# Machine Learning: Basi e Sue Applicazioni

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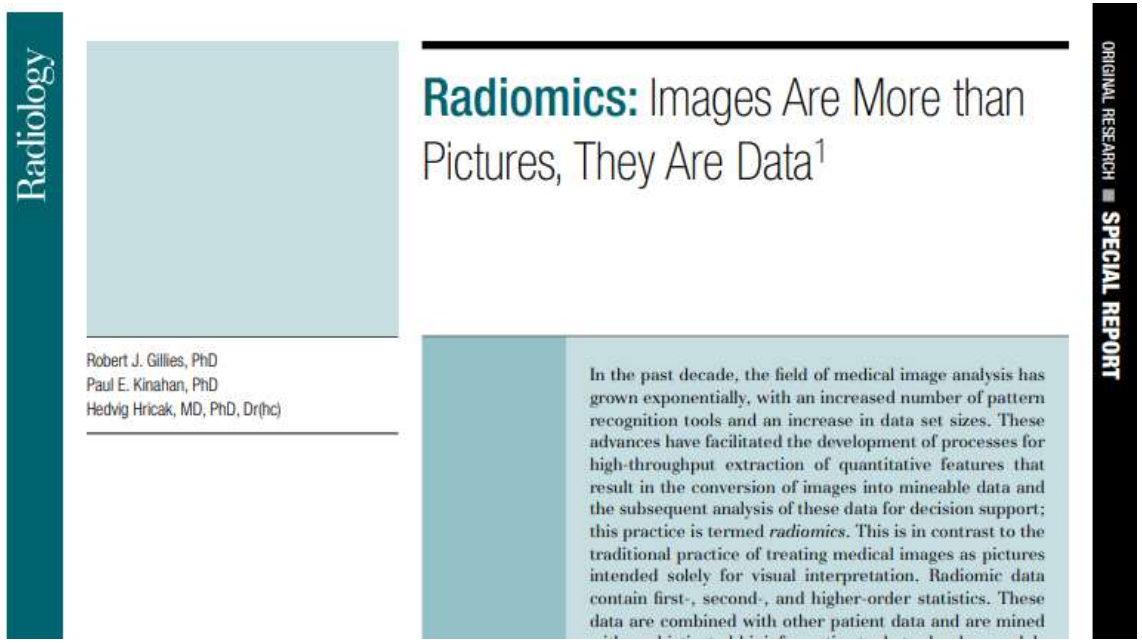
# Radiomic hypotesis

Molecular heterogeneity of cancer lesions is cause of different clinical outcome.

Such heterogeneity can be captured, *in vivo,* on the entire lesion volume, by high-throughput quantitative **radiomics** descriptors from 3D image of cancer lesion.

Different expression level of a signature of radiomic features are able to predict different prognosis or treatment response of patients with similar cancer diagnosis (statistical analysis and predictive models).


Radiology

Robert J. Gillies, PhD
Paul E. Kinahan, PhD
Hedvig Hricak, MD, PhD, Dr(hc)

**Radiomics:** Images Are More than Pictures, They Are Data[1]

ORIGINAL RESEARCH ■ SPECIAL REPORT

In the past decade, the field of medical image analysis has grown exponentially, with an increased number of pattern recognition tools and an increase in data set sizes. These advances have facilitated the development of processes for high-throughput extraction of quantitative features that result in the conversion of images into mineable data and the subsequent analysis of these data for decision support; this practice is termed *radiomics*. This is in contrast to the traditional practice of treating medical images as pictures intended solely for visual interpretation. Radiomic data contain first-, second-, and higher-order statistics. These data are combined with other patient data and are mined

# Radiomics: a new approach for the study of cancer

**HHS Public Access**
Author manuscript
*Eur J Cancer*. Author manuscript; available in PMC 2015 August 12.

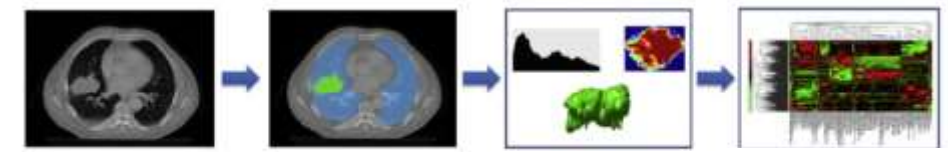
Published in final edited form as:
*Eur J Cancer*. 2012 March ; 48(4): 441–446. doi:10.1016/j.ejca.2011.11.036.

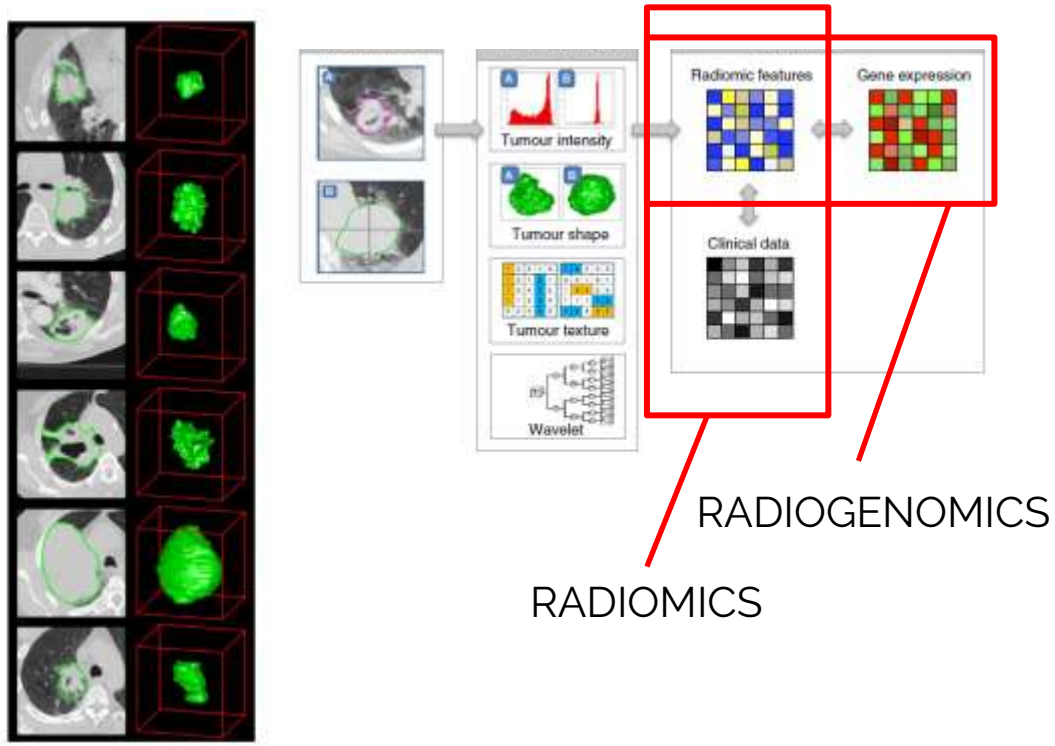
**Radiomics: Extracting more information from medical images using advanced feature analysis**

**Philippe Lambin**[a,*,e,f], **Emmanuel Rios-Velazquez**[a,e], **Ralph Leijenaar**[a,e], **Sara Carvalho**[a,e], **Ruud G.P.M. van Stiphout**[a,e], **Patrick Granton**[a,e], **Catharina M.L. Zegers**[a,e], **Robert Gillies**[b,e], **Ronald Boellard**[c,e], **André Dekker**[a,e], and **Hugo J.W.L. Aerts**[a,d,e]

[a]Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands [b]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA [c]U University Medical Center, Department of Nuclear Medicine & PET Research, Amsterdam, The Netherlands [d]Computational Biology and Functional Genomics Laboratory, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard School of Public Health, USA

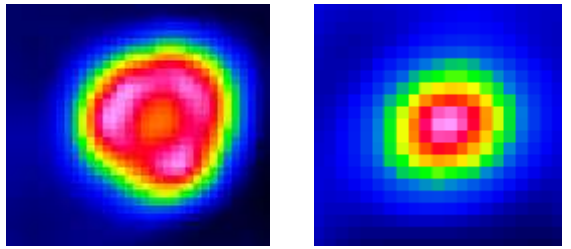
Comprehensive quantification of disease phenotypes by applying a large number of quantitative image features representing lesion heterogeneity and correlating with omics and clinical data

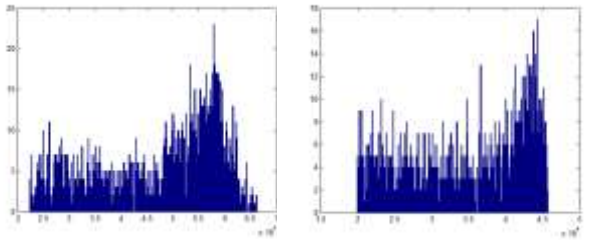


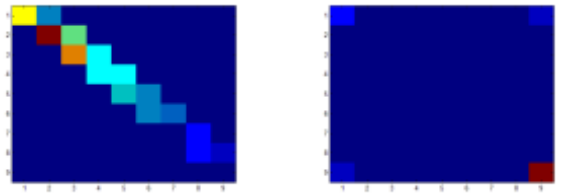



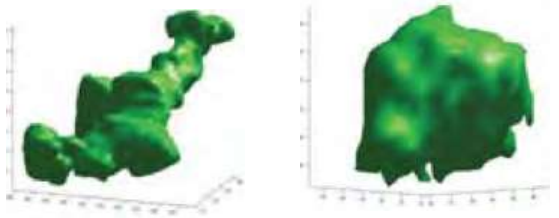
# Texture and shape features

| Feature | Description | | Examples |
|---|---|---|---|
| Texture-First order | Grey level frequency distribution from histogram Analysis | Global | Minimum, mean and maximum intensity<br>Standard deviation<br>Skewness<br>Kurtosis<br>Percentile values<br>Range of intensities |
| Texture-Second order | From spatial grey level dependence matrices (SGLDM) or co–occurrence matrices<br>*They express how often a pixel of intensity i finds itself within a certain relationship to another pixel of intensity j* | Local | Entropy<br>Energy<br>Contrast<br>Homogeneity<br>Dissimilarity<br>Uniformity<br>Correlation |
| Texture-Third order | From neighbourhood grey-tone difference matrices (NGTDMs) | Local | Coarseness<br>Contrast<br>Busyness<br>Complexity |
| | From voxel alignment matrices | Regional | Run-length and emphasis<br>Run-length variability |
| | From grey level size zone matrices<br>*They reflect regional intensity variations or the distribution of homogeneous regions* | Regional | Zone emphasis<br>Size-zone variability |
| Shape and Size | | | Sphericity<br>Compactness<br>Eccentricity<br>Surface Area<br>Sperical Disproportion<br>Surface to Volume ratio<br>Solidity |

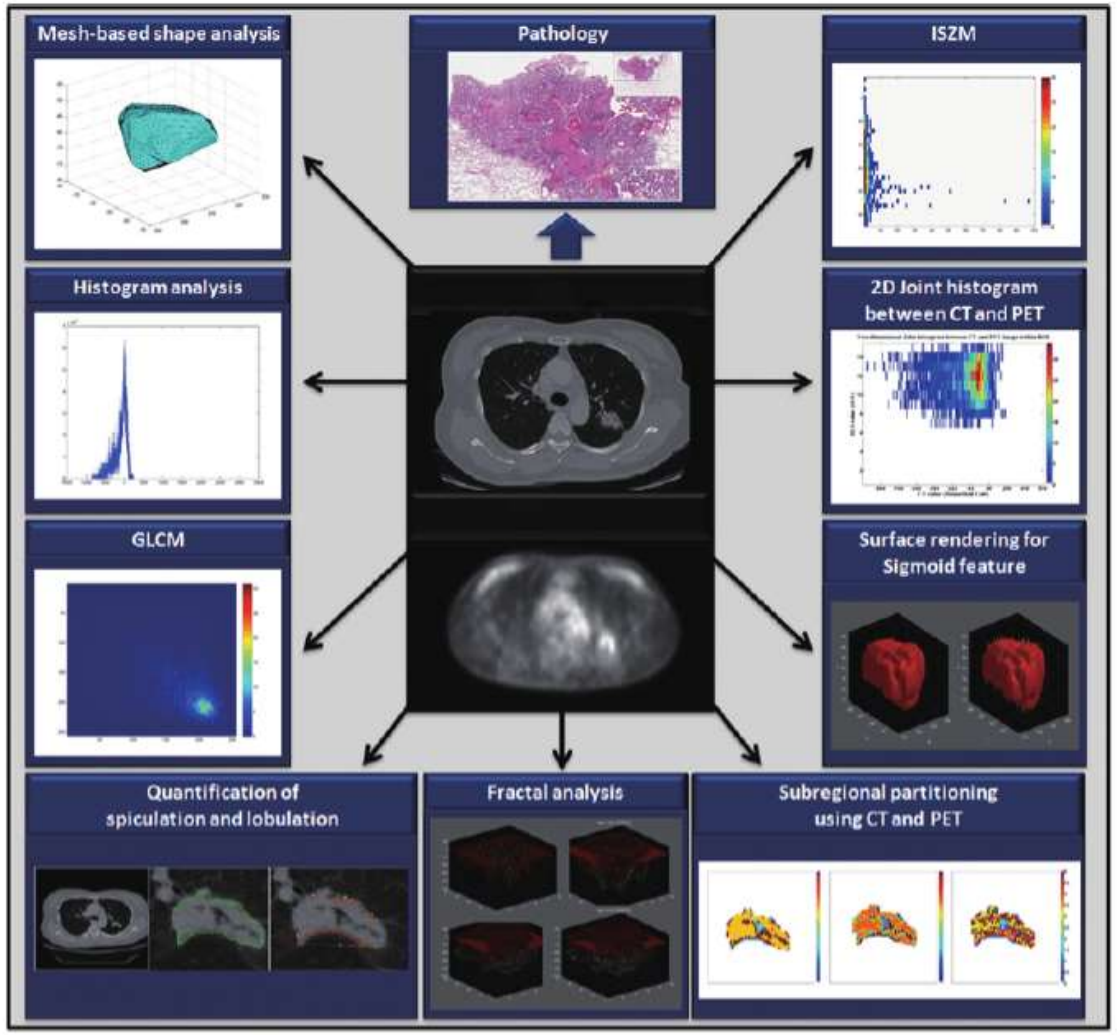








# Radiomics

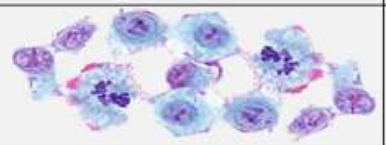
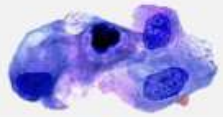



https://www.researchgate.net/figure/Various-radiomic-features-such-as-mesh-based-shape-histogram-gray-level-co-occurrence_fig3_315902486

# Radiomics

## Morphological features

1. Metabolic Target Volume (MTV)
2. Surface
3. Spherical disproportion
(ratio between measured surface of the lesion and surface of an equivalent-sphere in terms of volume)
4. Sphericity
5. Surface-to-volume ratio

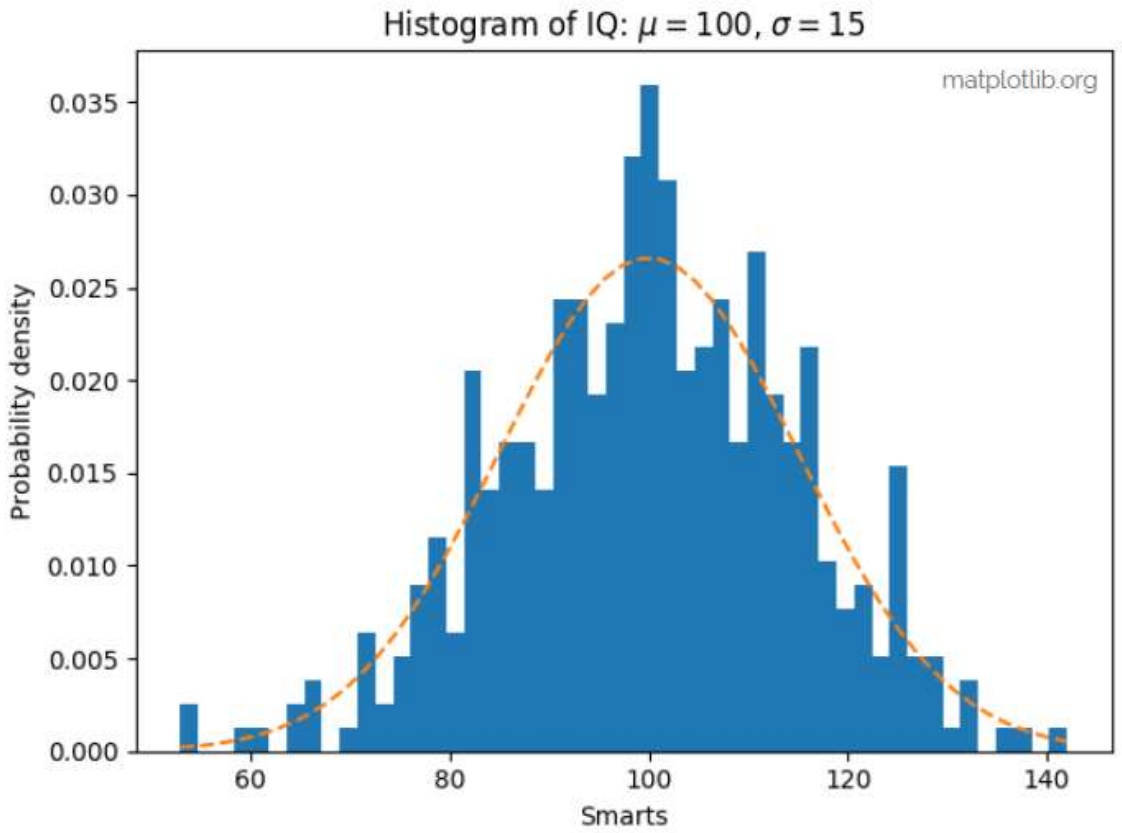
| Normal | Cancer | |
|---|---|---|
|  |  | Large, variably shaped nuclei |
|  |  | Many dividing cells;<br>Disorganized arrangement |
|  |  | Variation in size and shape |
|  |  | Loss of normal features |

http://sphweb.bumc.bu.edu/otlt/MPH-Modules/PH/PH709_Cancer/PH709_Cancer7.html

# Radiomics

## Histogram-based features

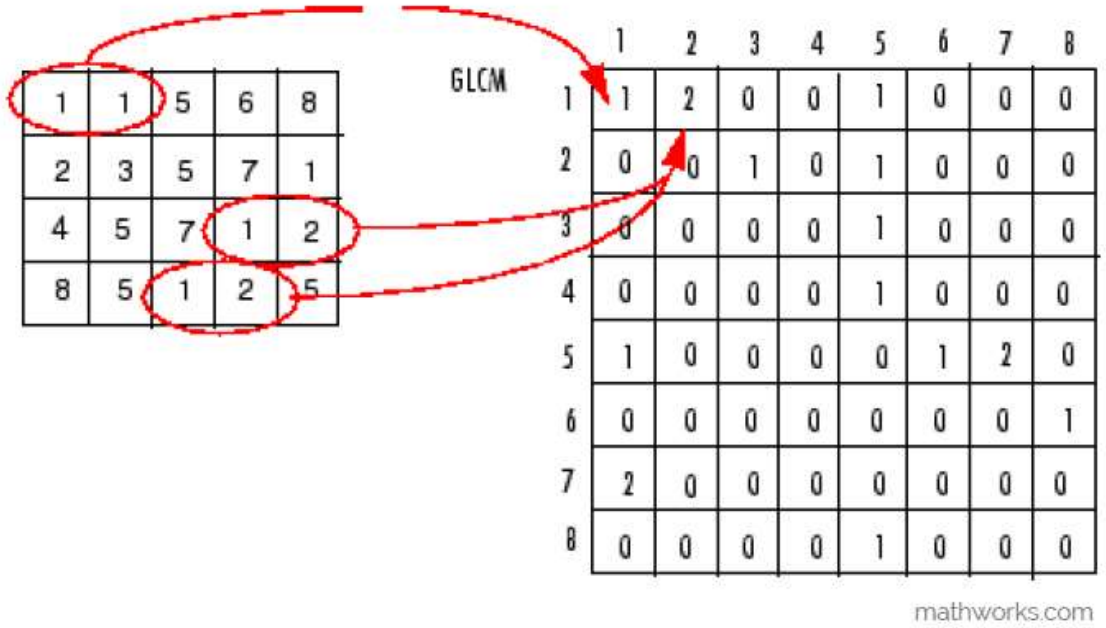
1. Maximum
2. Minimum
3. Mean
4. Median
5. Mean Absolute Deviation (MAD)
6. Root Mean Square (RMS)
7. Energy
8. Entropy
9. Kurtosis
10. Skewness
11. Standard Deviation
12. Uniformity
13. Variance



## Texture descriptors
### Gray-Level Co-occurrence Matrix (GLCM)*

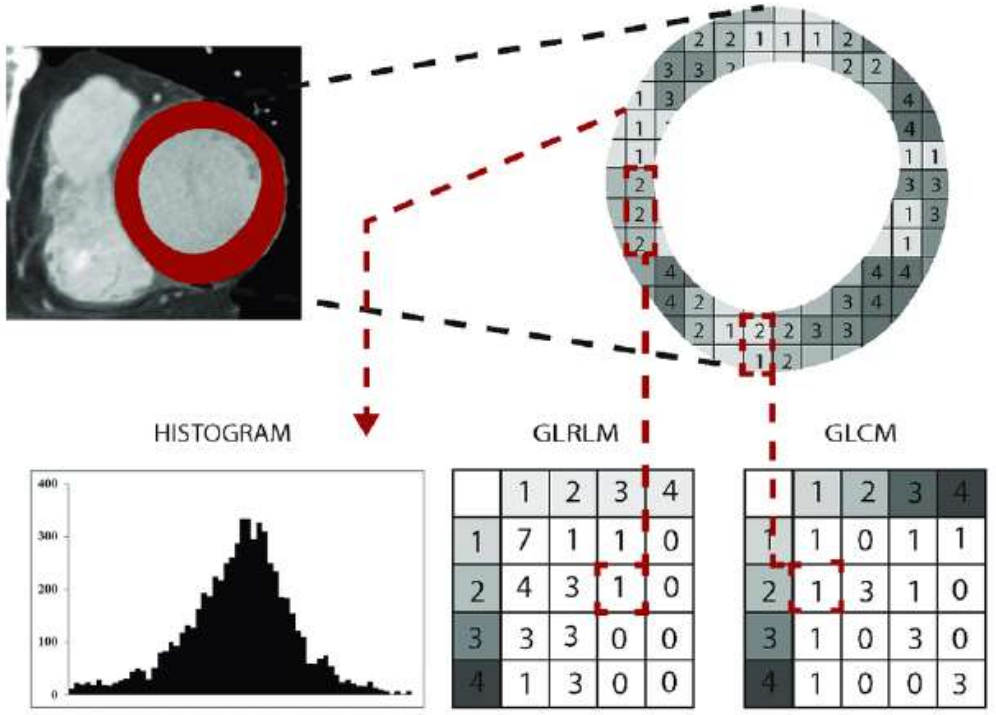
1. Energy
2. Contrast
3. Entropy
4. Homogeneity
5. Correlation
6. Sum Average
7. Variance
8. Dissimilarity
9. Auto Correlation

* A Gray Level Co-occurrence Matrix (GLCM) quantifies the number of times the combination of levels X and Y occur in two pixels in the image that are separated by a distance of D pixels along angle A.



# Radiomics

## Texture descriptors
### Gray-Level Run Length Matrix (GLRLM)*




https://www.researchgate.net/figure/Principles-of-generating-texture-analysis-features-Principles-of-generating-the_fig2_320821651

*A Gray Level Run Length Matrix (GLRLM) quantifies gray level runs, which are defined as the length in number of pixels, of consecutive pixels that have the same gray level value.

It describes # runs with gray level G and length L that occur in the image along angle A.

## Texture descriptors

### Gray-Level Size Zone Matrix (GLSZM)

| | | | |
|---|---|---|---|
| 1 | 2 | 3 | 4 |
| 1 | 3 | 4 | 4 |
| 3 | 2 | 2 | 2 |
| 4 | 1 | 4 | 1 |

| *Level* $g$ | *Size zone*, $s$ 1 | 2 | 3 |
|---|---|---|---|
| 1 | 2 | 1 | 0 |
| 2 | 1 | 0 | 1 |
| 3 | 0 | 0 | 1 |
| 4 | 2 | 0 | 1 |

http://thibault.biz/Research/ThibaultMatrices/GLSZM/GLSZM.html

* A gray level zone is defined as a the number of connected voxels that share the same gray level intensity.

Contrary to GLCM and GLRLM, the GLSZM is rotation independent, with only one matrix calculated for all directions in the ROI

## Texture descriptors

### Neighbouring Gray Tone Difference Matrix (NGTDM)*

$$\mathbf{I} = \begin{bmatrix} 1 & 2 & 5 & 2 \\ 3 & 5 & 1 & 3 \\ 1 & 3 & 5 & 5 \\ 3 & 1 & 1 & 1 \end{bmatrix}$$

| $i$ | $n_i$ | $p_i$ | $s_i$ |
|---|---|---|---|
| 1 | 6 | 0.375 | 13.35 |
| 2 | 2 | 0.125 | 2.00 |
| 3 | 4 | 0.25 | 2.63 |
| 4 | 0 | 0.00 | 0.00 |
| 5 | 4 | 0.25 | 10.075 |

https://pyradiomics.readthedocs.io/en/latest/features.html

* A Neighbouring Gray Tone Difference Matrix quantifies the difference between a gray value and the average gray value of its neighbours within distance D

# Textures in cancer by PET



Published in final edited form as:
*Pattern Recognit*. 2009 June 1; 42(6): 1162–1171. doi:10.1016/j.patcog.2008.08.011.



## Exploring feature-based approaches in PET images for predicting cancer treatment outcomes

I. El Naqa, Ph.D.[a], P. Grigsby, M.D.[a], A. Apte, M.Sc[a], E. Kidd, M.D.[a], E. Donnelly, M.D.[a], D. Khullar, M.Sc[a], S. Chaudhari, B.Sc[a], D. Yang, Ph.D.[a], M. Schmitt, B.Sc[b], Richard Laforest, Ph.D.[b], W. Thorstad, M.D.[a], and J. O. Deasy, Ph.D.[a]

[1]Department of Radiation Oncology, Washington University School of Medicine St. Louis, MO, USA

[2]Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA

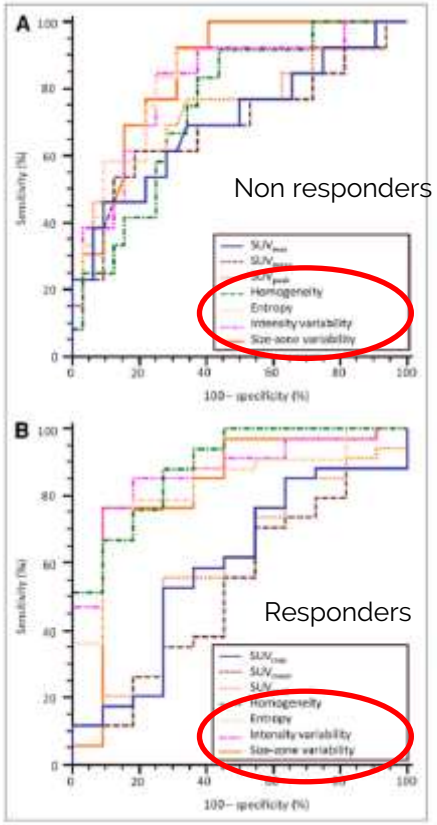



**Table 2**

Association between different extracted features and overall survival in a cohort of 9 head and neck patients measured by Spearman's rank correlation (rs) and the area under the ROC curve (AUC).

| Variable | | Spearman (rs) | AUC |
|---|---|---|---|
| *Tumor volume* | | *0.6928* | *0.8750* |
| SUV Measurements | Maximum | 0.3464 | 0.7000 |
| | Minimum | -0.2642 | 0.6000 |
| | Mean | 0.1732 | 0.6500 |
| | Standard deviation | 0.3464 | 0.6750 |
| IVH Intensity-volume metrics | $I_{10}$ | 0.1732 | 0.7000 |
| | $I_{90}$ | 0.0 | 0.5000 |
| | $I_{10-90}$ | 0.2598 | 0.6750 |
| | $V_{10}$ | -0.1732 | 0.5750 |
| | $V_{90}$ | *-0.7794* | *0.9500* |
| | $V_{10-90}$ | 0.0866 | 0.5000 |
| Texture-based features | Energy | 0.0866 | 0.5000 |
| | Contrast | -0.5196 | 0.8000 |
| | Local homogeneity | 0.5196 | 0.8250 |
| | Entropy | -0.1732 | 0.5250 |
| Shape-based features | Eccentricity | 0.2598 | 0.6500 |
| | *Euler Number* | *0.6166* | *0.8500* |
| | *Solidity* | *-0.6058* | *0.8500* |
| | *Extent* | *-0.6062* | *0.8500* |

J Nucl Med 2011; 52:369–378

## Intratumor Heterogeneity Characterized by Textural Features on Baseline $^{18}$F-FDG PET Images Predicts Response to Concomitant Radiochemotherapy in Esophageal Cancer

Florent Tixier[1], Catherine Cheze Le Rest[1,2], Mathieu Hatt[1], Nidal Albarghach[1,3], Olivier Pradier[1,3], Jean-Philippe Metges[3,4], Laurent Corcos[4], and Dimitris Visvikis[1]

[1]INSERM, U650, LaTIM, CHU Morvan, Brest, France; [2]Department of Nuclear Medicine, CHU Morvan, Brest, France; [3]Institute of

# A study in which we hope not to be cited…

PLOS ONE

RESEARCH ARTICLE

## False Discovery Rates in PET and CT Studies with Texture Features: A Systematic Review

**Anastasia Chalkidou*, Michael J. O'Doherty, Paul K. Marsden**

Division of Imaging Sciences and Biomedical Engineering, Kings College London 4th Floor, Lambeth Wing, St. Thomas Hospital, SE1 7EH, London, United Kingdom

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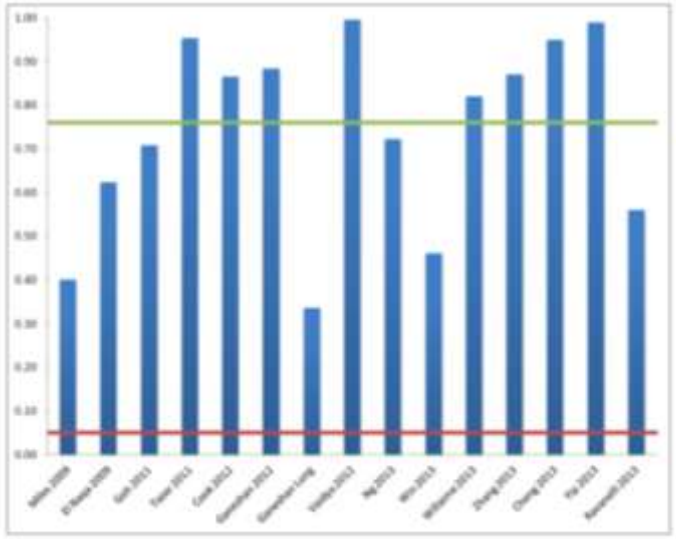


**Fig 2. Probability of a false positive result based on number of hypotheses tested per study (blue columns) for all study categories.** 5% type-I error probability = red line, average type-I error probability (76%) over all studies = green line (Note—additional inflation of the type-I error probability due to the use of the optimum cut-off approach is not included here).

doi:10.1371/journal.pone.0124165.g002

# Key methodological issues

- **Repeatability**, the closeness of the agreement between the results of successive radiomic measurements under the same conditions of measurement

- **Riproducibility**, the closensess of the agreement between the results of radiomic measurement under similar conditions of measurements

- **Significance**, the ability of radiomic in effectively characterizing cancer lesion heterogeneity

**Stability**

# Biological change or radiomics unstability?

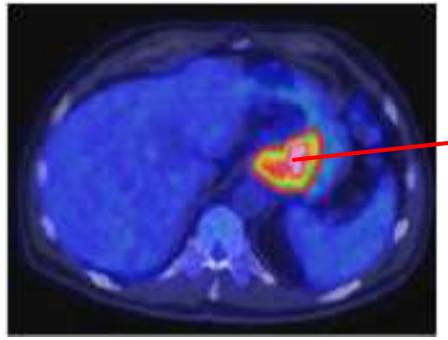
It is necessary that the radiomics features are **repeatable** for the same patient as part of the prognosis and therapeutic monitoring but also **reproducible** when performed across multiple centers and patients.

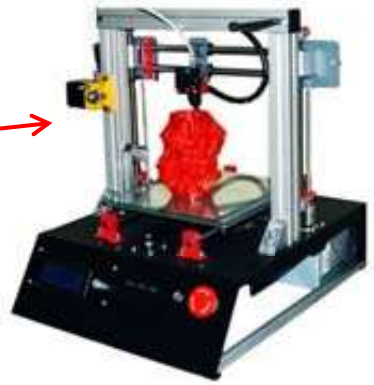
For the SUV and MTV metrics, a cut-off value of ±30% has been accepted for associating the changes to actual metabolic variations (PERCIST).

**There is currently no consensus** on the tolerated variability of radiomics features for the evaluation of prognosis or response to treatment.

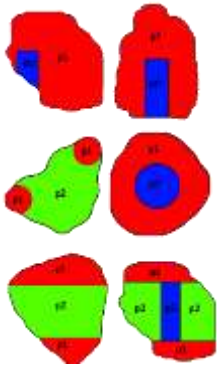
**Only radiomic features with high repeatability and reproducibility should be selected as candidate for predictive biomarkers.**

# Which model to study key radiomics issues?

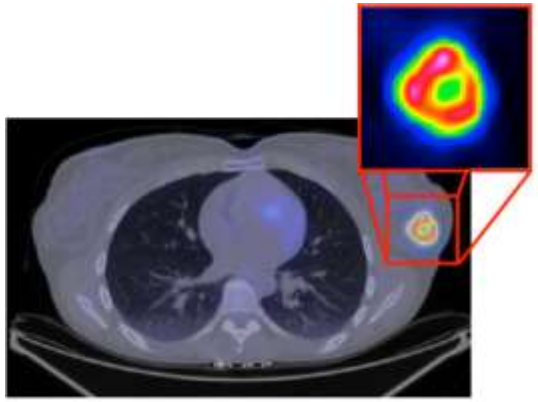




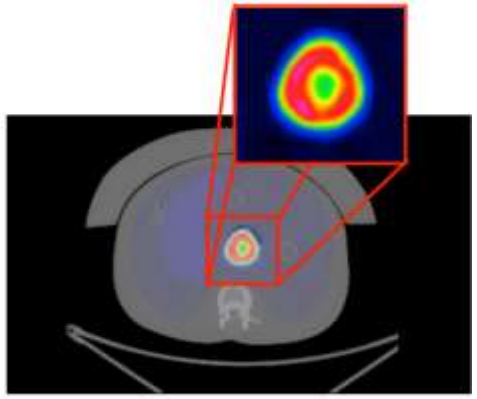
sodium alginate



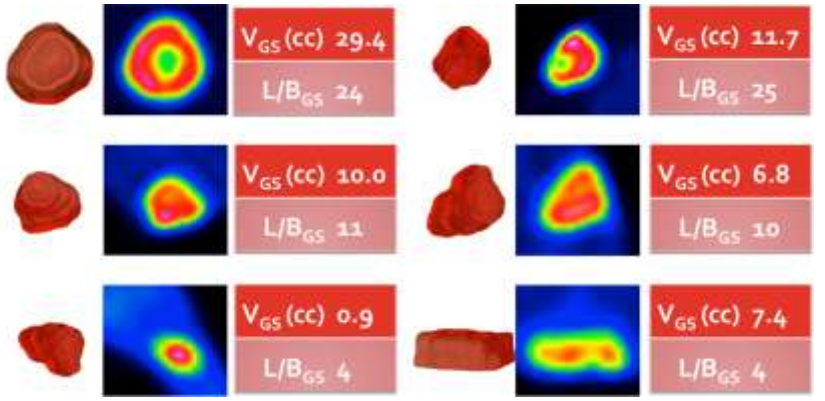
*Selected as highlight at IEEE NSS MIC, Strasburgh, November 2016*



*Real patient*



*Anthropomorphic phantom with syntehtic lesion*




*Research Article*

**A Method for Manufacturing Oncological Phantoms for the Quantification of 18F-FDG PET and DW-MRI Studies**


Francesca Gallivanone,[1] Irene Carne,[2] Matteo Interlenghi,[1] Daniela D'Ambrosio,[2] Maurizia Baldi,[3] Daniele Fantinato,[1] and Isabella Castiglioni[1]

[1]*Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Milan, Italy*
[2]*Medical Physics Unit, IRCCS Fondazione S. Maugeri, Pavia, Italy*
[3]*Department of Diagnostic Imaging, IRCCS Fondazione S. Maugeri, Pavia, Italy*

# Radiomics repeatability

Research Article

**Parameters Influencing PET Imaging Features: A Phantom Study with Irregular and Heterogeneous Synthetic Lesions**

Francesca Gallivanone,[1] Matteo Interlenghi,[1] Daniela D'Ambrosio,[2] Giuseppe Trifirò,[3] and Isabella Castiglioni[1]

[1]Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Milan, Italy
[2]Medical Physics Unit, IRCCS Fondazione S. Maugeri, Pavia, Italy
[3]Nuclear Medicine Unit, IRCCS Fondazione S. Maugeri, Pavia, Italy

- **Test-retest** is performed among the distributions of the radiomic values obtained in the subsequent measurements.
- The pairwise Intraclass Correlation coefficient (ICC) is calculated (ICC>0.7 is considered for stability).

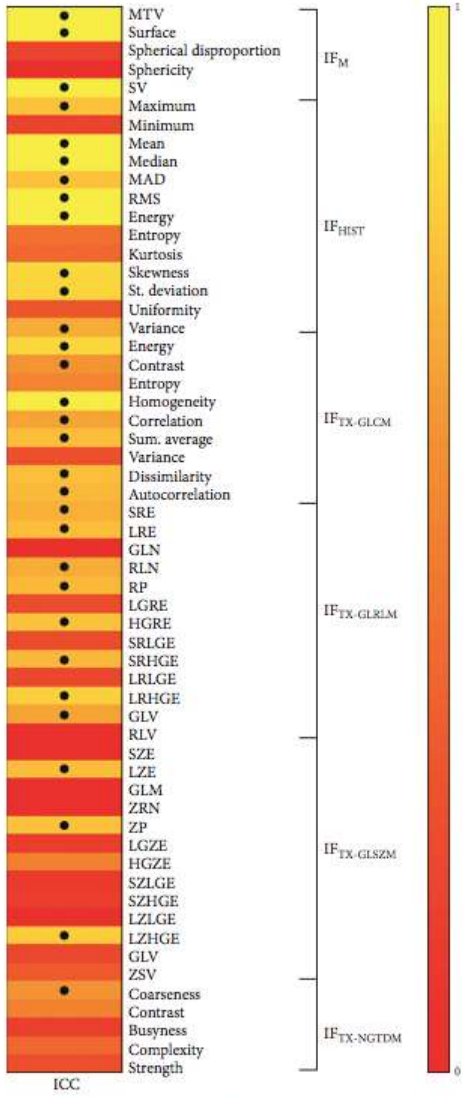



FIGURE 6: Reproducibility of radiomic features on test-retest datasets. ICC results. • indicates ICC ≥ 0.6.

**High repeatability**

# Radiomics reproducibility

- Preparation
- Acquisition
- Reconstruction
- Segmentation
- **Interpolation**
- **Re-segmentation**
- **Discretization**

# Preparation and acquisition

- Patient's conditions (e.g. Glycemia)
- Injected dose
- Scan time vs uptake time
- Time per bed position
- Respiratory motion

...

# Preparation and acquisition | Uptake time

*Lovat et al. 2017* – 54 neurofibromas
a significant **radiomic value change** between two different **uptake times** both for benign and malignant  lesions

# Preparation and acquisition | Respiratory motion

*Vaidya et al. 2012* - 27 lung cancer
**Radiomic value change** considering or not **respiratory motion** correction by image deconvolution. ***No change in radiotherapy response.***

*Yip et al. 2014* - 26 lung cancer/*Oliver et al. 2015* - 23 lung cancer
**Radiomic value change** considering or not **respiratory motion** correction by gating. ***No results on clinical outcome.***

*Grootjans et al. 2016* - 60 lung cancer
**Radiomic value change** in lower lobes considering or not **respiratory motion** correction by gating. ***No change in prognosis.***

# Image reconstruction

- Method (back-projection, iterative –n. it, n. subset…)
- PSF incorporation or not
- TOF incorporation or not
- Matrix size
- Filter
- PVC or not
- Statistical noise

…

# Image reconstruction

*Galavis et al. 2010* - 20 solid cancer
**Radiomic value change** with different **reconstruction** settings (method, n iter, matrix size, filter).

*Yan et al. 2015* - 20 lung cancer */ Orlhac et al*. 2017 - 54 breast cancer
**Radiomic value change with** different **reconstruction** settings (method, n iter, matrix size, filter) ±TOF± PSF.
**However, matrix size is the more impacting factor.**

*Shiri et al. 2017* - 25 lung, head, neck, liver cancer
**Poor  reproducibility of radiomic values** for different **reconstruction** settings (method, n iter, n subset, matrix size, filter, PSF, TOF, scan time).

# Radiomics reproducibility

Hindawi
Contrast Media & Molecular Imaging
Volume 2018, Article ID 5324517, 12 pages
https://doi.org/10.1155/2018/5324517

*Research Article*

**Parameters Influencing PET Imaging Features: A Phantom Study with Irregular and Heterogeneous Synthetic Lesions**

**Francesca Gallivanone**,[1] **Matteo Interlenghi**,[1] **Daniela D'Ambrosio**,[2] **Giuseppe Trifirò**,[3] **and Isabella Castiglioni**[1]

[1]*Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Milan, Italy*
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[3]*Nuclear Medicine Unit, IRCCS Fondazione S. Maugeri, Pavia, Italy*

Coefficient of Variation (COV) can be calculated (COV<0.10 is considered for stability)
but a statistical test is the best choice

**High reproducibility**

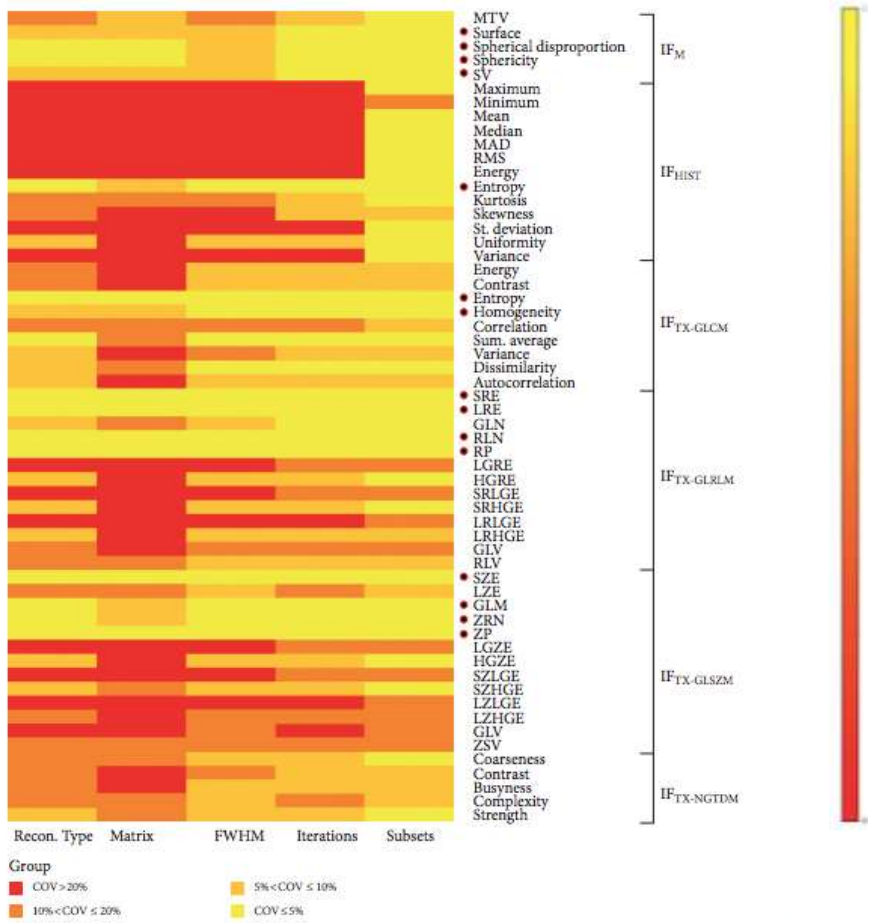
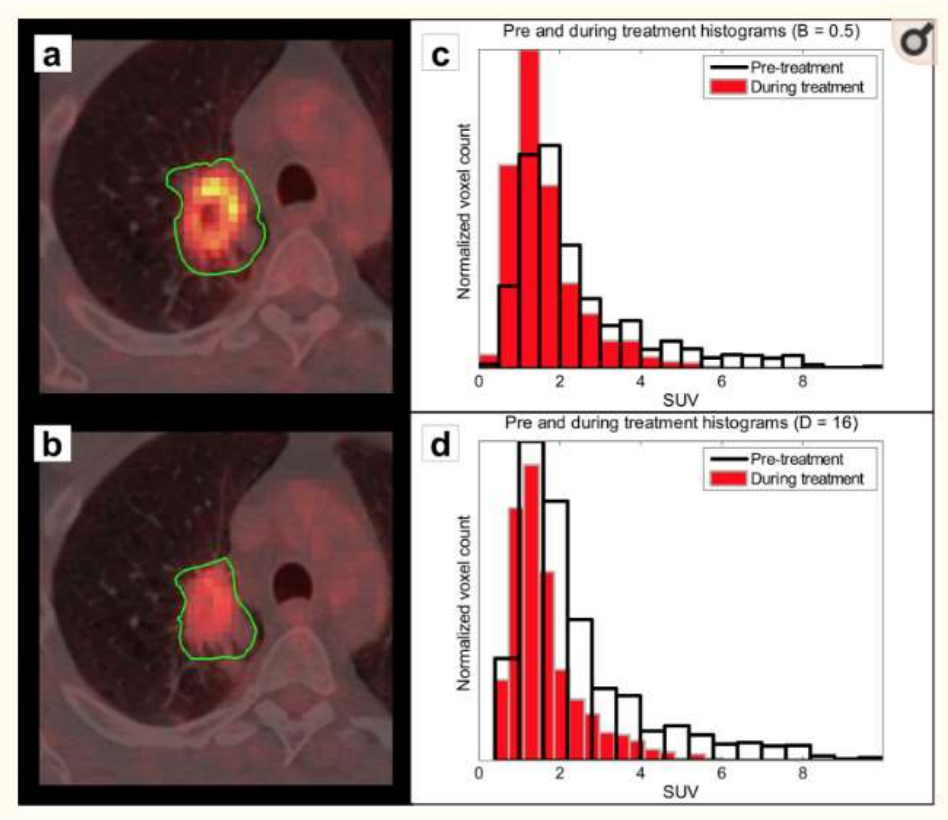



FIGURE 5: Stability of radiomic features on different reconstruction settings. COV results. • indicates COV ≤ 10%

# Discretization

Resampling voxels in a limited number of intensity values (bins) (for textural feature calculation).




Fixed bin size

Fixed bin number

# Discretization

*Leijenaar et al. 2015* - 35 lung cancer
Taxture value is dependent on the method of discretisation
**fixed bin size is recommended** (constant intensity resolution, more robust, repeatable and less sensitive to segmentation and reconstruction changes)

*Lu et al. 2016* - 40 nasopharyngeal carcinoma.
23% of texture features are stable vs **fixed bin size**

*Orlhac et al. 2015* - 48 lung cancer & phantom studies /
*Desseroit et al. 2017* - 73 lung cancer
**fixed bin size is recommended** (not requiring MTV of at least 45cc but less intuitive when imaged).

# Discretization

*Tixier et al.2011* – 41 oesophageal cancer
Textural features are stable and less correlated with MTV for **fixed bin number** (64 bins is recommended since it seems to be sufficient to cover SUV range of lesions with 0.25 increments).

# Segmentation

Segmentation of the tumour volume is a crucial step because **all the radiomics features are calculated starting from the segmented volume**.

A variety of methods exists (manual, thresholding, graph-based, region growing, statistical modelling, contour and gradient-based …)

In radiomics **robustness** (e.g. stability vs noise) is more important than accuracy

# Segmentation

*Hatt et al. 2013*- 50 oesophageal cancer
Entropy, homogeneity showed moderate variability for different segmentation.
**No change in radiochemotherapy response**.

*Leijenaar et al. 2013* - 23 lung cancer
Most textural features **are stable** vs4-operator  manual contouring .

*Orlhac et al. 2014* - 188 colorectal, lung, breast cancer
Entropy and regional textural **are quite stable** for different segmentation methods.

*Hatt et al. 2018* ***- 100 lung cancer***
Sphericity, homogeneity and dissimilarity **value changes**  depending on the segmentation method
**Change in prognosis and prediction of response to treament.**

# Radiomics significance

Hindawi
Contrast Media & Molecular Imaging
Volume 2018, Article ID 5324517, 12 pages
https://doi.org/10.1155/2018/5324517

*Research Article*

**Parameters Influencing PET Imaging Features: A Phantom Study with Irregular and Heterogeneous Synthetic Lesions**

**Francesca Gallivanone**,[1] **Matteo Interlenghi**,[1] **Daniela D'Ambrosio**,[2] **Giuseppe Trifirò**,[3] **and Isabella Castiglioni**[1]

[1]*Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Milan, Italy*
[2]*Medical Physics Unit, IRCCS Fondazione S. Maugeri, Pavia, Italy*
[3]*Nuclear Medicine Unit, IRCCS Fondazione S. Maugeri, Pavia, Italy*

Test correlation of radiomic feature with gold-standard heterogeneity $H_{GS}$

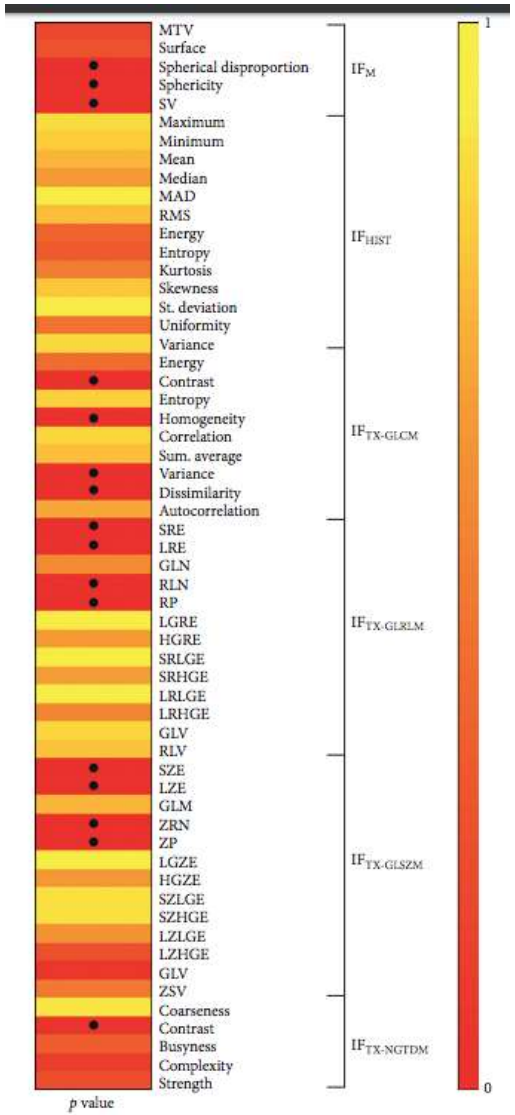



FIGURE 8: Results of correlation analysis between radiomic features and $H_{GS}$ ($p$ value), • indicates $p$ value < 0.05.

**High significance**

# Radiomics significance

Hindawi
Contrast Media & Molecular Imaging
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*Research Article*

**Parameters Influencing PET Imaging Features: A Phantom Study with Irregular and Heterogeneous Synthetic Lesions**

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[1]*Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Milan, Italy*
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[3]*Nuclear Medicine Unit, IRCCS Fondazione S. Maugeri, Pavia, Italy*

- test significant differences among each radiomic feature from heterogeneous vs. homogeneous uptake (e.g. Mann-Whitney test)
- measure the ability of radiomic features in discriminating heterogeneous from homogeneous lesions

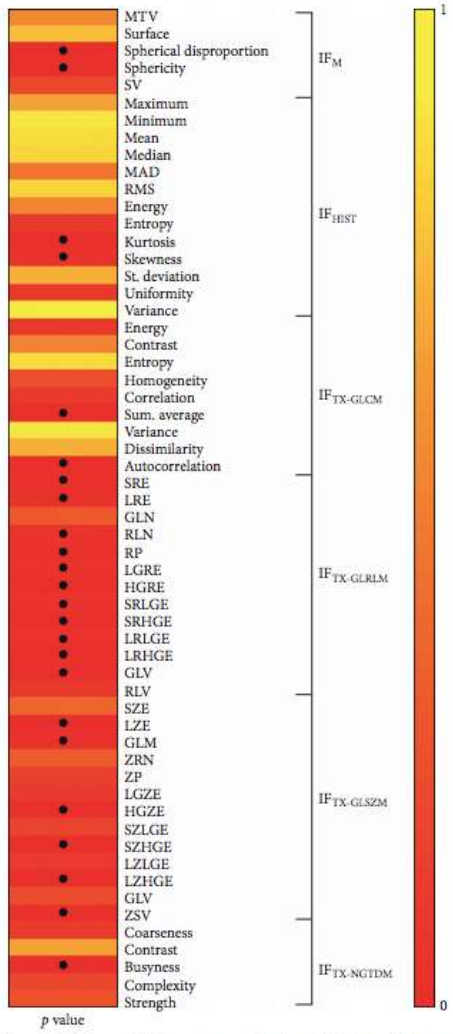



FIGURE 7: Mann–Whitney test results ($p$ value), • indicates $p$ value < 0.05.

**High significance**

# Image Biomarker Standardization Initiative (IBSI)

They are providing:

- image biomarker nomenclature and definitions
- benchmark data sets and values
- reporting guidelines
- consensus-based guidelines for stable radiomic biomarkers

*Zwanenburg A, Leger S, Valli`eres M, L¨ock S. Image biomarker standardisation initiative. arXiv preprint arXiv:1612.07003.*

*Lambin P. Radiomics Digital Phantom, CancerData (2016), DOI:10.17195/candat.2016.08.1*

# Image Biomarker Standardization Initiative (IBSI)

Some recommandations are delivered:
e.g. re-segmentation and discretization

| Imaging intensity units[1] | Re-segmentation range | FBN[2] | FBS[3] |
|---|---|---|---|
| definite | $[a, b]$ | ✔ | ✔ |
| | $[a, \infty)$ | ✔ | ✔ |
| | none | ✔ | × |
| arbitrary | none | ✔ | × |

**Table 2.1** — Recommendations for the possible combinations of different imaging intensity definitions, re-segmentation ranges and discretisation algorithms. Checkmarks (✔) represent recommended combinations of re-segmentation range and discretisation algorithm, whereas crossmarks (×) represent non-recommended combinations.
(1) PET and CT are examples of imaging modalities with *definite* intensity units (e.g. SUV and HU, respectively), and raw MRI data of arbitrary intensity units.
(2) *Fixed bin number* (FBN) discretisation uses the actual range of intensities in the analysed ROI (re-segmented or not), and not the re-segmentation range itself (when defined).
(3) *Fixed bin size* (FBS) discretisation uses the lower bound of the re-segmentation range as the minimum set value. When the re-segmentation range is not or cannot be defined (e.g. arbitrary intensity units), the use of the FBS algorithm is not recommended.

They are working on tolerated variability of radiomics features but results are not currently disclosed ....

# A possible solution?

JNM The Journal of NUCLEAR MEDICINE

**A post-reconstruction harmonization method for multicenter radiomic studies in PET**

Fanny Orlhac, Sarah Boughdad, Cathy Philippe, Hugo Stalla-Bourdillon, Christophe Nioche, Laurence Champion, Michaël Soussan, Frédérique Frouin, Vincent Frouin and Irène Buvat

*J Nucl Med.*
Published online: January 4, 2018.
Doi: 10.2967/jnumed.117.199935

**Harmonization method**

To pool SUV and textural features measured from different PET protocols, we tested a harmonization method previously described for genomic studies to correct the so-called batch effect. The ComBat harmonization model developed by Johnson et al (*25*) assumes that the value of each feature $y$ measured in VOI $j$ and scanner $i$ can be written as:

$$y_{ij} = \alpha + X_{ij}\beta + \gamma_i + \delta_i \varepsilon_{ij} \qquad \text{Equation 1}$$

where $\alpha$ is the average value for feature $y$, $X$ is a design matrix for the covariates of interest, $\beta$ is the vector of regression coefficients corresponding to each covariate, $\gamma_i$ is the additive effect of scanner $i$ on features supposed to follow a normal distribution, $\delta_i$ describes the multiplicative scanner effect supposed to follow an inverse gamma distribution, and $\varepsilon_{ij}$ is an error term (normally distributed with a zero mean), as explained in Fortin et al (*30*). ComBat harmonization consists in estimating $\gamma_i$ and $\delta_i$ using Empirical Bayes estimates (noted $\gamma_i^*$ and $\delta_i^*$) as described in (*25*). The normalized value of feature $y$ for VOI $j$ and scanner $i$ is then obtained as:

$$y_{ij}^{ComBat} = \frac{y_{ij} - \hat{\alpha} - X_{ij}\hat{\beta} - \gamma_i^*}{\delta_i^*} + \hat{\alpha} + X_{ij}\hat{\beta} \qquad \text{Equation 2}$$

where $\hat{\alpha}$ and $\hat{\beta}$ are estimators of parameters $\alpha$ and $\beta$ respectively. The ComBat harmonization determines a transformation for each feature separately based on the batch (here Department) effect observed on feature values. In the first part of this study, we used ComBat without accounting for any biological covariate (ie $X$=0), and, in the second part, we used the TN status as the covariate of interest.

For each tissue separately (tumor and liver tissues), we applied ComBat harmonization on all features using the R function called "combat" available at https://github.com/Jfortin1/ComBatHarmonization/.

# Results

## “Centre effect” on 9 radiomic features from breast cancer patients (63 A vs 74 B)

| | | | | | After ComBat | | | |
|---|---|---|---|---|---|---|---|---|
| | TN(A) vs TN(B) | non-TN(A) vs non-TN(B) | TN(A+B) vs non-TN(A+B) | TN(B) vs non-TN(A) | TN(A) vs TN(B) | non-TN(A) vs non-TN(B) | TN(A+B) vs non-TN(A+B) | TN(B) vs non-TN(A) |
| **Homogeneity** | 0.4232 | **0.0074** | **0.0014** | 0.4635 | 0.5986 | 0.8737 | **0.0015** | **0.0093** |
| **Entropy** | 0.5196 | 0.3906 | **0.0031** | 0.0875 | 0.7405 | 0.9139 | **0.0027** | **0.0254** |
| **SRE** | 0.2995 | **0.00044** | **0.0063** | 0.9481 | 0.1294 | 0.8338 | **0.0062** | **0.0061** |
| **LRE** | 0.2814 | **0.0004** | **0.0072** | 0.9352 | **0.0055** | 0.3871 | **0.0162** | **0.0004** |
| **LGZE** | **0.0405** | **0.0244** | **5.69e-05** | 0.3786 | 0.1102 | 0.3059 | **0.0002** | **0.0003** |
| **HGZE** | **0.0494** | **0.0282** | **3.20e-05** | 0.2886 | 0.2814 | 0.3337 | **2.27e-05** | **0.0058** |
| **SUVmax** | 0.0544 | **0.0278** | **7.54e-05** | 0.4058 | 0.5717 | 0.7943 | **4.47e-05** | **0.0072** |
| **SUVmean** | **0.0448** | **0.0359** | **3.20e-05** | 0.2394 | 0.4463 | 0.7747 | **3.05e-05** | **0.0052** |
| **SUVpeak** | **0.0267** | **0.0306** | **9.75e-05** | 0.4736 | 0.3581 | 0.7894 | **4.99e-05** | **0.0061** |

**Table 3:** P-values of Wilcoxon’s test for all features between TN and non-TN lesions from Departments A and B, before and after ComBat harmonization. Bold values are less than 0.05.

# A recommendation

**Test radiomic results on many different and independent image data sets!**

# Radiomics: a new approach for the study of cancer



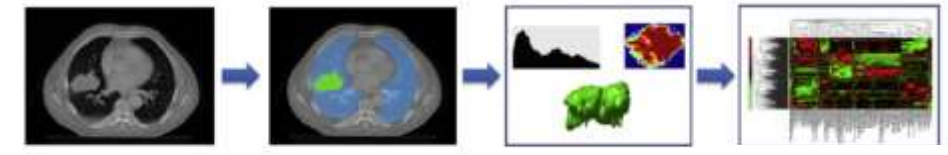
Published in final edited form as:
*Eur J Cancer*. 2012 March ; 48(4): 441–446. doi:10.1016/j.ejca.2011.11.036.

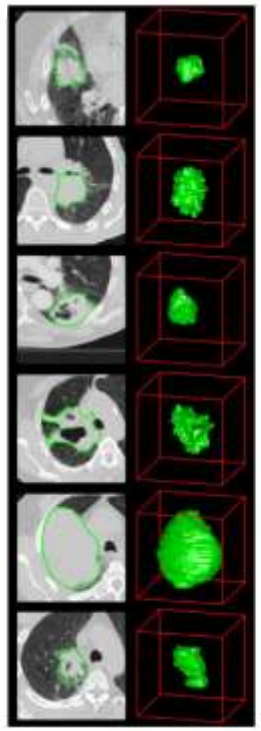
## Radiomics: Extracting more information from medical images using advanced feature analysis

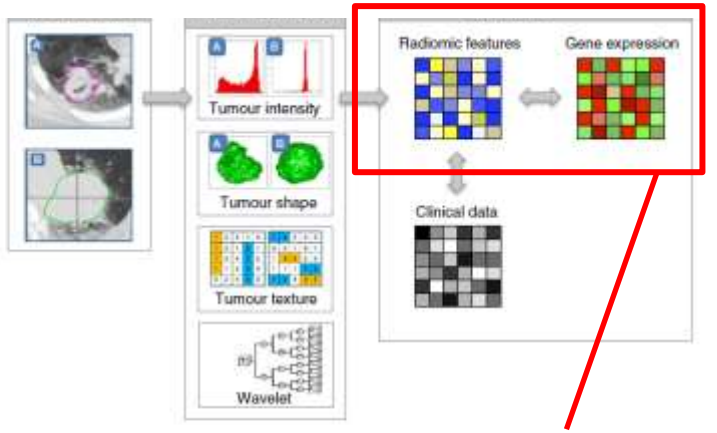
**Philippe Lambin**[a,*,e,f], **Emmanuel Rios-Velazquez**[a,e], **Ralph Leijenaar**[a,e], **Sara Carvalho**[a,e], **Ruud G.P.M. van Stiphout**[a,e], **Patrick Granton**[a,e], **Catharina M.L. Zegers**[a,e], **Robert Gillies**[b,e], **Ronald Boellard**[c,e], **André Dekker**[a,e], and **Hugo J.W.L. Aerts**[a,d,e]

[a]Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands [b]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA [c]U University Medical Center, Department of Nuclear Medicine & PET Research, Amsterdam, The Netherlands [d]Computational Biology and Functional Genomics Laboratory, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard School of Public Health, USA

Comprehensive quantification of disease phenotypes by applying a large number of quantitative image features representing lesion heterogeneity and correlating with omics and clinical data

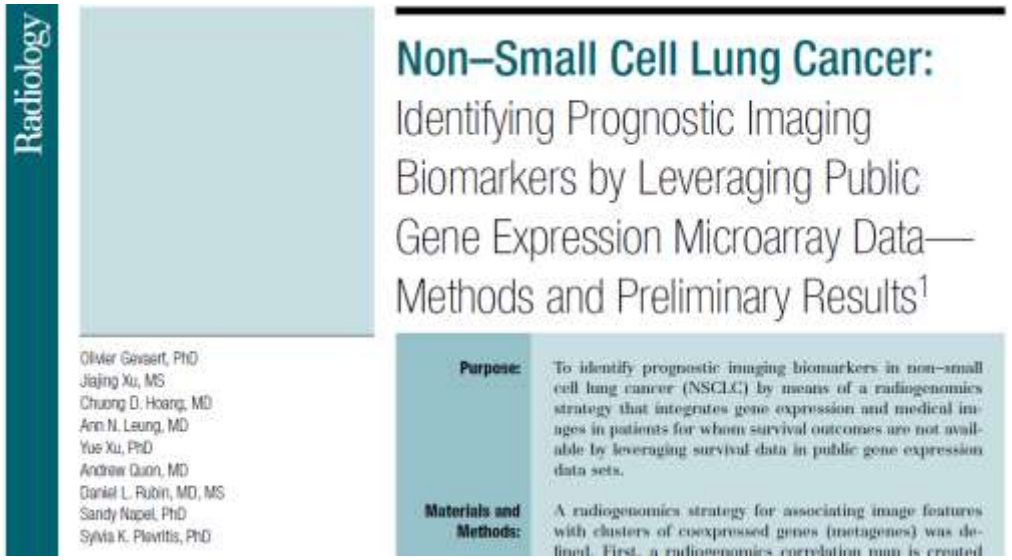





RADIOGENOMICS

# CT radiogenomics for cancer


Radiology

**Non–Small Cell Lung Cancer: Identifying Prognostic Imaging Biomarkers by Leveraging Public Gene Expression Microarray Data—Methods and Preliminary Results**[1]

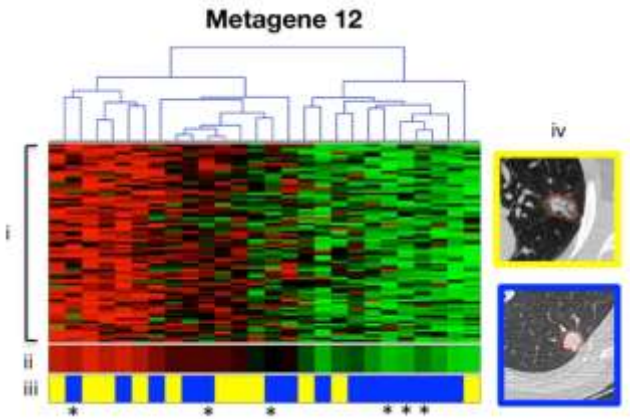
Olivier Gevaert, PhD
Jiajing Xu, MS
Chuong D. Hoang, MD
Ann N. Leung, MD
Yue Xu, PhD
Andrew Quon, MD
Daniel L. Rubin, MD, MS
Sandy Napel, PhD
Sylvia K. Plevritis, PhD

**Purpose:** To identify prognostic imaging biomarkers in non–small cell lung cancer (NSCLC) by means of a radiogenomics strategy that integrates gene expression and medical images in patients for whom survival outcomes are not available by leveraging survival data in public gene expression data sets.

**Materials and Methods:** A radiogenomics strategy for associating image features with clusters of coexpressed genes (metagenes) was de-

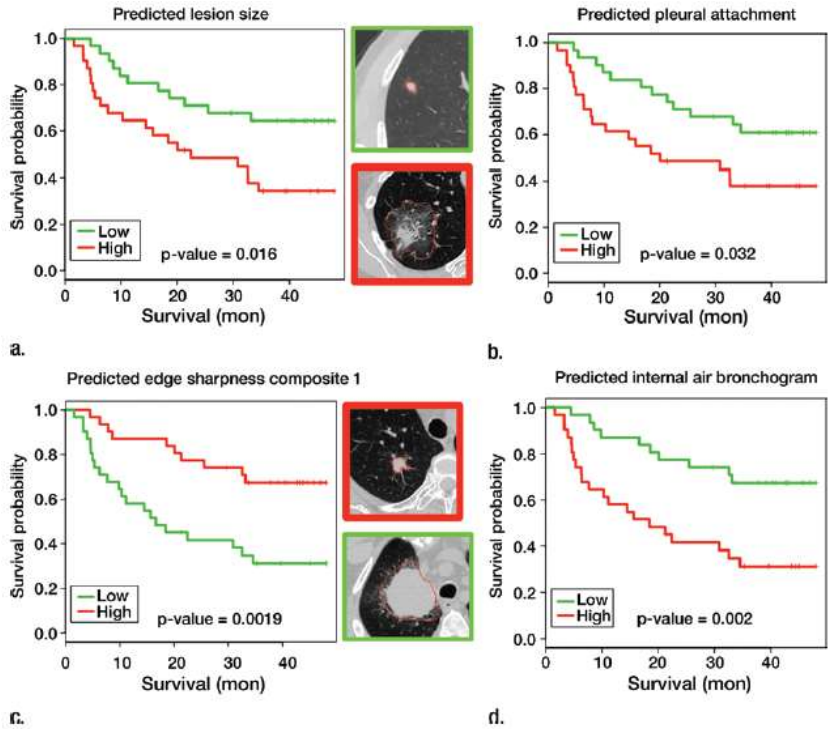
***Radiology:*** Volume 264: Number 2—August 2012 ▪ *radiology.rsna.org*

153 CT features




*Non-Small Cell lung cancer*

4 CT image features



# An approach to radiogenomics: system medicine

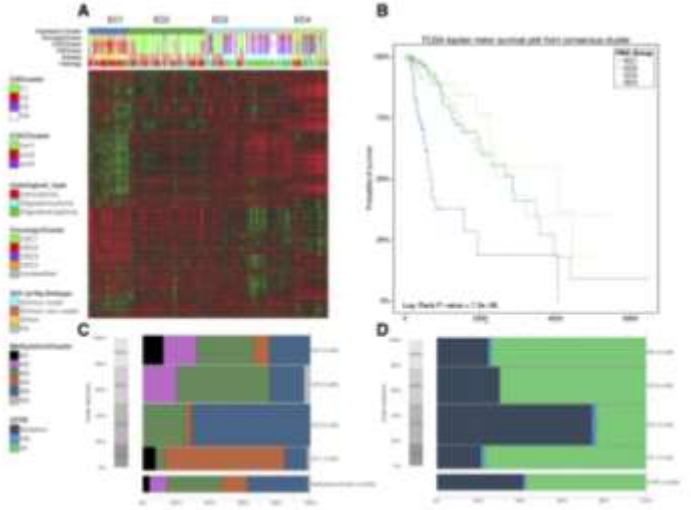
*Published online 23 December 2015*

*Nucleic Acids Research, 2016, Vol. 44, No. 8 e71*
*doi: 10.1093/nar/gkv1507*

## *TCGAbiolinks*: an R/Bioconductor package for integrative analysis of TCGA data

**Antonio Colaprico[1,2,†], Tiago C. Silva[3,4,†], Catharina Olsen[1,2], Luciano Garofano[5,6], Claudia Cava[7], Davide Garolini[8], Thais S. Sabedot[3,4], Tathiane M. Malta[3,4], Stefano M. Pagnotta[5,9], Isabella Castiglioni[7], Michele Ceccarelli[10], Gianluca Bontempi[1,2,*] and Houtan Noushmehr[3,4,*]**

[1]Interuniversity Institute of Bioinformatics in Brussels (IB)[2], Brussels, Belgium, [2]Machine Learning Group (MLG), Department d'Informatique, Université libre de Bruxelles (ULB), Brussels, Belgium, [3]Department of Genetics Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil, [4]Center for Integrative Systems Biology - CISBi, NAP/USP, Ribeirão Preto, São Paulo, Brazil, [5]Department of Science and Technology, University of Sannio, Benevento, Italy, [6]Unlimited Software srl, Naples, Italy, [7]Institute of Molecular Bioimaging and Physiology of the National Research Council (IBFM-CNR), Milan, Italy, [8]Physics for Complex Systems, Department of Physics, University of Turin, Italy, [9]Bioinformatics Laboratory, BIOGEM, Ariano Irpino, Avellino, Italy and [10]Qatar Computing Research Institute (QCRI), HBKU, Doha, Qatar




*Theranostics 2015, Vol. 5, Issue 10* 1122

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*Theranostics*

2015; 5(10): 1122-1140. doi: 10.7150/thno.11545

*Review*

## MicroRNAs: New Biomarkers for Diagnosis, Prognosis, Therapy Prediction and Therapeutic Tools for Breast Cancer

Gloria Bertoli, Claudia Cava, and Isabella Castiglioni

Received: 2015.01.09; Accepted: 2015.06.17; Published: 2015.07.11

*International Journal of Molecular Sciences*

MDPI

*Article*

## SpidermiR: An R/Bioconductor Package for Integrative Analysis with miRNA Data

Claudia Cava [1,*], Antonio Colaprico [2,3], Gloria Bertoli [1], Alex Graudenzi [1], Tiago C. Silva [4], Catharina Olsen [2,3], Houtan Noushmehr [4,5], Gianluca Bontempi [2,3], Giancarlo Mauri [6,7] and Isabella Castiglioni [1,*]

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[2] Interuniversity Institute of Bioinformatics in Brussels (IB)2, Brussels 1050, Belgium; antonio.colaprico@ulb.ac.be (A.C.); colsen@ulb.ac.be (C.O.); gbonte@ulb.ac.be (G.B.)
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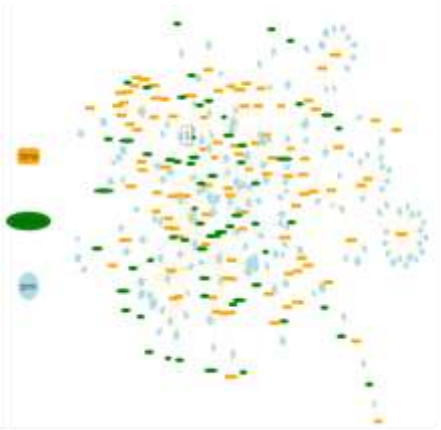


# Breast-cancer system biology

The Author(s) BMC Bioinformatics 2016, 17(Suppl 12):348
DOI 10.1186/s12859-016-1196-1

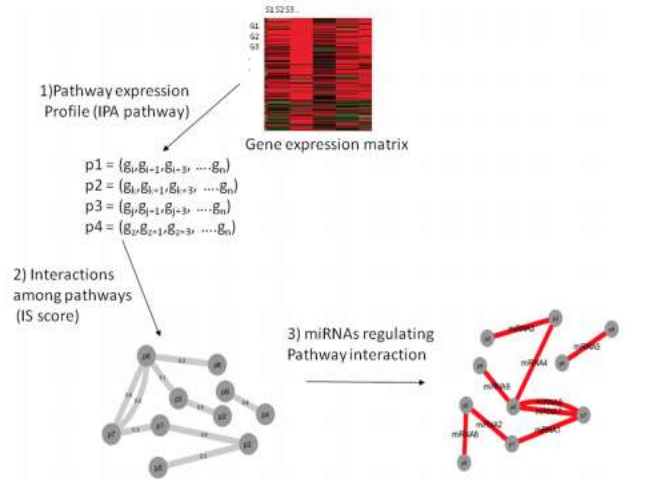
BMC Bioinformatics

RESEARCH Open Access

## How interacting pathways are regulated by miRNAs in breast cancer subtypes

Claudia Cava[1], Antonio Colaprico[2,3], Gloria Bertoli[1], Gianluca Bontempi[2,3], Giancarlo Mauri[4] and Isabella Castiglioni[1*]

From Twelfth Annual Meeting of the Italian Society of Bioinformatics (BITS)
Milan, Italy. 3-5 June 2015




[Frontiers In Bioscience, Landmark, 22, 1697-1712, June 1, 2017]

**Pathway-based classification of breast cancer subtypes**

**Alex Graudenzi[1,2], Claudia Cava[1], Gloria Bertoli[1], Bastian Fromm[3], Kjersti Flatmark[3,4,5], Giancarlo Mauri[2,6], Isabella Castiglioni[1]**

*[1]Institute of Molecular Bioimaging and Physiology of the Italian National Research Council (IBFM-CNR), Milan, Italy, [2]Department of Informatics, Systems and Communication, University of Milan-Bicocca, Milan, Italy, [3]Department of Tumor Biology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway, [4]Department of Gastroenterological Surgery, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway, [5]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [6]SYSBIO Centre of Systems Biology (SYSBIO), 20126 Milan, Italy*

**Table 1.** Unique pathways enriched of differentially expressed genes for each breast cancer subtype: 17 pathways for luminal A, 5 for luminal B, 19 for basal and 16 for HER2

| LUMINAL A | LUMINAL B | BASAL | HER2 |
|---|---|---|---|
| REACTOME degradation of the extracellular matrix | KEGG arrhythmogenic right ventricular cardiomyopathy arvc | REACTOME rrna splicing | REACTOME activation of the mrna upon binding of the cap binding complex and eifs and subsequent binding to 43s |
| BIOCARTA mirnas pathway | REACTOME cmgs in sensilla signaling | REACTOME activation of the pre replicative complex | REACTOME unfolded protein response |
| REACTOME abc family proteins mediated transport | BIOCARTA cellcycle pathway | KEGG spliceosome | REACTOME developmental biology |
| REACTOME ethanol oxidation | KEGG ribosome | KEGG apoptosis | KEGG ether lipid metabolism |
| BIOCARTA ecm pathway | REACTOME cell junction organization | REACTOME activation of atr in response to replication stress | REACTOME axon guidance |
| REACTOME metabolism of carbohydrates | | KEGG dna replication | REACTOME nucleotide like purinergic receptors |
| REACTOME glycosaminoglycan biosynthesis | | REACTOME interferon alpha beta signaling | REACTOME cgmp effects |
| REACTOME platelet activation signaling and aggregation | | BIOCARTA nerve pathway | REACTOME fgfr ligand binding and activation |
| KEGG chemokine signaling pathway | | KEGG type i diabetes mellitus | REACTOME phosphatidylinositol 3 kinase pi3k mediated signaling |
| BIOCARTA erythr pathway | | BIOCARTA g2 pathway | REACTOME glycolysis |
| BIOCARTA longevity pathway | | KEGG bladder cancer | KEGG histidine metabolism |
| REACTOME triglyceride biosynthesis | | REACTOME s phase | KEGG natural killer cell mediated cytotoxicity |
| REACTOME transmembrane transport of small molecules | | REACTOME g1 s transition | REACTOME asparagine n linked glycosylation |
| BIOCARTA dhr pathway | | REACTOME amino acid synthesis and interconversion transamination | REACTOME p2y receptors |
| REACTOME o linked glycosylation of mucins | | REACTOME metabolism of amino acids and derivatives | REACTOME keratan sulfate keratin metabolism |
| REACTOME transport of glucose and other sugars bile salts and organic acids metal ions and amine compounds | | KEGG arginine and proline metabolism | KEGG melanoma |
| REACTOME factors involved in megakaryocyte development and platelet production | | KEGG glycolysis gluconeogenesis | |
| | | BIOCARTA mcm pathway | |
| | | REACTOME activation of ampk downstream of nmdars | |

# Conclusions

Radiomic features have been shown to be sensitive to many factors, i.e. preparation & acquisition, reconstruction, segmentation and new ones, more specific of radiomic (e.g discretization).

Factors not only influence the values of radiomics but their extent is highly variable with different results.

These instability generate fluctuations that should not be misinterpreted as being of biological meaning.

# Conclusions

Some solutions are coming and collecting from research groups involved in radiomic harmonization initiatives (e.g. IBSI)

Until clear recommendations on how to harmonize data are defined, you should select only highly repeatable and reproducible radiomic features from your clinical imaging studies and validate in independent studies to select candidates radiomic biomarkers for prognosis and prediction.

However, it is currently not possible to formally exclude any radiomics feature from future investigations solely based upon their low repeatability and riproducibility.

# Conclusions

Advanced image processing such as radiomics combined with machine learning can develop models based on imaging signatures for predicting phenotype subtype prognosis and response to therapy

They are opening new role to in vivo medical imaging in predictive personalized medicine

Some radiomic methodological issues (e.g. lesion segmentation, feature harmonization and stability) need robust solutions and validations prior to be traslated in clinicial studies

Radiomic predicting models can be improved by
liquid epigenomics for integrated phenotype models

christian.salvatore@iusspavia.it

https://christiansalvatore.github.io/machinelearning-iuss/