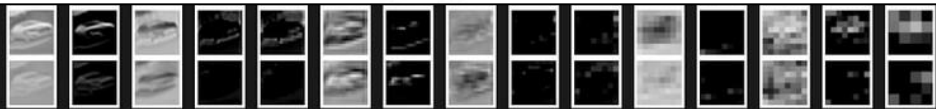
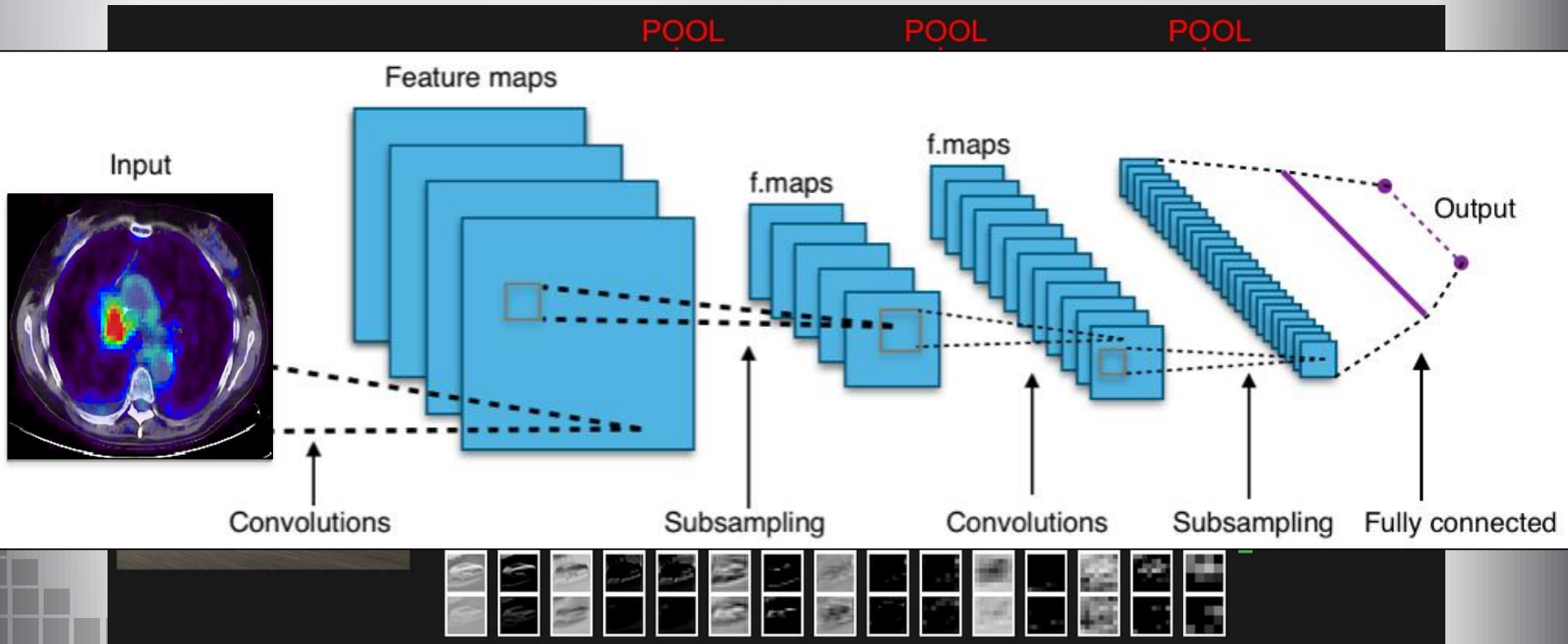


Apprentissage automatique (machine learning)



- Apprentissage profond (deep learning)

- Evolution récente des réseaux de neurones
- Performances impressionnantes



Deep learning

