Methods for assessing quantitative imaging biomarkers (qIB) in breast cancer RT within the TETRIS project

C. Fiorino
Medical Physics, San Raffaele Institute – Vita_Salute University, Milano, Italy

tetris

Risk assessment *Tools* for severe side *Effects* after *breasT Radiotherapy*: radiation safety through biological extended models and *digital twinS*

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EU Grant Agreement n. 101166699

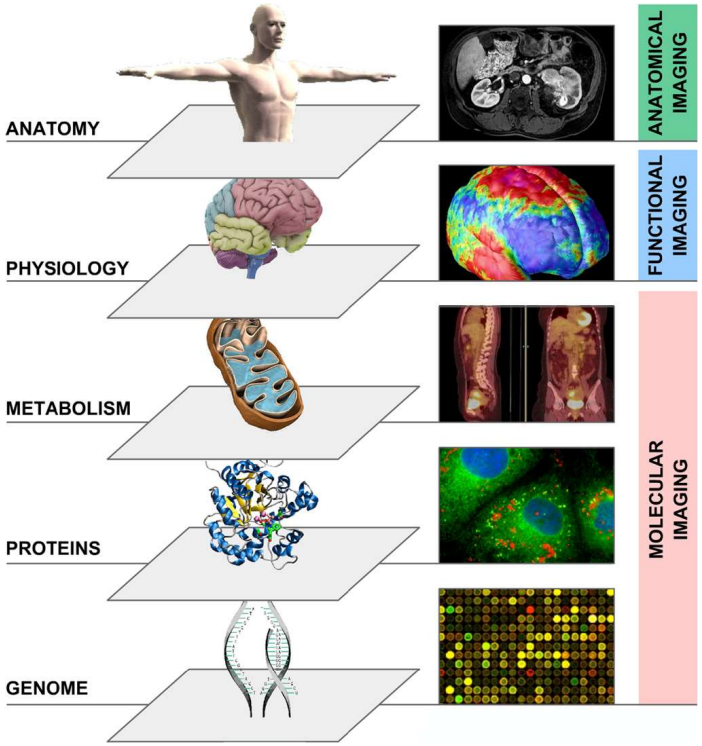
I.R.C.C.S. Ospedale San Raffaele

QUID EST HOMO?
UniSR

Summary

- Intro: qIB to assess/predict Tox, why ?
- Extending qIB to Radiomics
- The (still topical) issue of qIB clinical usability, reliability, reproducibility…..

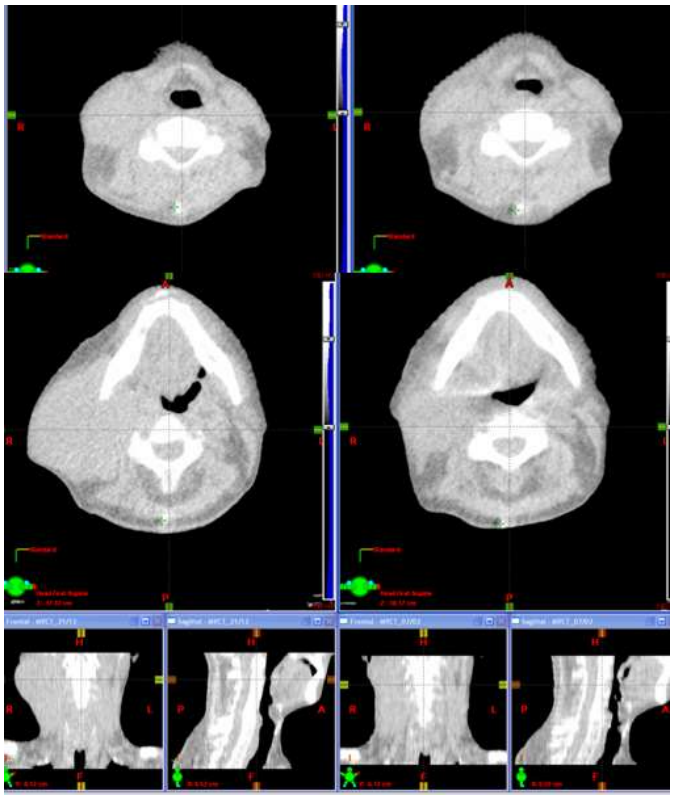
- The philosophy of qIB in TETRIS
- Planning CT & densitometry of lung and heart
- «Simple» vs «Advanced» (multi-centric) qIB analyses



Lambin et al., EJC 2012; 48 (4): 441-446.

qIB to assess/predict Tox, why ?

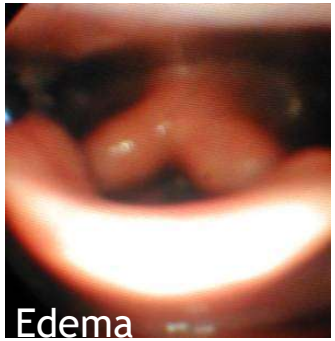
- Medical images are available wout additional costs for all RT patients
- They rely on «familiar» and often «explainable» features
- They capture changes after (and during !!!) RT
- They often assist in the diagnosis of RT-related side-effects
- They can depict morphological and/or functional information
- Images contains potentials for «objective» scoring of pts/tox

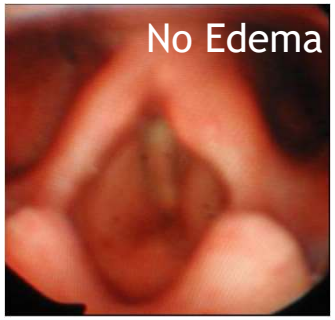


Invited lecture, London, ESTRO 2011 (!!)

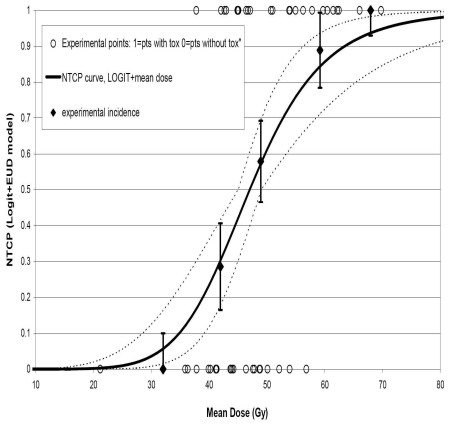
qIB to assess/predict Tox, why ?

- …some «historical» paradigmatic examples in assessing/scoring RT-tox

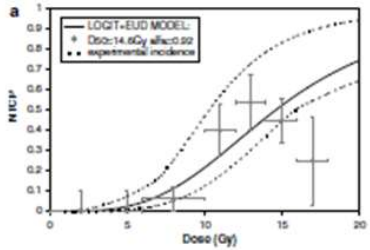




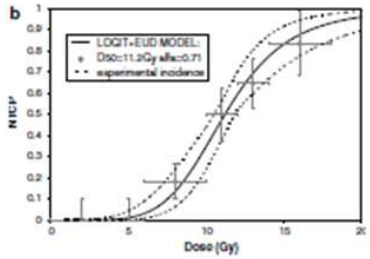
Edema scored by videofluoroscopy



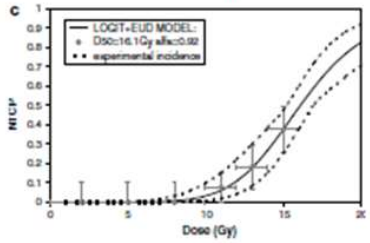
Pulmonary tox scored by X-Rays



Clinical assessment



Density changes assessment (X-Rays)

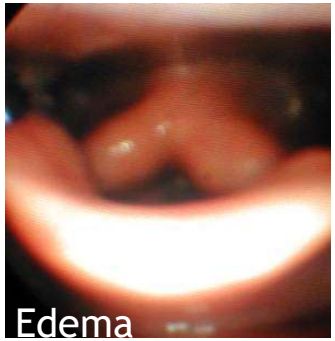


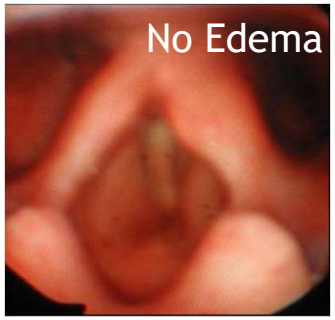
Density changes assessment (CT)

qIB to assess/predict Tox, why ?

- …some «historical» paradigmatic examples in assessing/scoring RT-tox

Pulmonary tox scored by X-Rays





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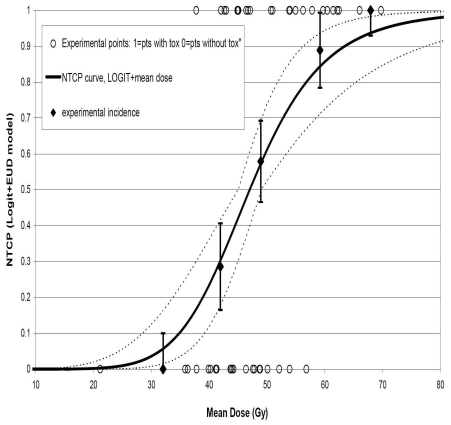
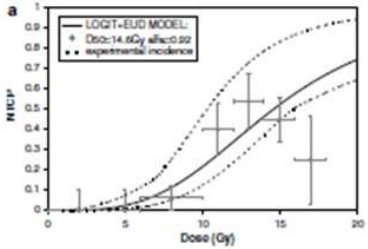
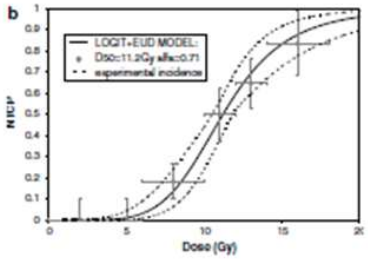


Rancati 2010



Clinical assessment



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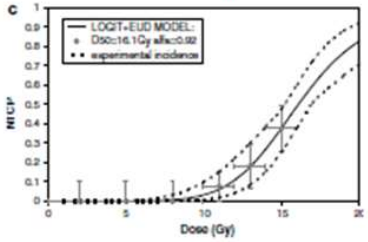


Density changes assessment (CT)

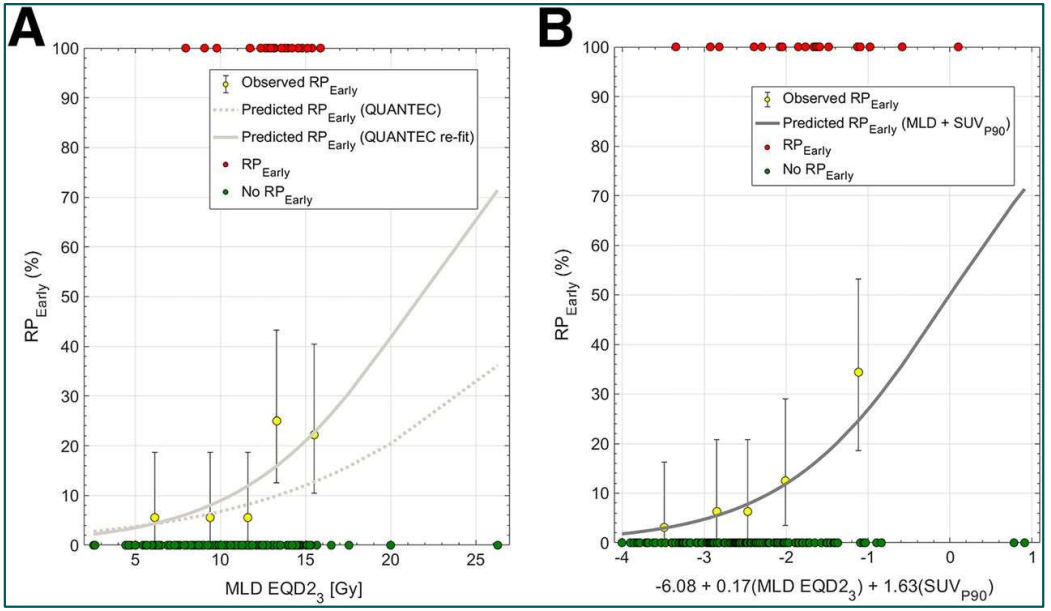
Rancati 2007

qIB to assess/predict Tox, why ?

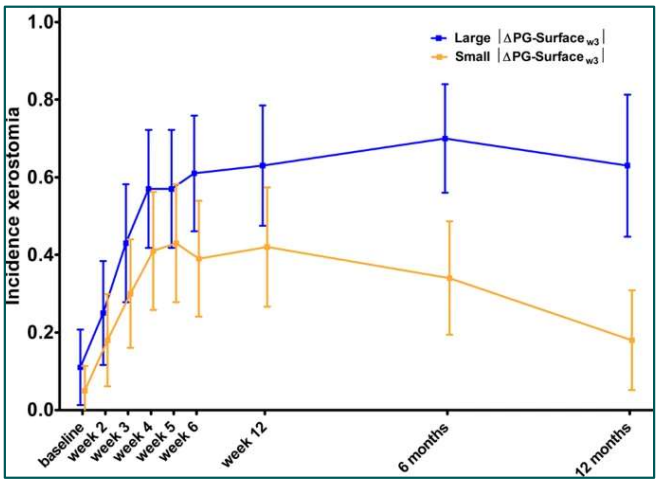
- qIB to predict RT-tox based on:

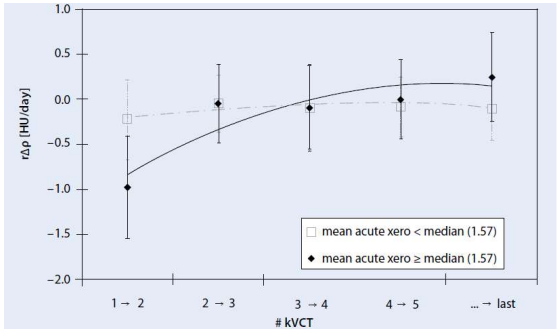
- pre-RT imaging

- Imaging during or early after RT



Thor 2024: Pre-RT FDG PET & MLD outperform MLD alone model to predict pneumonitis

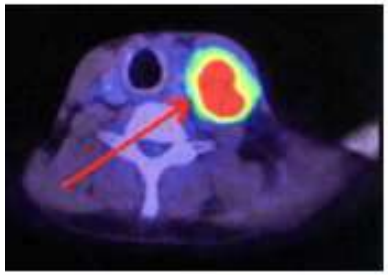


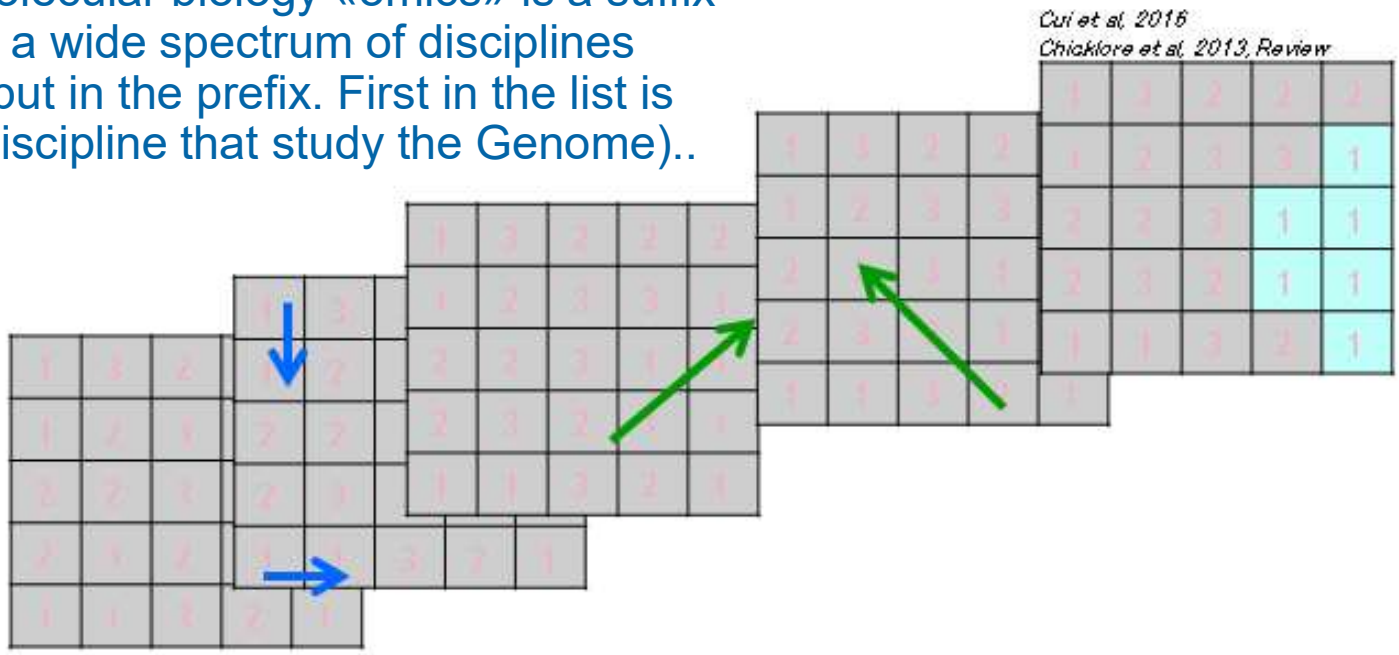


Belli 2014, van Dijk 2019: early changes of parotid volume/density predict acute and late xerostomia

Extending qIB to Radiomics

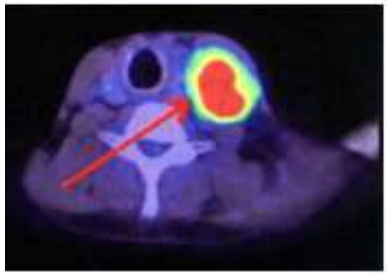
- RADIO - : recall «Radiology», more in general «medical imaging» (not only from X-Rays)
- OMICS - : in molecular biology «omics» is a suffix that is applied to a wide spectrum of disciplines whose object is put in the prefix. First in the list is the Genomics (discipline that study the Genome)..

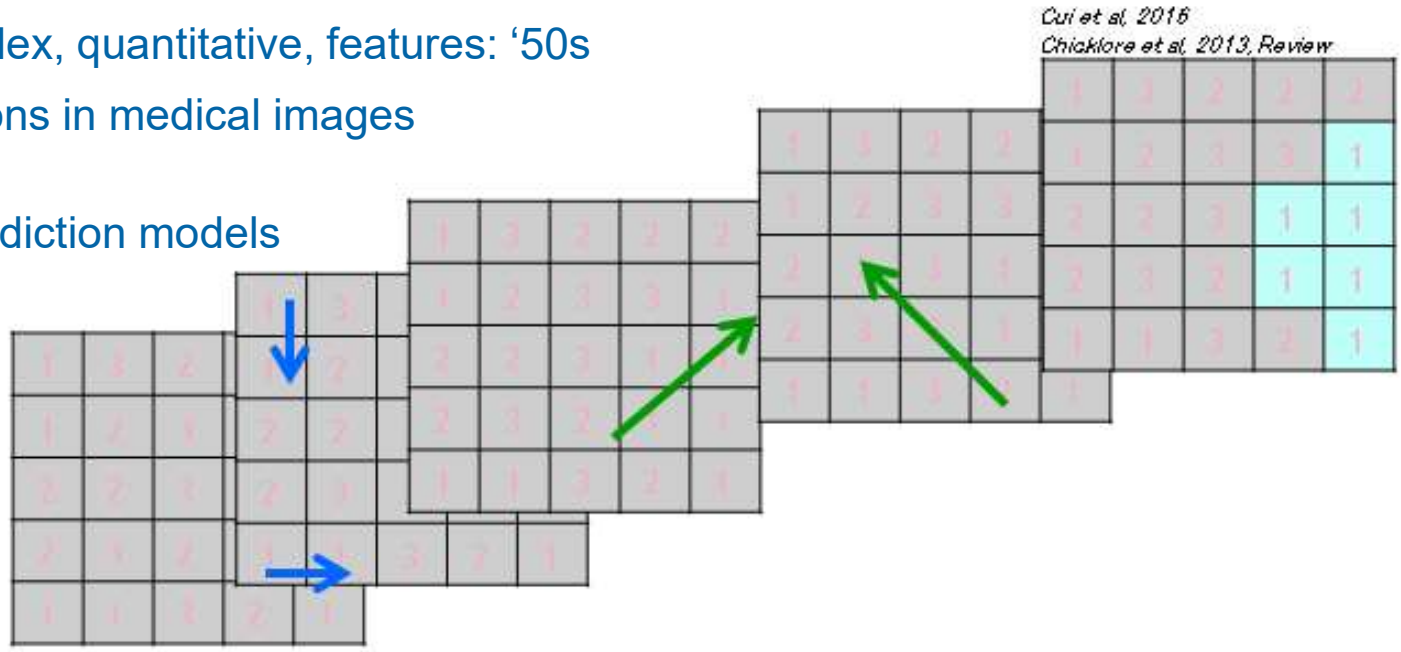




Extending qIB to Radiomics

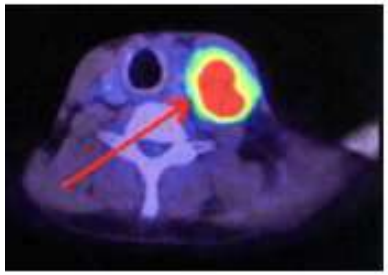
- This «unfocused» word includes the whole spectrum of applications concerning quantitative «features» that may be extracted from medical images
- Looking for complex, quantitative, features: ‘50s
- System applications in medical images (i.e.: CAD): ‘80s
- Application to prediction models in Medicine: ‘00s

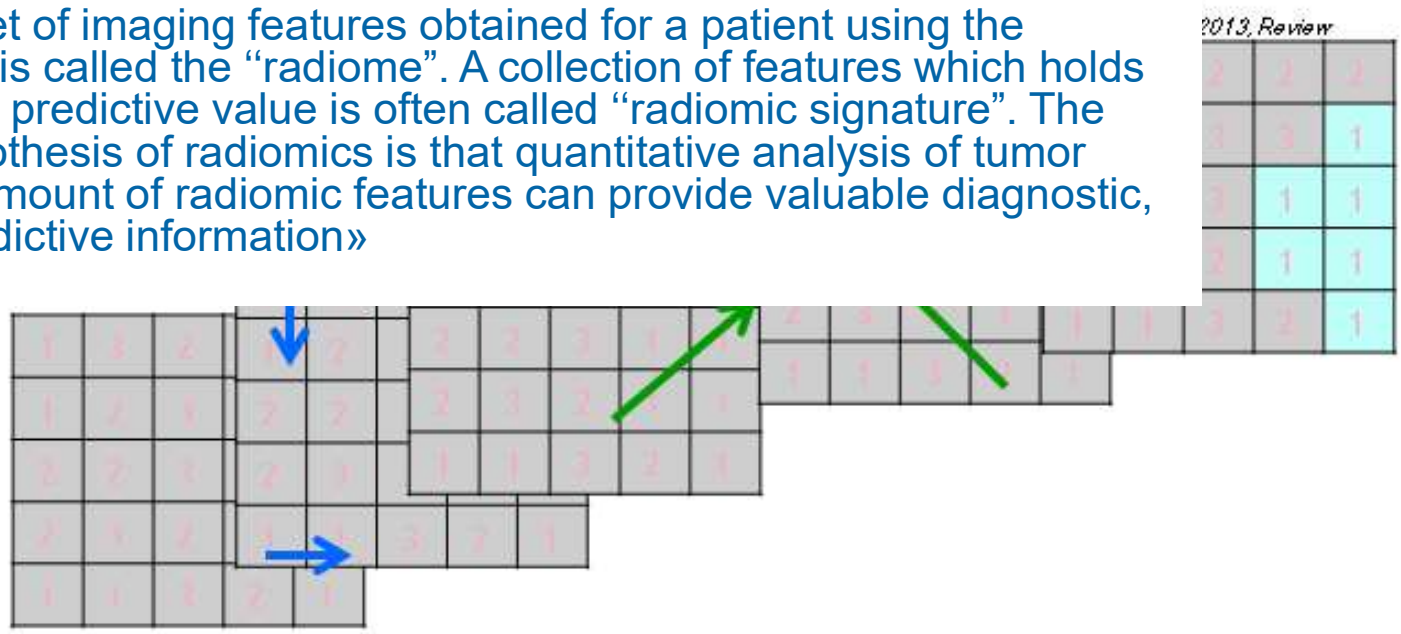




Extending qIB to Radiomics

- Assessment of the use of this word: ≈ 2010
- Of particular value, in the field of Oncology, is the following statement (Avanzo, Stancanello, El Naqa 2017, Phys Med):
- «The complete set of imaging features obtained for a patient using the available images is called the ‘‘radiome”. A collection of features which holds prognostic and/or predictive value is often called ‘‘radiomic signature”. The fundamental hypothesis of radiomics is that quantitative analysis of tumor through a large amount of radiomic features can provide valuable diagnostic, prognostic or predictive information»





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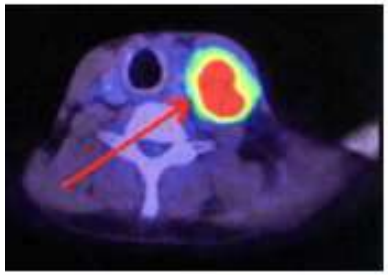
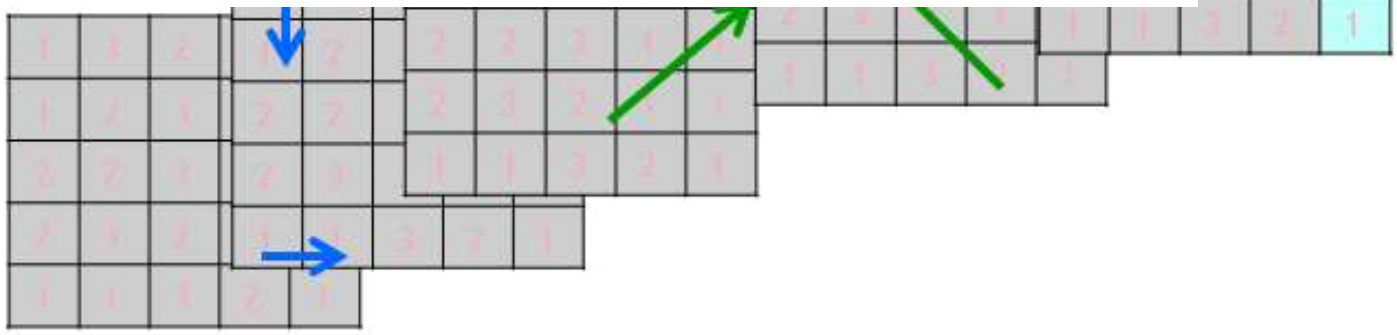
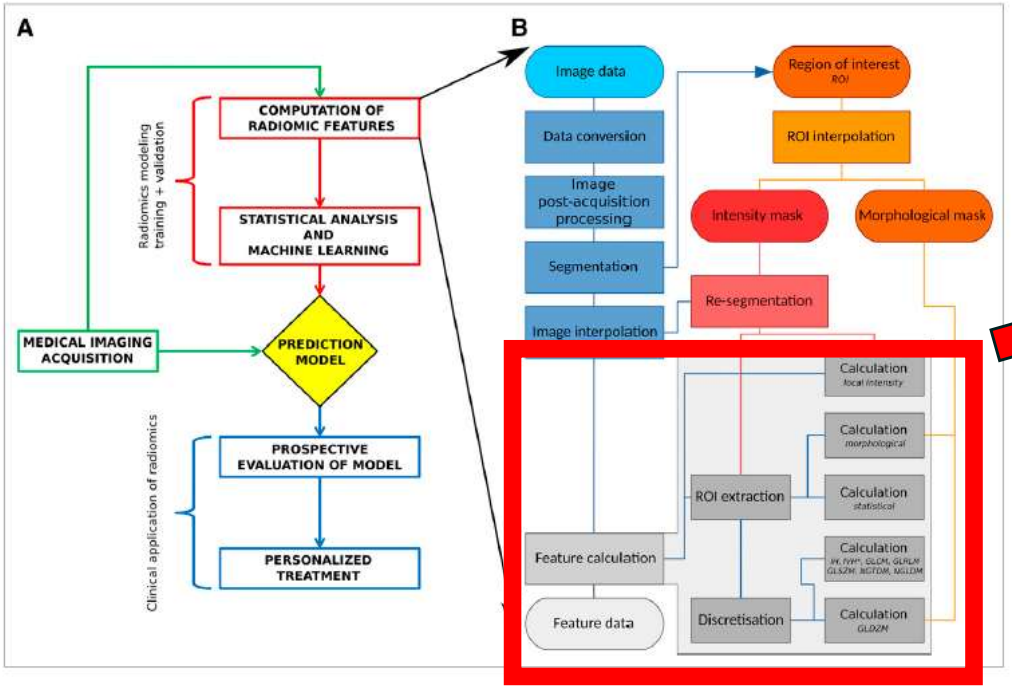


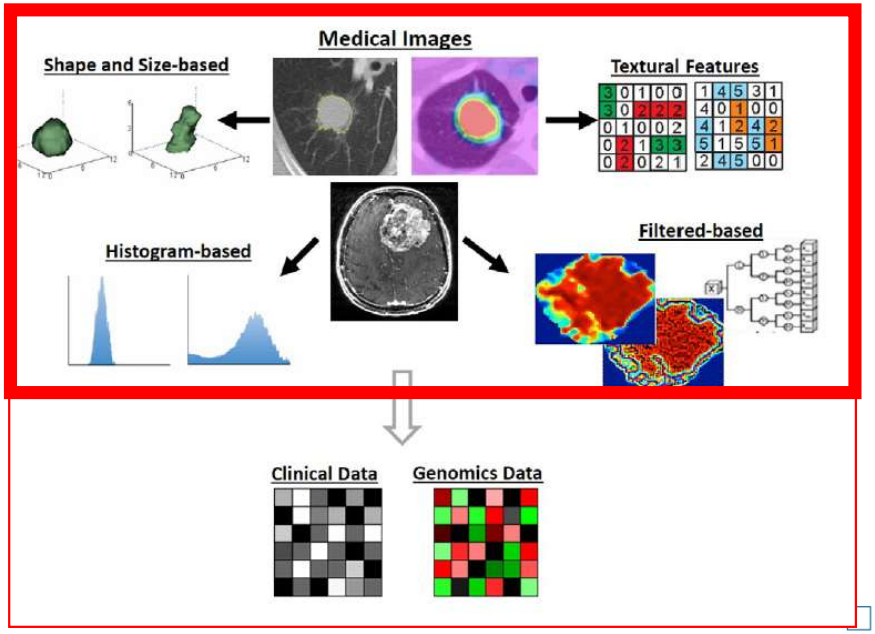


Extending qIB to Radiomics

- The whole qIB/Radiomic picture



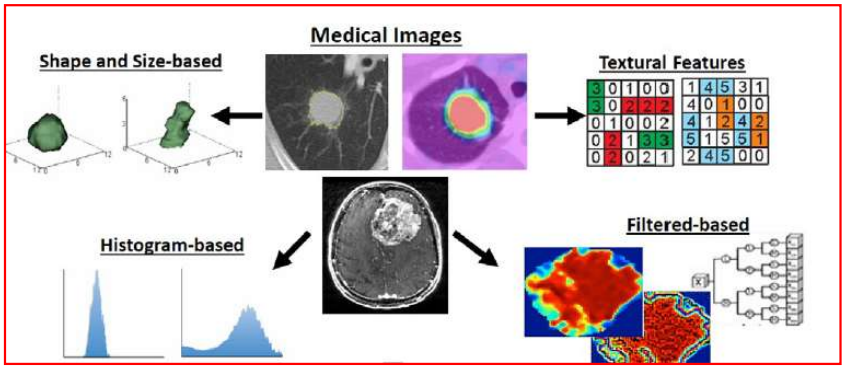
Vallieres, JNM 2018



Yip & Aerts, pmb 2016

Extending qIB to Radiomics

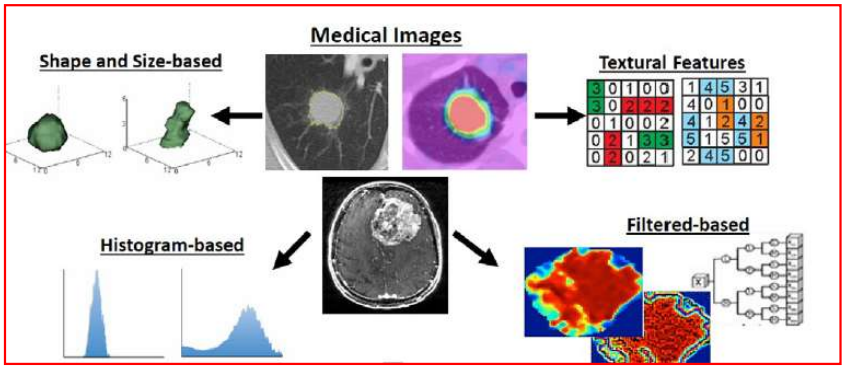
- Families of Radiomic Features



Class	Type	Texture interpretation
Shape	Geometry	Size and shape of the ROI
First order	Grey-level Histogram	Global distribution of intensity value.
Texture (second and higher order)	Grey-level Co-occurrence Matrix (GLCM).	Spatial relationship between pixel in a specific direction.
	Neighbourhood grey-tone difference matrix (NGTDM)	Spatial relationship among three or more pixels.
	Grey-level Run-Length matrix (GLRLM)	Texture in a specific direction.
	Grey-level Size Zone Matrix (GLSZM)	Regional intensity variations or the distribution of homogeneous regions

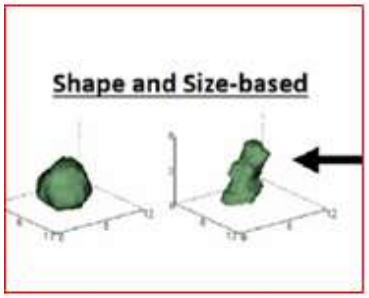
Class	Type	Texture interpretation
Model-based method	Fractal models	Complexity of the image.
Transform-based method	Fourier transform	Analysis of the frequency content without spatial localization
	Wavelet and Gabor filters	Frequency and spatial localization
	Laplacian transform of Gaussian filter (LoG)	Extraction of areas with increasingly coarse texture patterns

Extending qIB to Radiomics



- Families of Radiomic Features

Geometry & shape (order 0)



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Volume

Area

A/V

Compacteness

Sphericity/Asphericity

Max/min length

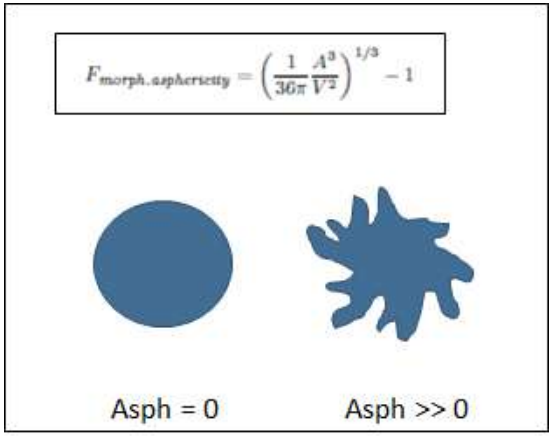
Elongation/Flattnes

Elliptic shape

Area/Volume density

Convexity

Spatial autocorrelation …….

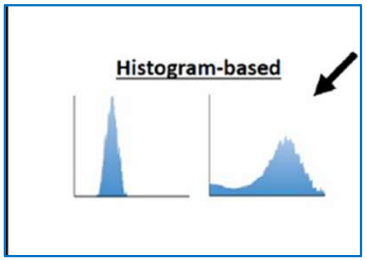


Extending qIB to Radiomics

- Families of Radiomic Features

Intensity-based (order 1)

Mean/median, Min/max, SD, Variance, percentiles, Range, interquartiles, Skeweness, Kurtosis, Dispersion, Energy/entropy, Histogram gradients, Areas under histograms…….



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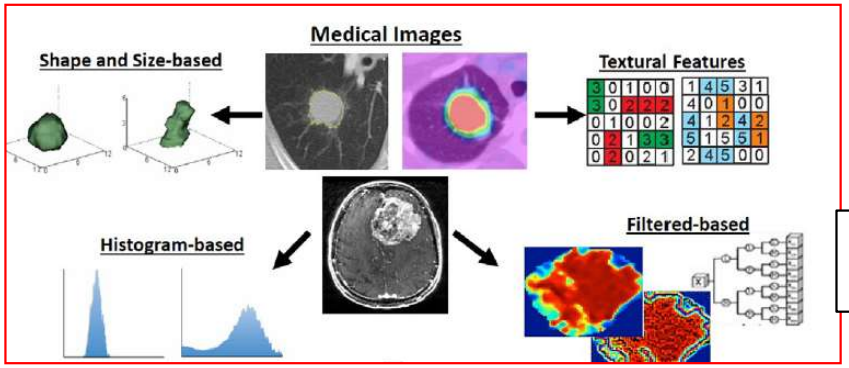
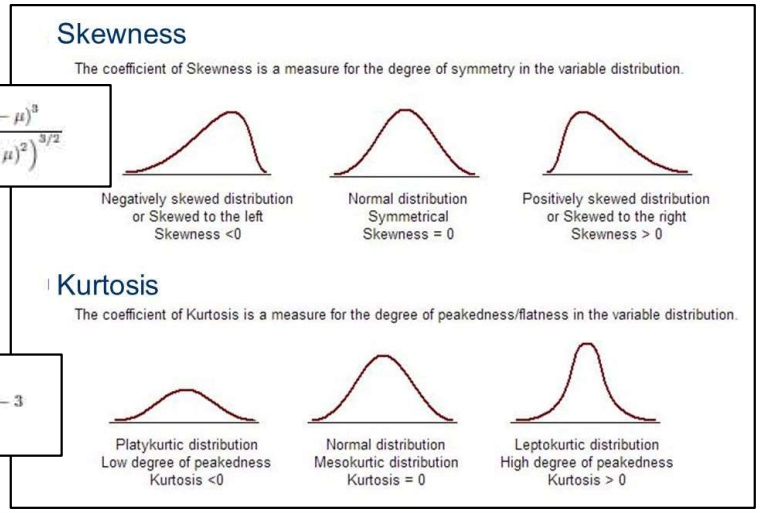


$$F_{stat.skew} = \frac{\frac{1}{N_v}\sum_{k=1}^{N_v}(X_{gl,k}-\mu)^3}{\left(\frac{1}{N_v}\sum_{k=1}^{N_v}(X_{gl,k}-\mu)^2\right)^{3/2}}$$



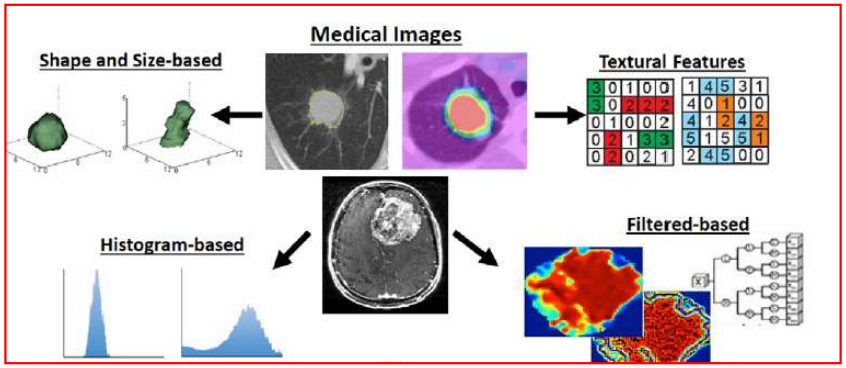
$$F_{stat.kurt} = \frac{\frac{1}{N_v}\sum_{k=1}^{N_v}(X_{gl,k}-\mu)^4}{\left(\frac{1}{N_v}\sum_{k=1}^{N_v}(X_{gl,k}-\mu)^2\right)^2} - 3$$

Extending qIB to Radiomics

- Families of Radiomic Features

Order 2 and higher….

Looking to the relative similarity/dissimilarity between adjacent/neighbour voxels (co-occurrence, relationship between pixels in one direction, relationship between 3 or more pixels, alignment of pixels with the same intensity…..)



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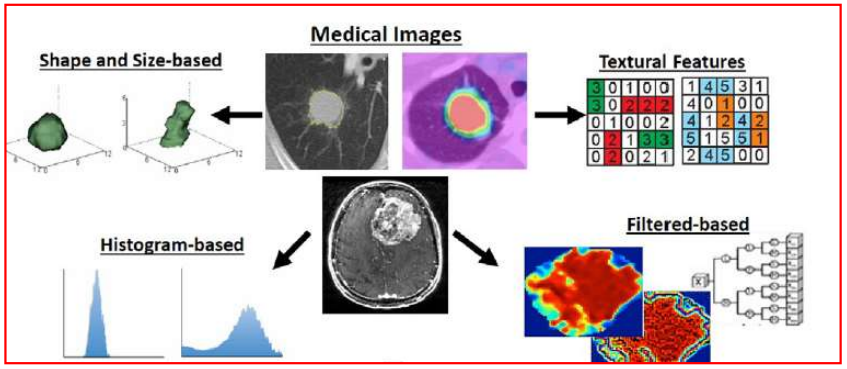


Ex: GLCM….from the co-occurrence matrix

Entropy:

$$Z = -\sum_{i=1}^{G_{max}} \sum_{j=1}^{G_{max}} p(i,j) \cdot \ln(p(i,j))$$

Contrast:

$$Z = -\sum_{i=1}^{G_{max}} \sum_{j=1}^{G_{max}} p(i,j) \cdot (i-j)^2$$

Dissimilarity:

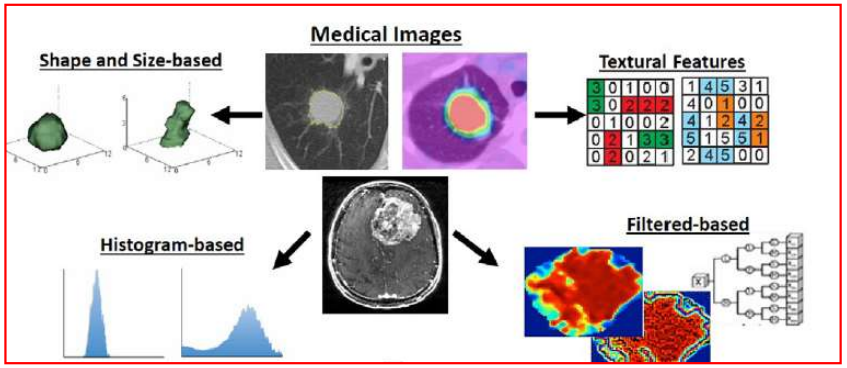
$$Z = -\sum_{i=1}^{G_{max}} \sum_{j=1}^{G_{max}} p(i,j) \cdot |i-j|$$

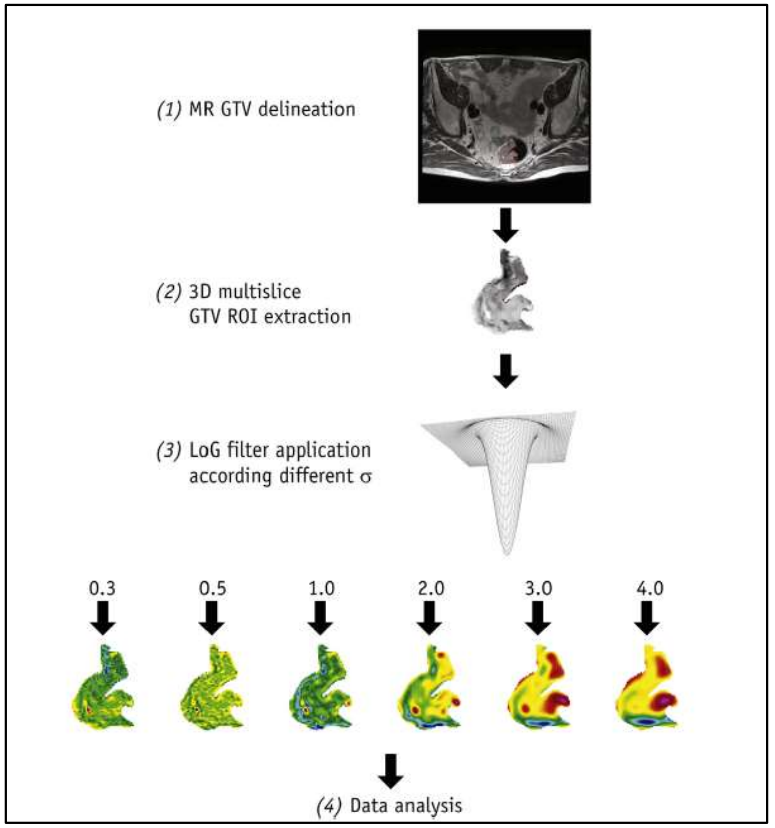
Extending qIB to Radiomics

- Families of Radiomic Features

Filter/Transform based.

Extracting features after imaging processing through, for instance, filtering…



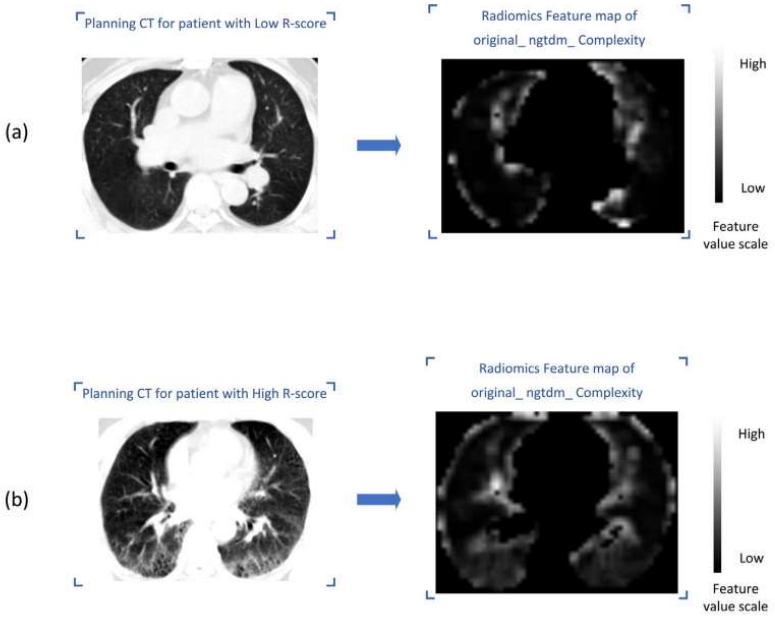


Di Napoli, IJROBP 2018

Extending qIB to Radiomics

- Radiomics & RT tox prediction

Ex: predicting prenumonia



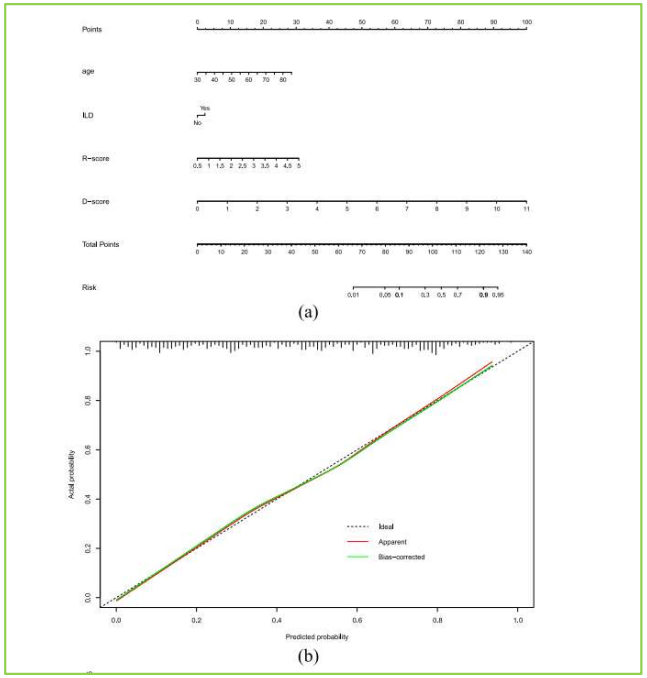


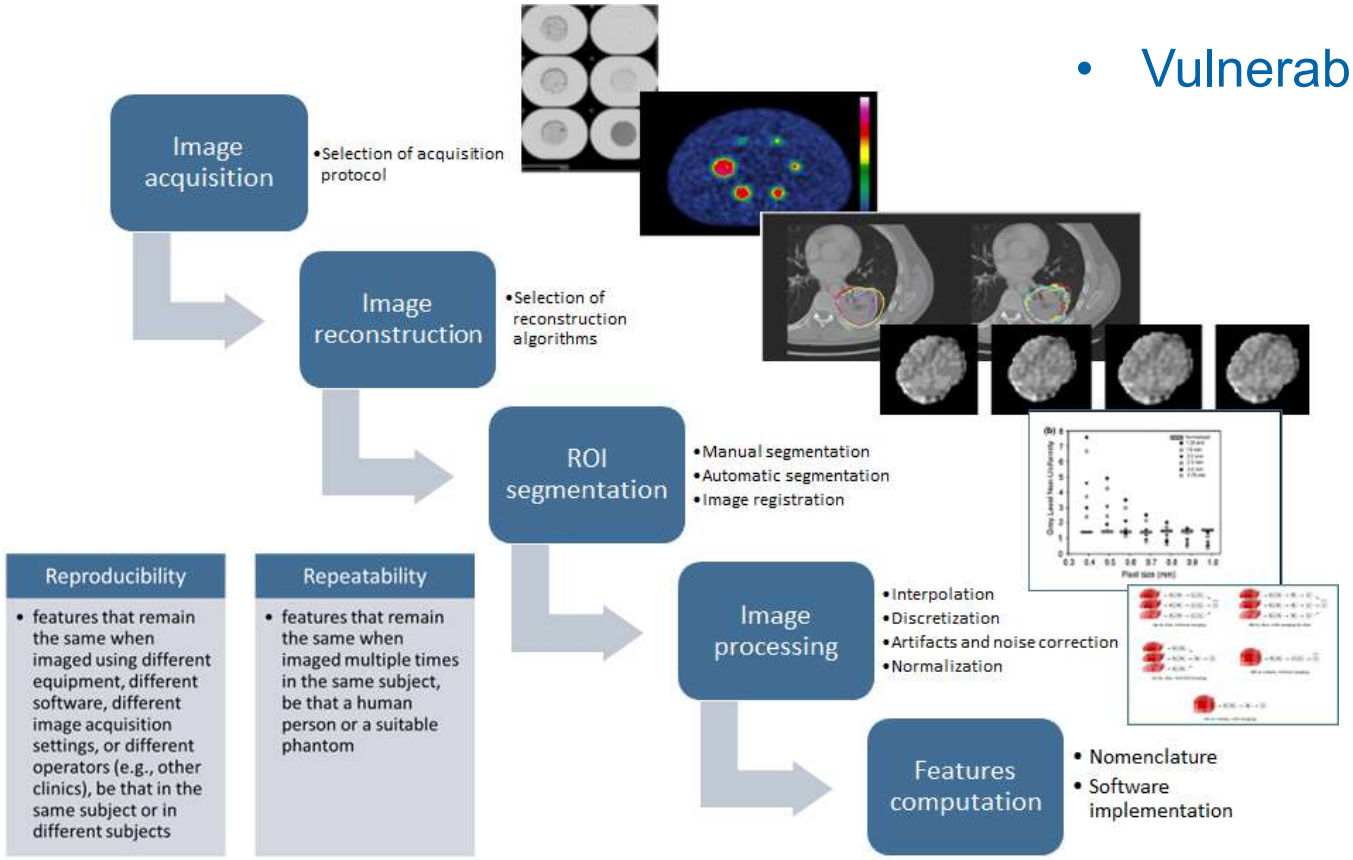
Table 2 Discrimination ability of different models according to area under the curve with 95% CI

Model	Train (95% CI)	Validation by bootstrapping (95% CI)	Testing (95% CI)
R score	0.676 (0.606-0.745)	0.619 (0.592-0.646)	0.671 (0.558-0.899)
D score	0.728 (0.665-0.790)	0.687 (0.667-0.706)	0.684 (0.573-0.883)
DVH score	0.637 (0.570-0.705)	0.628 (0.613-0.642)	0.661 (0.551-0.856)
C	0.664 (0.594-0.735)	0.654 (0.628-0.680)	0.709 (0.509-0.91)
R score + DVH score + C	0.728 (0.674-0.803)	0.719 (0.703-0.736)	0.782 (0.686-0.832)
R score + D score + C	0.793 (0.735-0.851)	0.774 (0.762-0.786)	0.855 (0.719-0.990)

CI, confidence interval; C, clinical parameters; DVH, dose-volume histogram; D, dosiomics risk; R, radiomics risk.

Zhang, IJROBP 2023

The (still topical) issue of qIB clinical usability, reliability, reproducibility…..



- Vulnerability of Radiomics/qIB

Modified from E Scalco IBFM, Milano

The (still topical) issue of qIB clinical usability, reliability, reproducibility…..

TABLE 1
Reporting Guidelines on Computation of Radiomics Features

Category	Guideline.
General	
Image acquisition	Acquisition protocols and scanner parameters such as equipment vendor, reconstruction algorithms and filters, field of view and acquisition matrix dimensions, MRI sequence parameters, PET acquisition time and injected dose, CT x-ray energy (kVp), and exposure (mAs).
Volumetric analysis	Specification of whether imaging volumes were analyzed as separate images (2-dimensional) or as fully-connected volumes (3-dimensional).
Workflow structure	Sequence of processing steps leading to extraction of features.
Software	Software type and version of code used for computation of features.
Image preprocessing	
Conversion	How data were converted from input images (e.g., conversion of PET activity counts to SUV and calculation of ADC maps from raw diffusion-weighted MRI signal).
Processing	Image-processing steps after acquisition (e.g., noise filtering, intensity nonuniformity correction in MRI, and partial-volume effect corrections).
ROI segmentation*†	How ROIs were delineated in images (e.g., software or algorithms used, number of persons and their level of expertise [specialty, experience], method of reaching consensus, and mode [automatic or semiautomatic]).
Interpolation	
Voxel dimensions	Original and interpolated voxel dimensions.
Image interpolation method	Method used for interpolating voxel values (e.g., linear, cubic, or spline) and for aligning original and interpolated grids.
Intensity rounding	Rounding procedures for noninteger interpolated gray levels (if applicable) (e.g., rounding of Hounsfield units in CT images after interpolation).
ROI interpolation method	Methods used for interpolating ROI masks and for aligning original and interpolated grids.
ROI partial volume	Minimum partial-volume fraction required to include an interpolated mask voxel in the interpolated ROI (if applicable) (e.g., minimum partial-volume fraction of 0.5 when using linear interpolation).
ROI resegmentation	
Inclusion/exclusion criteria	Criteria for inclusion or exclusion of voxels from the ROI intensity mask (if applicable) (e.g., exclusion of voxels with Hounsfield unit values outside predefined range inside the ROI intensity mask on CT images).
Image discretization	
Discretization method	Method used for discretizing image intensities before feature extraction (e.g., fixed bin number, fixed bin width, and histogram equalization).
Discretization parameters	Parameters for image discretization (e.g., number of bins, bin width, and minimal value of discretization range).
Feature calculation	
Feature set	Description and formulas of all calculated features.
Feature parameters	Settings for calculation of features (e.g., voxel connectivity, with or without merging by slice, and with or without merging directional texture matrices).
Calibration	
Image-processing steps	Specification of which image-processing steps match benchmarks of the IBSI.
Feature calculation	Specification of which feature calculations match benchmarks of the IBSI.

*To reduce interobserver variability, automatic and semiautomatic methods are favored.
†In multimodal applications (e.g., PET/CT or PET/MRI), ROI definition may involve propagation of contours between modalities via coregistration. In that case, technical details of registration should also be provided.
ROI = region of interest.

Vallieres, 2018

Image biomarker standardisation initiative
version 1.5

Alex Zwanenburg Stefan Leger Martin Vallières Steffen Löck
on behalf of the image biomarker standardisation initiative

17th November 2017

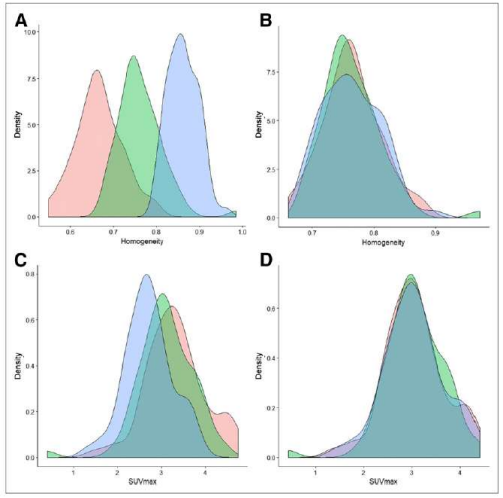
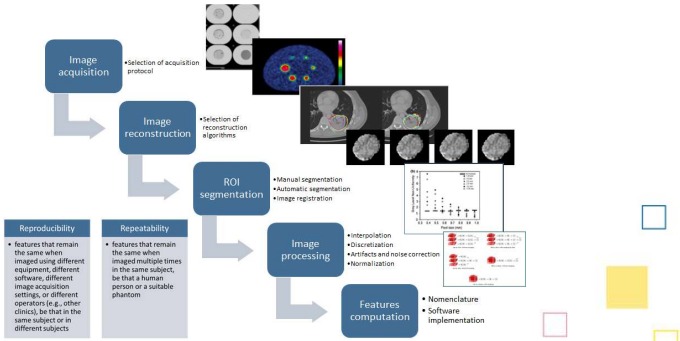


FIGURE 2. Probability density function (%) of homogeneity (A and B) and SUV_{max} (C and D) in liver tissue as observed in departments A (pink), B (green), and A-S (blue), before (left) and after (right) harmonization.

Orlhac, 2019

- Standardization (IBSI !)
- Reducing the impact
- Quantifying the impact
- Identifying stable features
- Harmonizing, if (when) possible



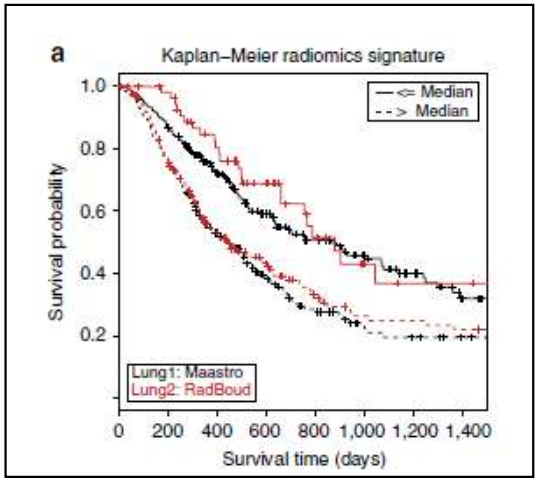
The (still topical) issue of qIB clinical usability, reliability, reproducibility…..

ARTICLE
Received 25 Nov 2013 | Accepted 29 Apr 2014 | Published 3 Jun 2014 | Updated 7 Aug 2014
DOI: 10.1038/ncomms5006

Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach

Hugo J.W.L. Aerts[1,2,3,4,*], Emmanuel Rios Velazquez[1,2,*], Ralph T.H. Leijenaar[1], Chintan Parmar[1,2], Patrick Grossmann[2], Sara Carvalho[1], Johan Bussink[5], René Monshouwer[5], Benjamin Haibe-Kains[6], Derek Rietveld[7], Frank Hoebers[1], Michelle M. Rietbergen[8], C. René Leemans[8], Andre Dekker[1], John Quackenbush[4], Robert J. Gillies[9] & Philippe Lambin[1]

>5600 citations !



- Vulnerability of models incorporating Radiomics/qIB

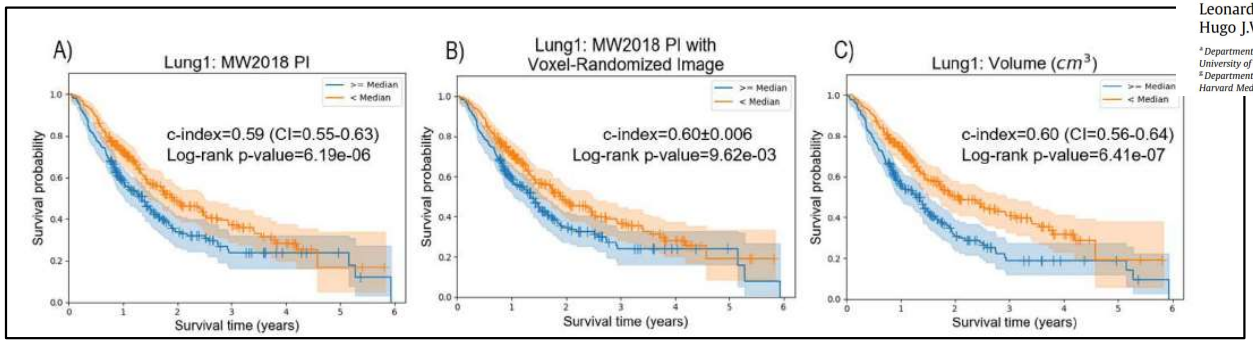
Radiotherapy and Oncology 130 (2019) 2–9
Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Original article

Vulnerabilities of radiomic signature development: The need for safeguards

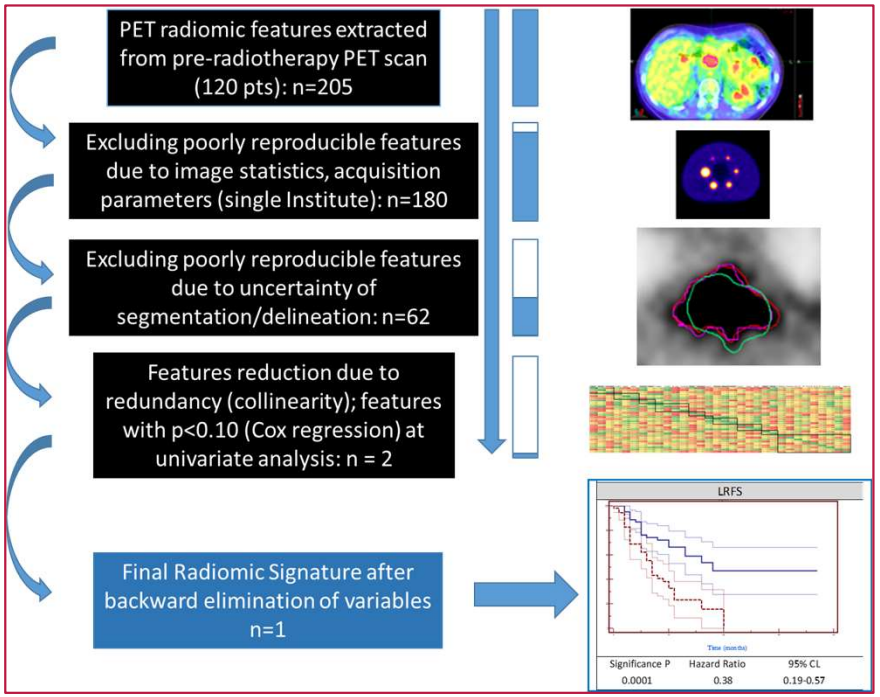
Mattea L. Welch[a,f,i], Chris McIntosh[e,f,i], Benjamin Haibe-Kains[a,c,i,j], Michael F. Milosevic[b,e,i], Leonard Wee[g], Andre Dekker[g], Shao Hui Huang[b,i], Thomas G. Purdie[b,e,f,i], Brian O'Sullivan[b,i], Hugo J.W.L. Aerts[h], David A. Jaffray[a,b,d,e,f,i,*]

[a] Department of Medical Biophysics, University of Toronto; [b] Department of Radiation Oncology, University of Toronto; [c] Ontario Institute of Cancer Research, Toronto; [d] IBBME, University of Toronto; [e] Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto; [f] The Techna Institute for the Advancement of Technology for Health, Toronto, Canada; [g] Department of Radiation Oncology (MAASTRO), GROW Research Institute, Maastricht University, the Netherlands; [h] Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, USA; [i] Princess Margaret Cancer Centre, University Health Network; and [j] Vector Institute, Toronto, Canada



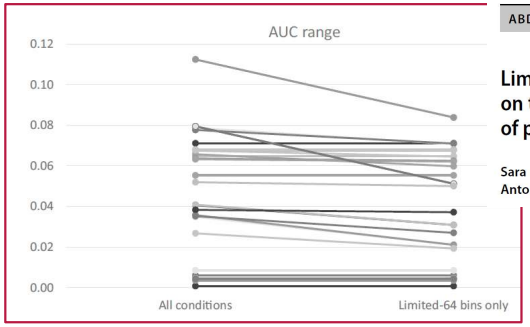
345 citations !

The (still topical) issue of qIB clinical usability, reliability, reproducibility…..



Mori, Radiother Oncol 2020

- Accurate ML methodology to avoid overfit
- Few-features models to be preferred
- Explainability issues
- Validate !!!
- Robustness of informative content



La radiologia medica (2023) 128:799–807
https://doi.org/10.1007/s11547-023-01649-y

ABDOMINAL RADIOLOGY

Limited impact of discretization/interpolation parameters on the predictive power of CT radiomic features in a surgical cohort of pancreatic cancer patients

Sara Loi[1] · Martina Mori[1] · Diego Palumbo[2] · Stefano Crippa[3,4] · Gabriele Palazzo[1] · Emiliano Spezi[5] · Antonella Del Vecchio[1] · Massimo Falconi[3,4] · Francesco De Cobelli[2,4] · Claudio Fiorino[1]

Loi, Radiol Med 2023

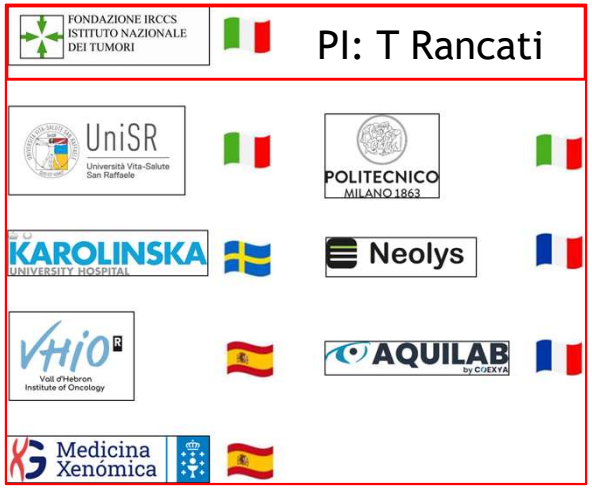
The philosophy of exploring qIB in TETRIS

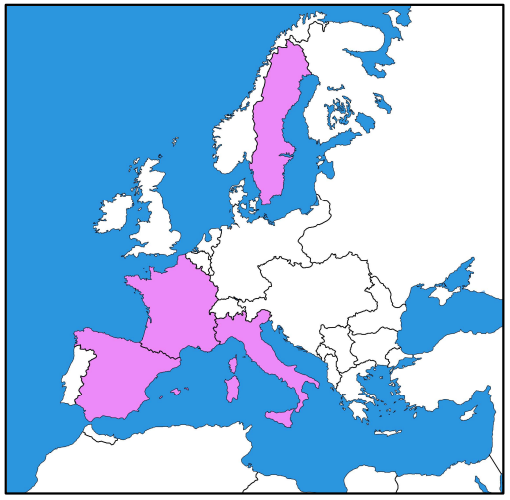
- the TETRIS project is set to develop **quantitative personalised risk scores for late severe cardiac/pulmonary disease and second cancers following RT for BCa**.

RISK ASSESSMENT TOOLS FOR SEVERE SIDE EFFECTS AFTER BREAST RADIOTHERAPY:

RADIATION SAFETY THROUGH BIOLOGICAL EXTENDED MODELS AND DIGITAL TWINS

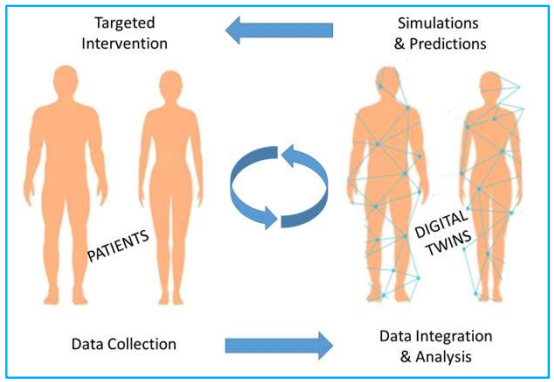
HORIZON-EURATOM-2023-NRT-01-10
Nuclear Research and Training EURATOM
Innovation Actions

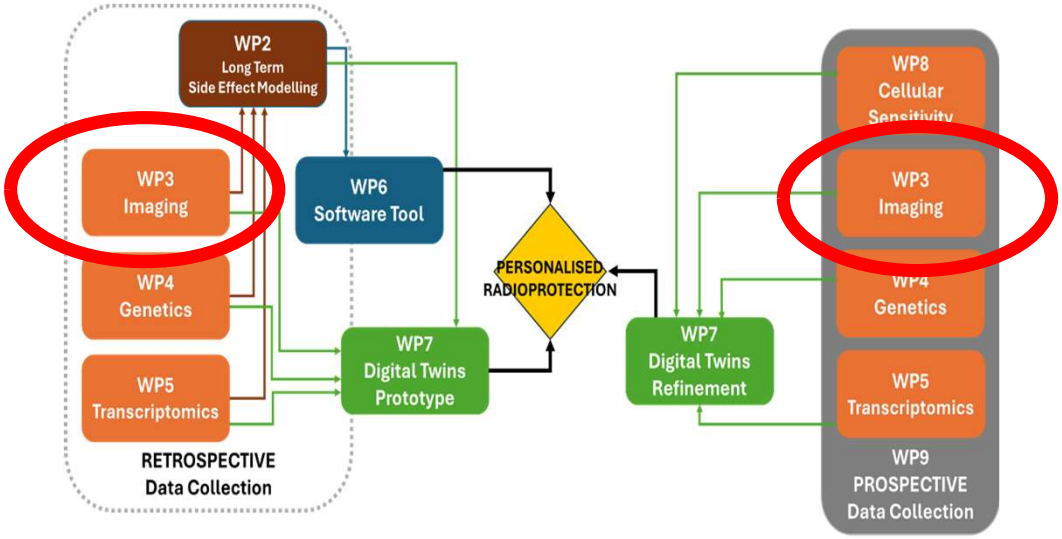




The philosophy of exploring qIB in TETRIS

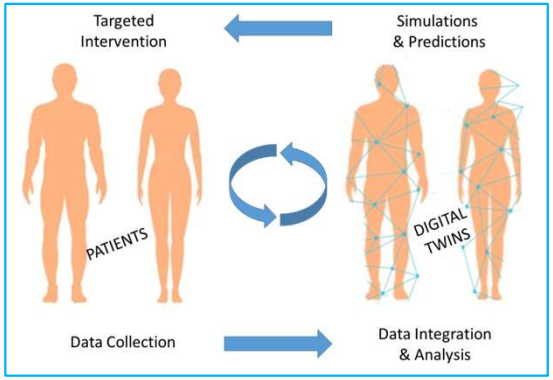
- the TETRIS project is set to develop **quantitative personalised risk scores for late severe cardiac/pulmonary disease and second cancers following RT for BCa**.
- The main objectives of the TETRIS project are: (1) to design and test quantitative personalised risk scores for severe side effects after BCa RT based on dose-response relationships and patients specific risk factors already published in the literature; (2) to develop a CE-marked tool to automatically compute and record the risk scores from the RT treatment data and single patient features. and (3) to prototype digital twins in RT

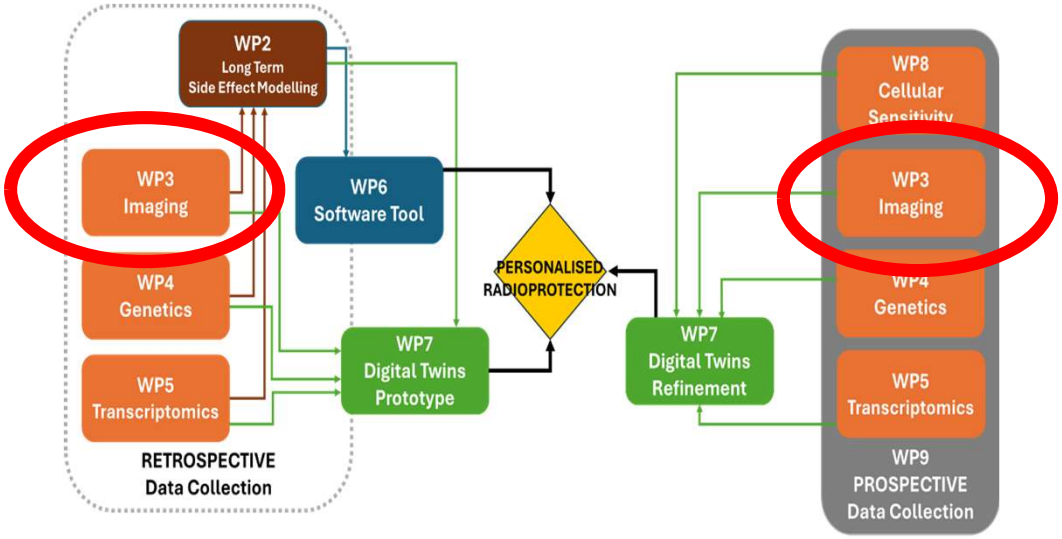




The philosophy of exploring qIB in TETRIS

- the TETRIS project is set to develop **quantitative personalised risk scores for late severe cardiac/pulmonary disease and second cancers following RT for BCa**.
- WP3 will analyse **CT images** to retrieve quantitative information on patient-specific risk factors. This possibility is crucial, as it allows personalisation of the risk scores without any additional investment, as CT images are routinely available for RT simulation and planning.



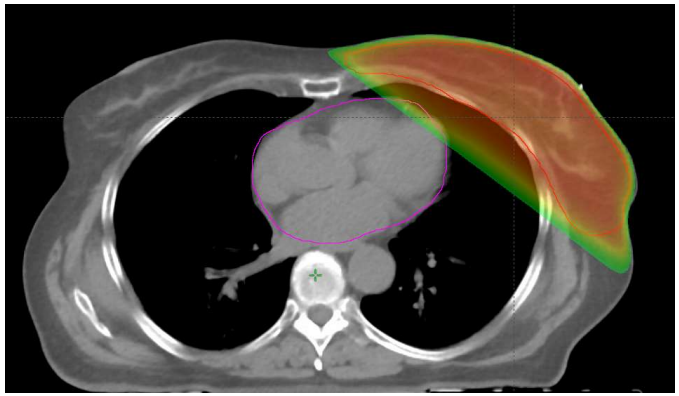


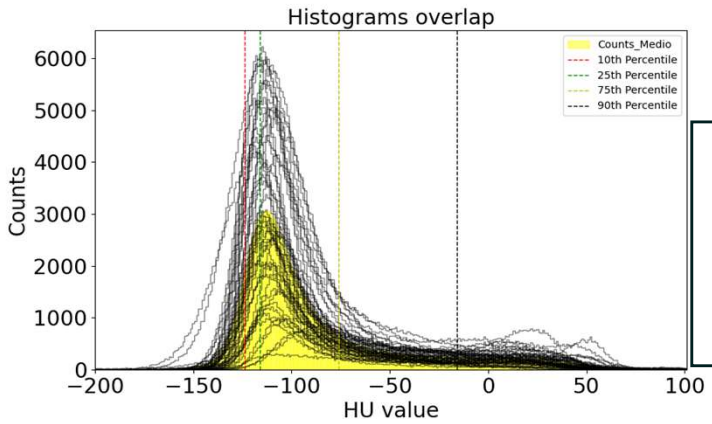
Planning CT & densitometry of lung and heart

- CT densitometry !

Corresponding to order 1 radiomic features based on HU (density) 3D maps…

Being focused on cardiac and respiratory side-effect….lung & heart densitometry. Breast for SC ??





Breast (CTV) HU histogram Mori PRO 2026

Additional pro's: Planning CT includes HU and dose maps, HU (and dose) spatial info available

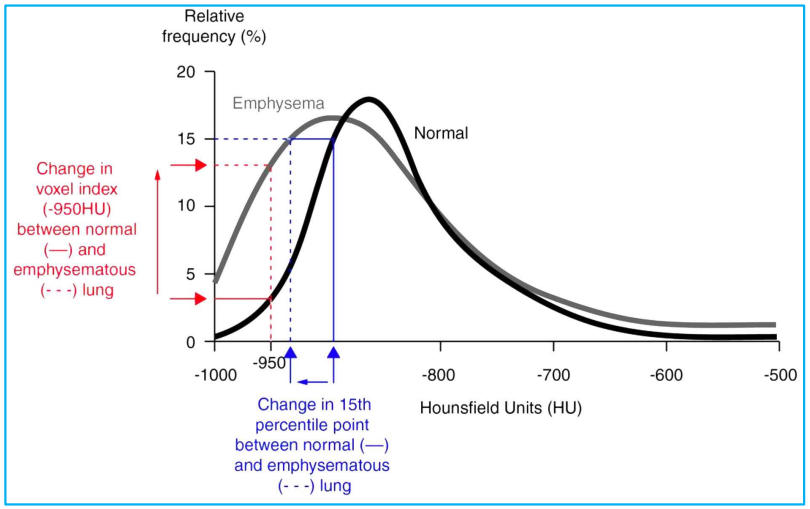
Planning CT & densitometry of lung and heart

- Lung CT densitometry: out of the box

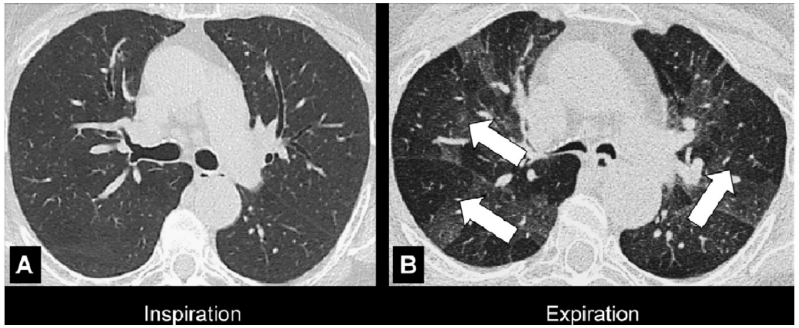
Ex: well assessed quantitative methodology for diagnosis, monitoring and ranking of emphisema and emphisema-related problems

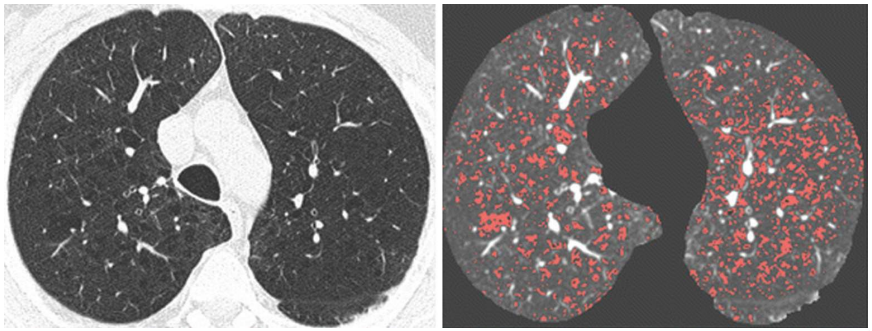
HU histogram – derived values from insp-CT for emphisema

…from exp-CT (and free breathing CT) for «air trapping»



Bankier, Radiology 2024



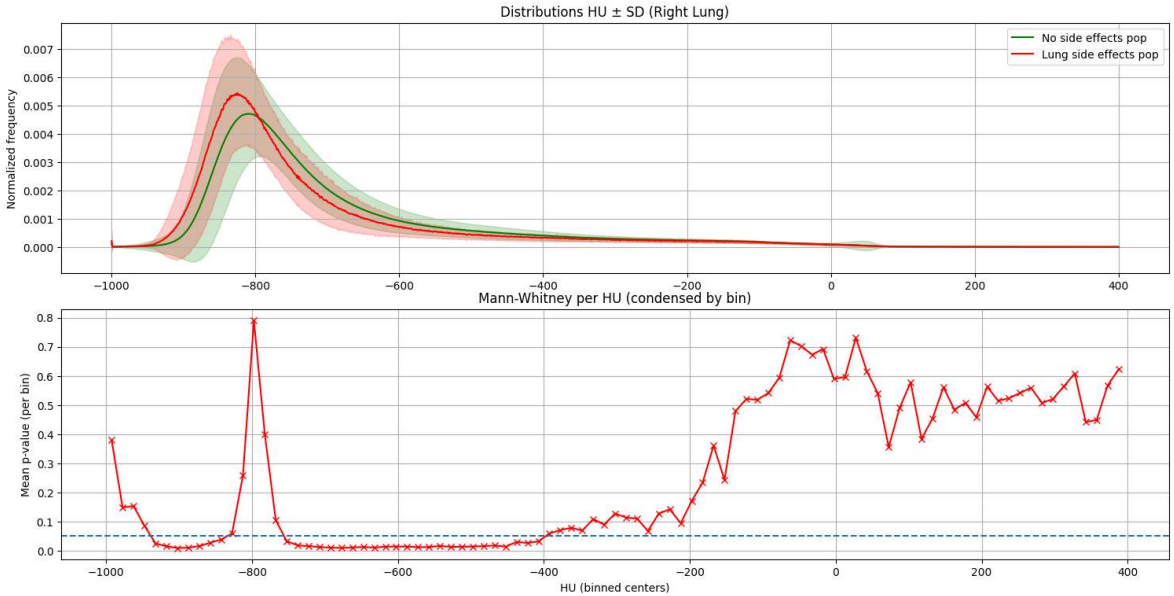


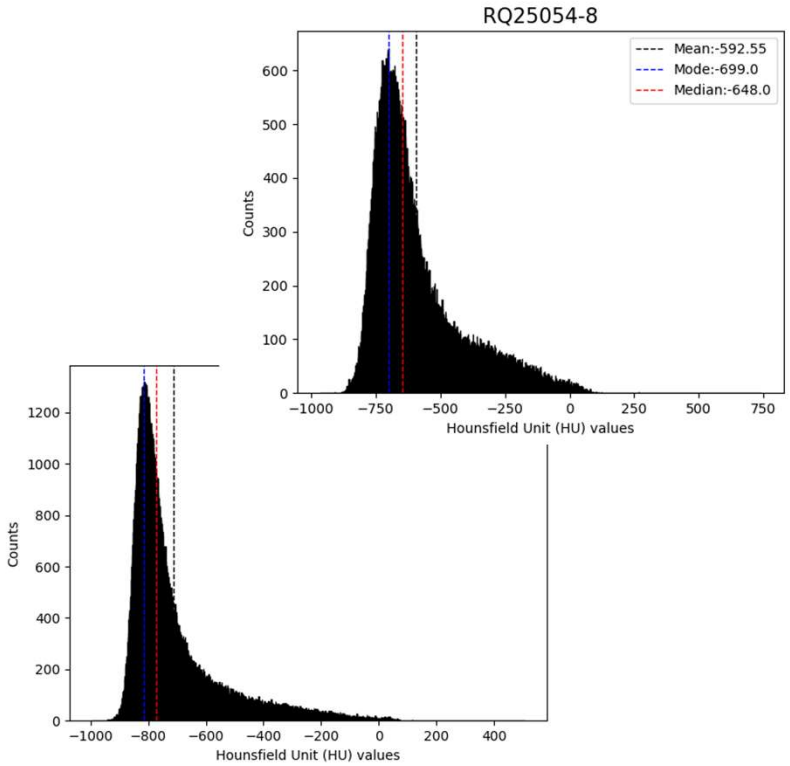
Mascalchi J Thorac Dis 2017

Planning CT & densitometry of lung and heart

- Lung CT densitometry & late respiratory events after breast BCa

Ongoing within TETRIS, OSR cohort (1172 pts, 18 events)





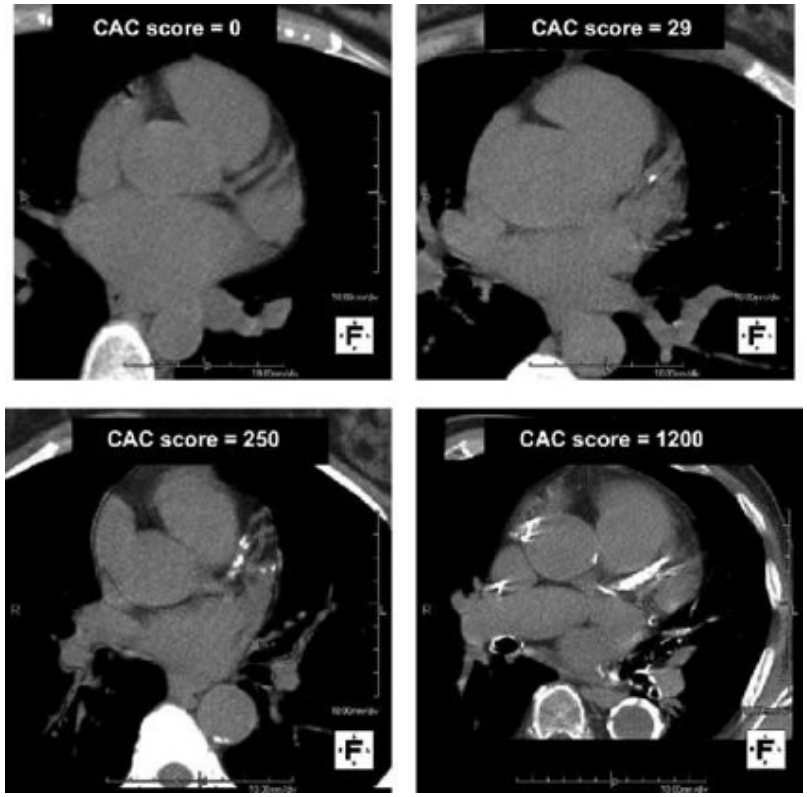
- Heart CT densitometry out/in the box

Calcification in the coronary artery and in the heart largely used in Cardiology to assess CVD

Agatston score (AS): weighted sum of the calcified lesion area (in mm^2), where a lesion is made of contiguous pixels with HU >130 HU and min $1mm^2$

AS is the sum, slice-by-slice of the resulting areas of each single CAC lesion multiplied by its weight, taking the corresponding Max_HU of each lesion

- $w_{pixel} = 1$ if $130\,\text{HU} \leq Pixel \leq 199\,\text{HU}$
- $w_{pixel} = 2$ if $200\,\text{HU} \leq Pixel \leq 299\,\text{HU}$
- $w_{pixel} = 3$ if $300\,\text{HU} \leq Pixel \leq 399\,\text{HU}$
- $w_{pixel} = 4$ if $Pixel \geq 400\,\text{HU}$



Agatston J Am Coll Cardiol 1990

Planning CT & densitometry of lung and heart

- Heart CT densitometry

Cardiac/coronary calcifications (CAC) predict cardiac mortality/events in Oncology patients

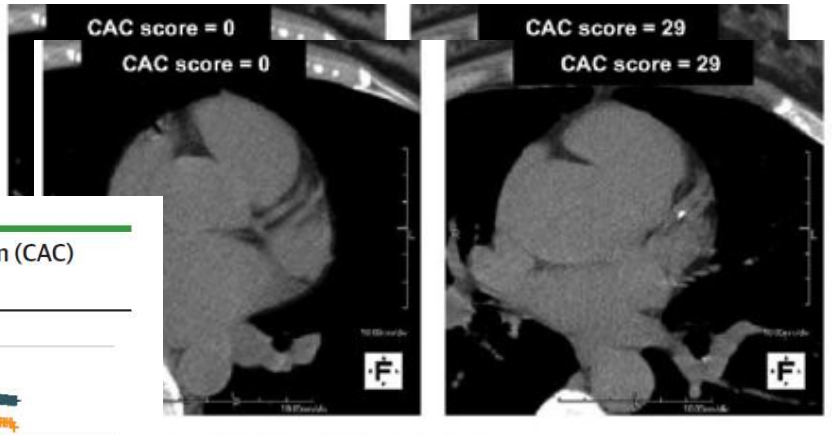
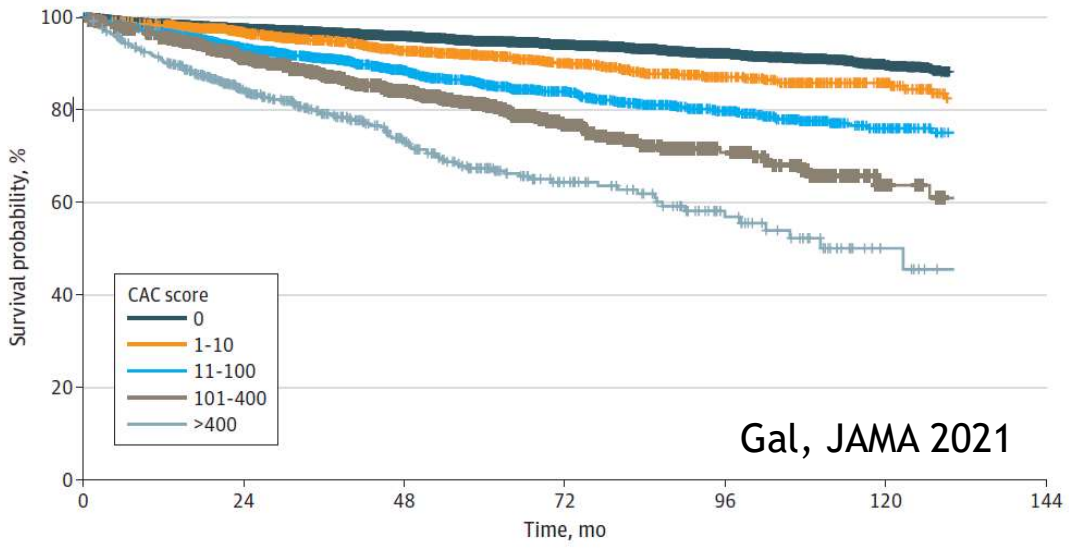
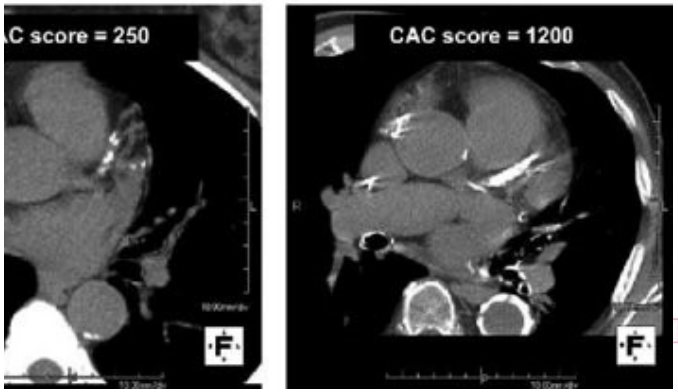


Figure. Kaplan-Meier Plot for Fatal and Nonfatal Cardiovascular Disease by Coronary Artery Calcium (CAC) Score Category

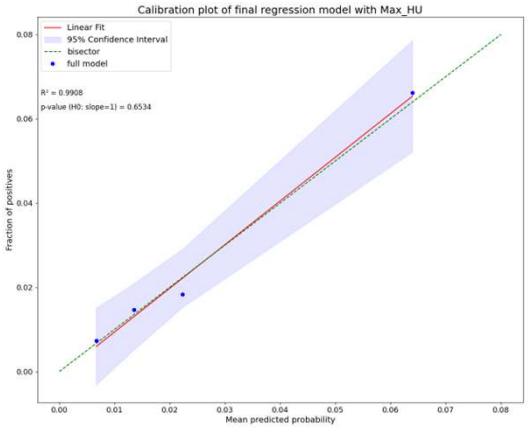




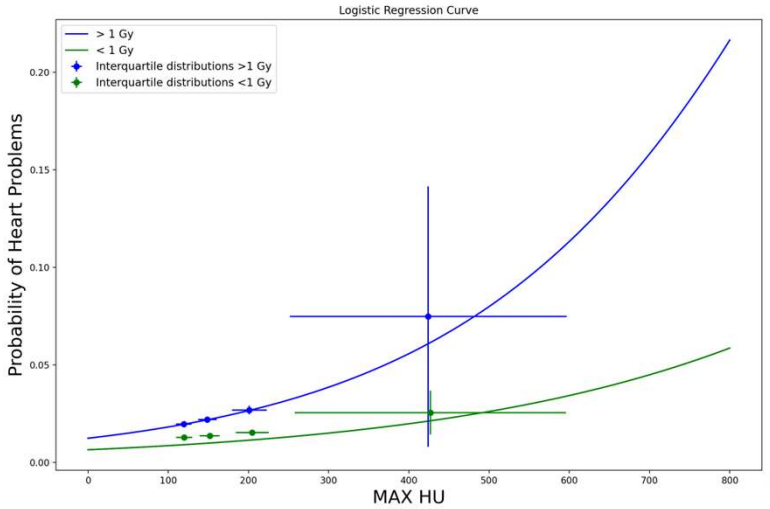
Planning CT & densitometry of lung and heart

- Heart CT densitometry

Ongoing within TETRIS, OSR cohort (1172 pts, 32 events)



	Model p-value: <0.0001 ROC p-value: <0.0001 AUC [95% CI]: 0.770 [0.744, 0.795]		Model p-value: <0.0001 ROC p-value: <0.0001 AUC [95% CI]: 0.771 [0.745, 0.796]		Model p-value: <0.0001 ROC p-value: <0.0001 AUC [95% CI]: 0.753 [0.726, 0,778]	
	Volume score		**Agatson score**		**Maximum HU score**	
	p-value	**Odds [95% CI]**	**p-value**	**Odds [95% CI]**	**p-value**	**Odds [95% CI]**
Age	0.0343	1.0406 [1.003, 1.0797]	0.0337	1.0408 [1.0031, 1.0800]	0.0158	1.0455 [1.0084, 1.0839]
MHD >1Gy	0.0093	3.3086 [1.343, 8.1493]	0.0123	3.1338 [1.2811, 7.6660]	0.0202	2.8082 [1.1747, 6.7132]
CAC Score	<0.0001	1.0005 [1.001, 1.002]	<0.0001	1.0013 [1.0008, 1.0019]	0.0004	1.0029 [1.0013, 1.0045]



Belardo, Radiother Oncol 2025

«Simple» vs «Advanced» (multi-centric) qIB analyses

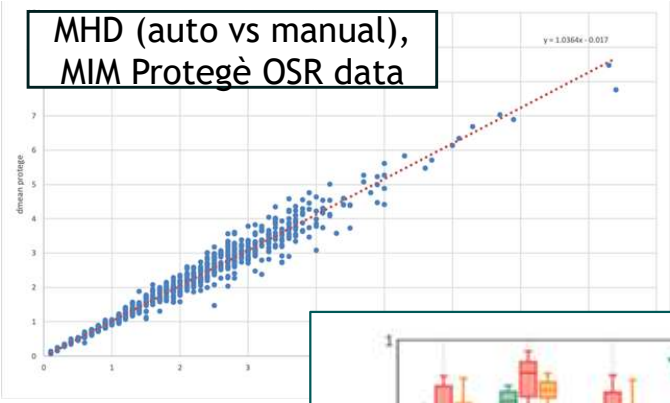
- Inter-Institute variability

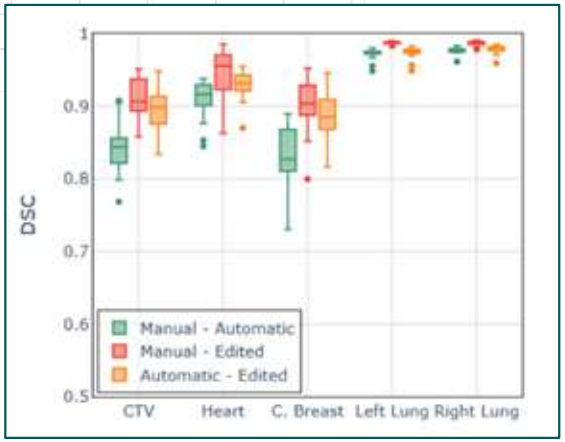
Auto-segmentation of lungs and heart

HU variability (CT calibration)

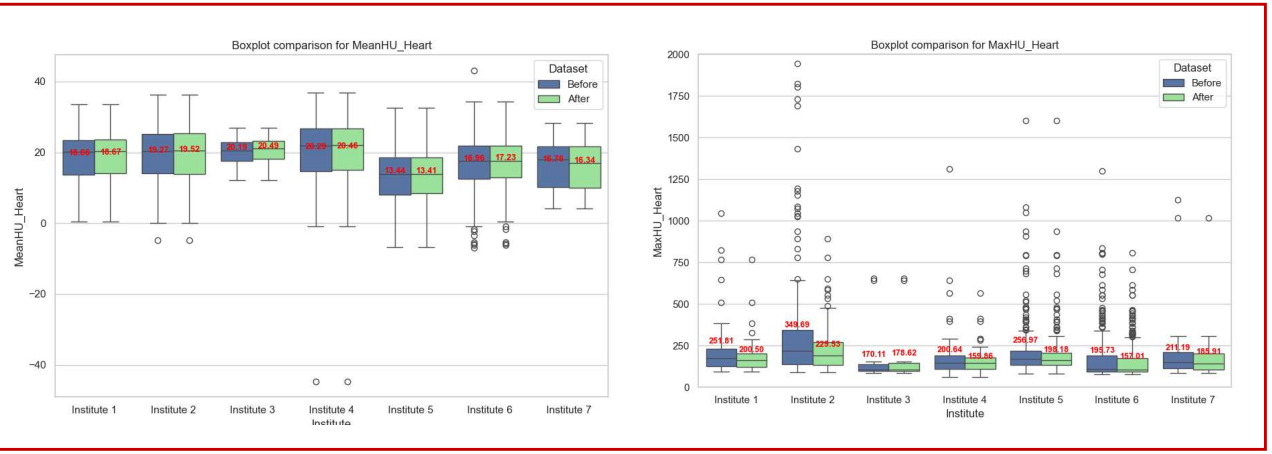
Impact on densitometric and radiomics IB, harmonization (?)

MHD (auto vs manual), MIM Protegè OSR data





Maddaloni, Submitted



Ex: ongoing analyses on REQUITE data within TETRIS:
Inter-Institute variability of Mean and Max HU of the heart

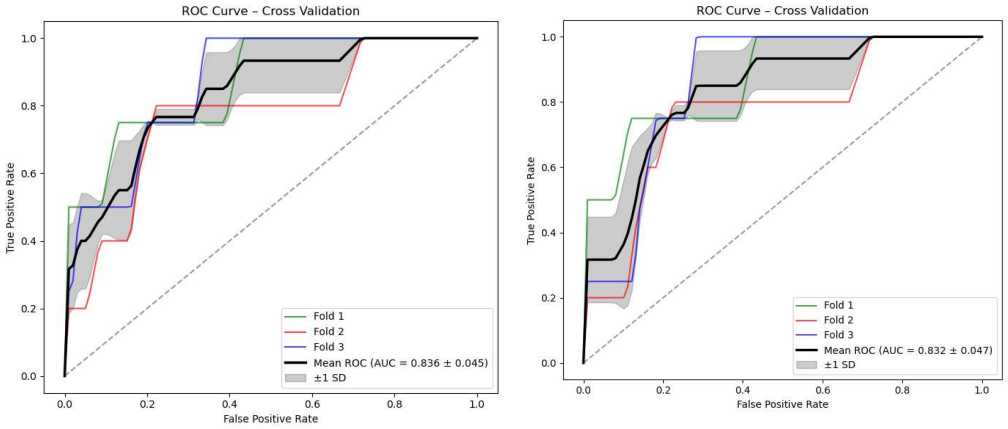
«Simple» vs «Advanced» (multi-centric) qIB analyses

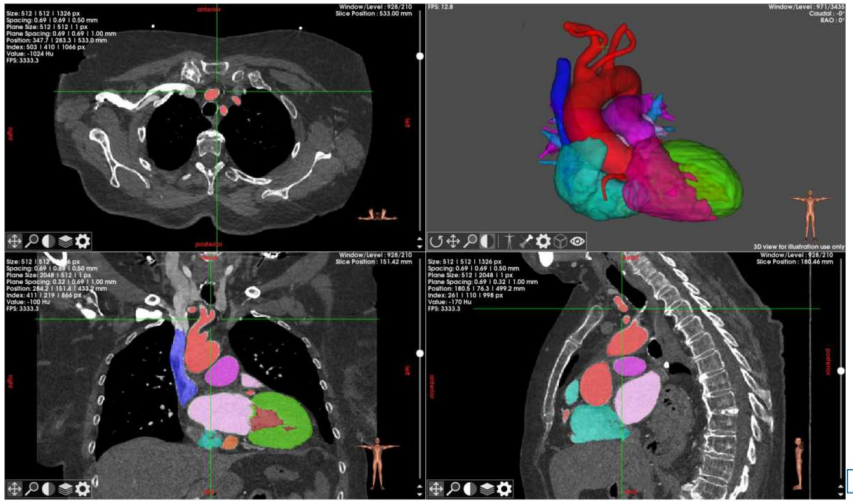
- Sub-segmentation/spatial info

Exploring potential value of CAC and Dose in the cardiac substructures

HU 3D distribution, Voxel-wise approaches….

Sharobeen, JCTR, 2021





Ex: ongoing analyses on OSR/REQUITE data within TETRIS: Impact of cardiac sub-structure segmentation

«Simple» vs «Advanced» (multi-centric) qIB analyses

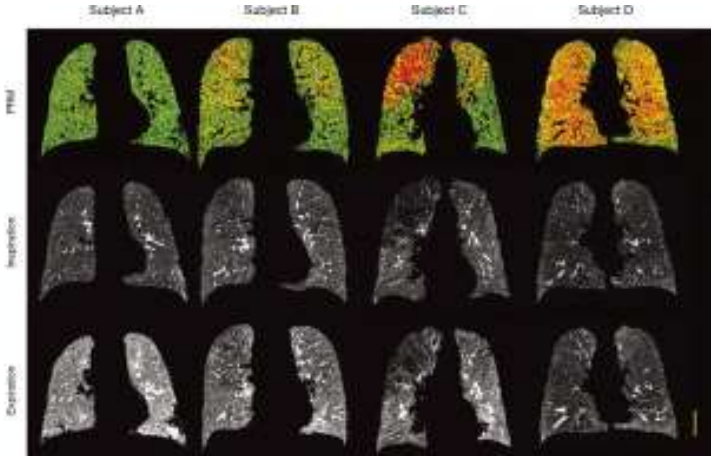
- Sub-segmentation/spatial info

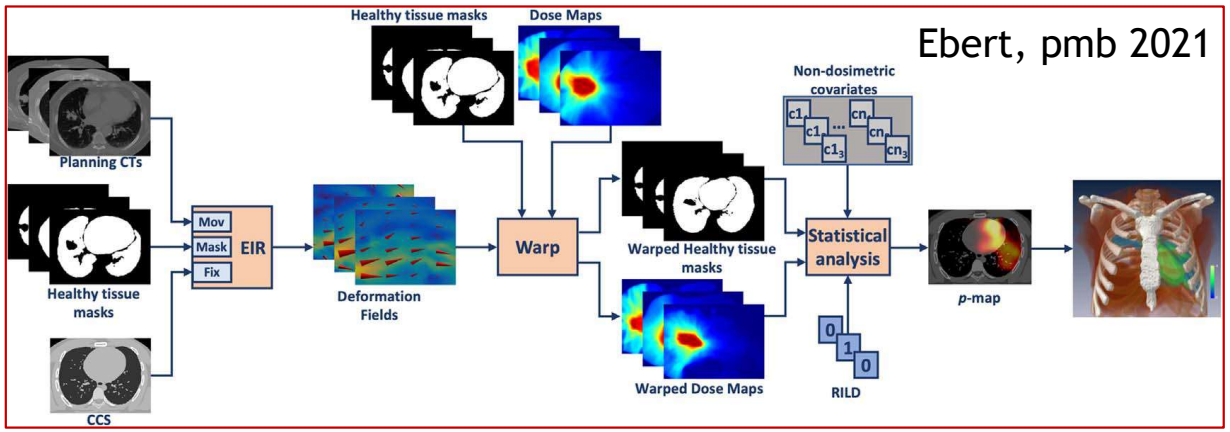
Exploring potential value of CAC and Dose in the cardiac substructures

HU 3D distribution, Voxel-wise approaches….

Extending to higher order Radiomics

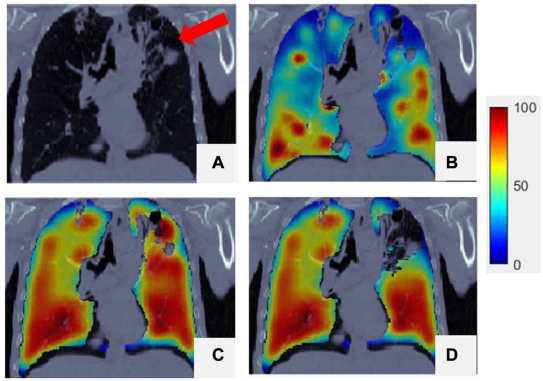
Mascalchi J Thorac Dis 2017





Ebert, pmb 2021

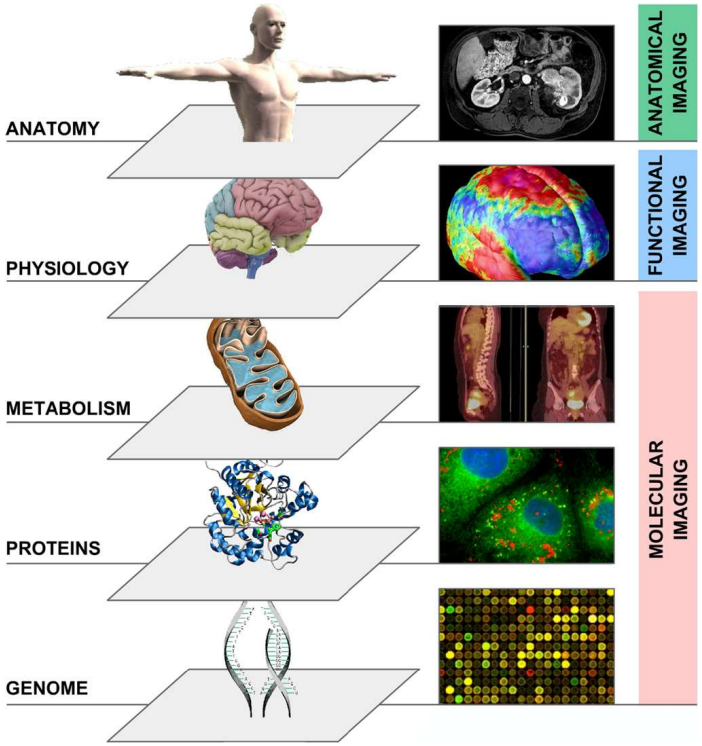
Chen, Front Physiol, 2023



Conclusions

- Intro: qIB to assess/predict Tox, why ?
- Extending qIB to Radiomics
- The (still topical) issue of qIB clinical usability, reliability, reproducibility…..

- The philosophy of qIB in TETRIS
- Planning CT & densitometry of lung and heart
- «Simple» vs «Advanced» (multi-centric) qIB analyses



Lambin et al., EJC 2012; 48 (4): 441-446.

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TETRIS - Risk assessment *Tools* for severe side *Effects* after *breasT Radiotherapy*: radiation safety through biological extended models and *digital twinS*

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