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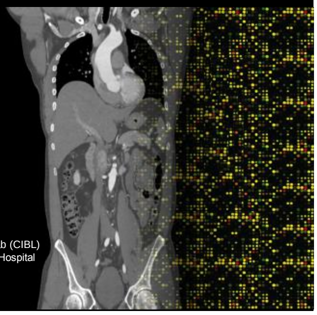
Robust Radiomics Methods



Hugo Aerts

Director, Computational Imaging and Bioinformatics Lab (CIBL)
Dana-Farber Cancer Institute, Brigham and Women's Hospital
Harvard Medical School

Objectives

- Describe the motivation for integrating imaging with genomic and clinical data
- Describe robust methodology underlying quantitative radiomic analysis
- Describe biomarker quantification studies in Radiomics and Imaging-Genomics (Radiogenomics)

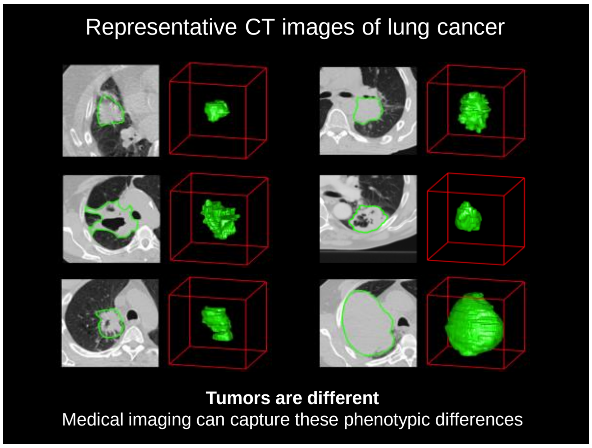
Imaging for personalized medicine

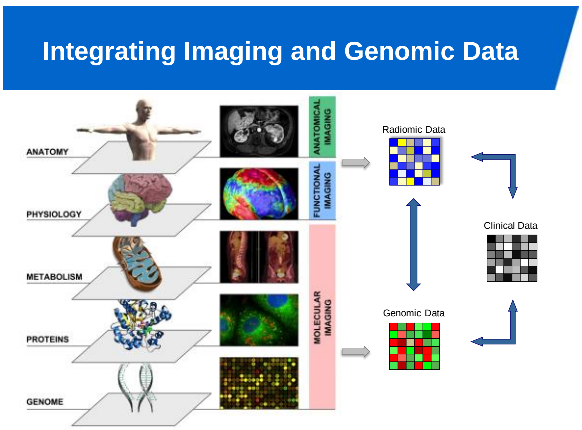
Advantages of Imaging:

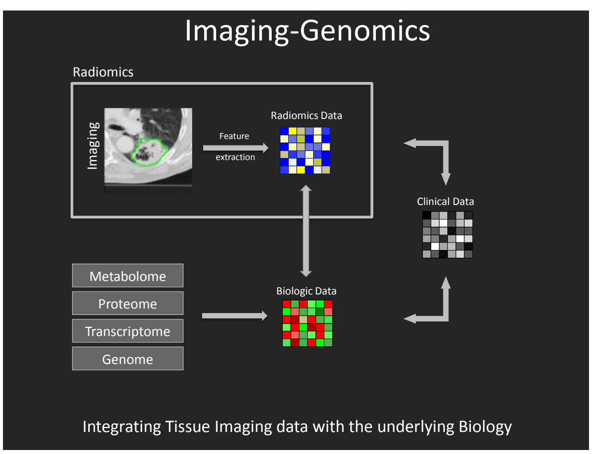
- Performed non-invasively
- Covers the total 3D volume
- Already performed in clinical practice
- Multiple times during treatment for diagnosis, staging, radiation oncology planning, response assessment

Disadvantages of Imaging:

- Probes the cancer at the macroscopic level
- Often qualitative not quantitative
- Very heterogeneous acquisition protocols:
  - comparisons between patients difficult
  - comparisons same patient in time difficult
- Storage of only reconstructed images (not the raw data)


Representative CT images of lung cancer
Tumors are different
Medical imaging can capture these phenotypic differences


Integrating Imaging and Genomic Data
ANATOMY
PHYSIOLOGY
METABOLISM
PROTEINS
GENOME
ANATOMICAL IMAGING
FUNCTIONAL IMAGING
MOLECULAR IMAGING
Radiomic Data
Clinical Data
Genomic Data

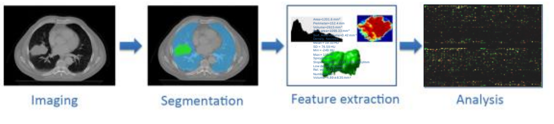

Imaging-Genomics
Radiomics
Imaging
Feature extraction
Radiomics Data
Clinical Data
Metabolome
Proteome
Transcriptome
Genome
Biologic Data
Integrating Tissue Imaging data with the underlying Biology

Radiomics rational

- Radiographic images are typically analysed qualitatively by radiologist, often with non-standard lexicon.
- At most, unidirectional measurements (RECIST)
- Radiomics aims to provide a comprehensive quantification of the tumor phenotype using automated image characterisation algorithms
- We hypothesize that radiomic analyses of standard of care images can improve diagnostic, prognostic and predictive power
- Automation is key: automatic quantitative feature algorithms to extract quantitative data instead of qualitative data, reduce observer variation by manual annotation, and increase speed of workflow.

Radiomics: Quantify the tumor phenotype

Convert Images to mineable data in high throughput (radiomics)



*Lambin *et al.* Eur J Cancer 2012
*Kumar *et al.* Magn Reson Imaging 2012

Radiomics: Workflow & Challenges

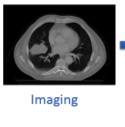


Image Acquisition, Reconstruction, Standardization, Storage

Radiomics: Workflow & Challenges

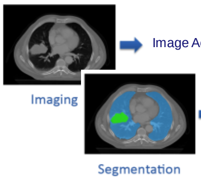


Image Acquisition, reconstruction, standardization, storage

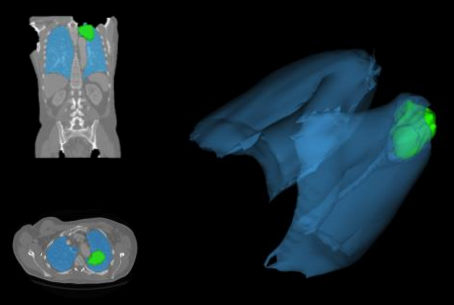
Automate, Validate, Reproducibility

Automatic segmentation:

1) Automated method for high throughput of images.

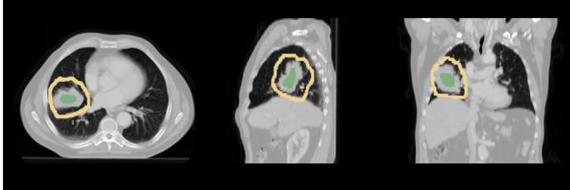
2) Reducing the **high intra- and inter-observer variability** observed for target definition.

Automatic tumor delineation using 3D-Slicer



Developing algorithms for fast, semi-automated, and accurate delineation

Automatic tumor delineation using 3D-Slicer

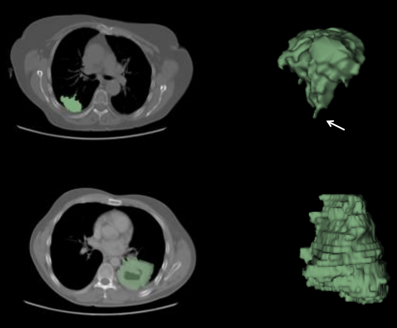


**Velazquez et al, Sci Rep. 2013*

3D-Slicer region growing algorithm

3D-Slicer

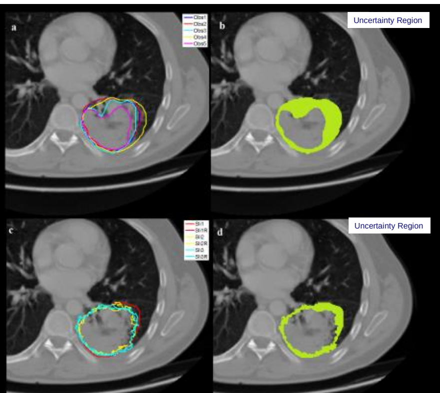
Manual



*Velazquez et al, Sci Rep. 2013

Manual

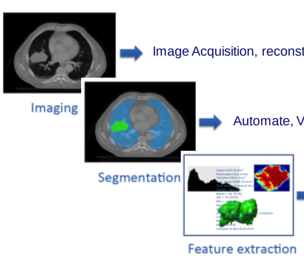
3D-Slicer



Segmentation uncertainty was significantly smaller with 3D-Slicer (*Velazquez et al, Sci Rep. 2013)*

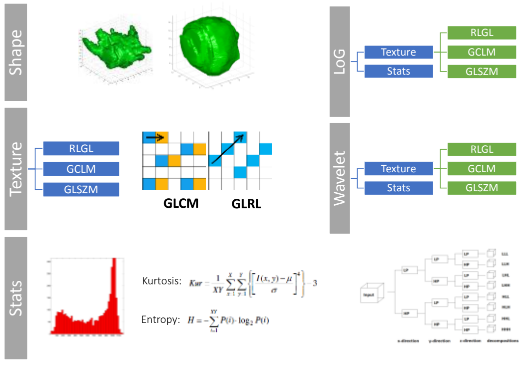
Radiomics features based on 3D-Slicer delineations are more stable (Parmar *et al.* PLOS One 2014)

Radiomics: Workflow & Challenges



- Imaging → Image Acquisition, reconstruction, standardization, storage
- Segmentation → Automate, Validate, Reproducibility
- Feature extraction → Definition, Informative, Reproducibility, Robustness

Radiomic Feature Set (current release ~1600 features)



Radiomic features can capture tumor phenotypic details

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Robust Radiomics Data Analysis (Feature Selection & Machine learning)

Motivation

- Predictive/Prognostic models having high accuracy, reliability and efficiency can be vital factors driving success of "Radiomics".
- Need for the machine-learning models.
- Radiomics suffers from the curse of dimensionality.
- Need for the feature selection.
- Different feature selection and machine-learning classification methods have to be investigated.

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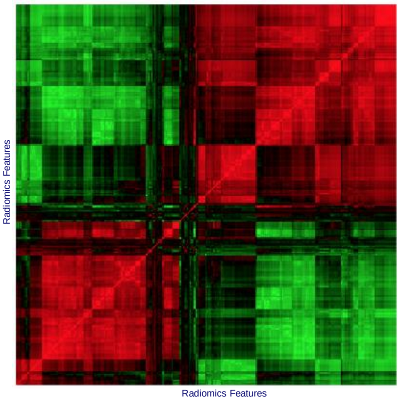
Radiomics Dimensionality Reduction

Matrix of 440 Radiomics features
(422 NSCLC patients)

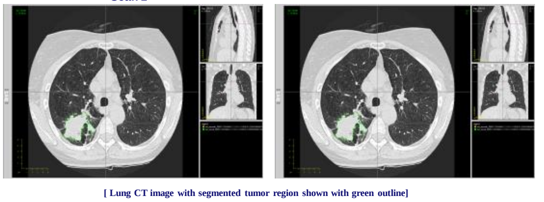


Spearman's rank correlation coefficient

Feature selection: RIDER test retest

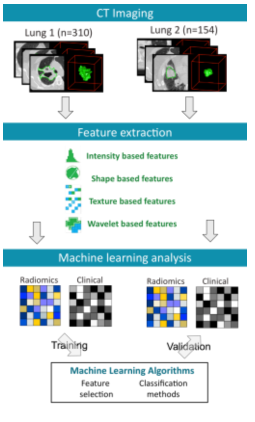
- Rider test retest reproducibility to select the most reproducible tumor image features extracted from CT images of 31 non-small cell lung cancer (NSCLC) patients.
- CT scans acquired within fifteen minutes.
- All primary lung cancers were segmented using Definiens
- 440 radiomics features were extracted from these segmented tumor regions
- Intraclass Correlation Coefficient (ICC) was calculated for each feature as a stability index

Scan 1 **Scan 2**



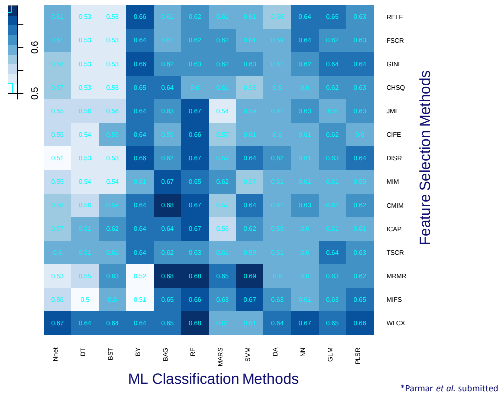
[Lung CT image with segmented tumor region shown with green outline]

Robust Machine Learning in Radiomics



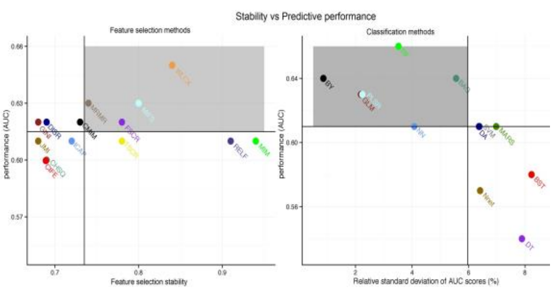
*Parmar *et al.* submitted

Machine Learning in Radiomics



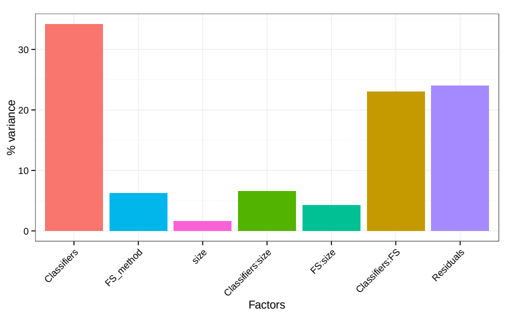
*Parmar *et al.* submitted

Stability for feature selection and Classification



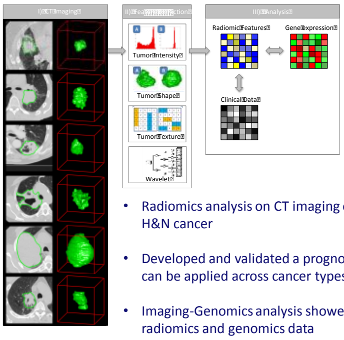
*Parmar *et al.* submitted

Machine Learning in Radiomics



*Parmar *et al.* submitted

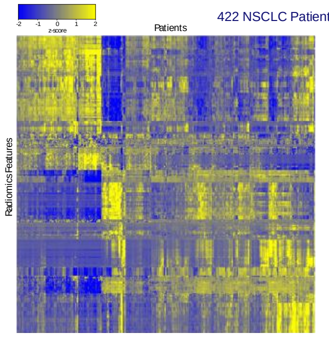
Imaging-Genomics across cancer types



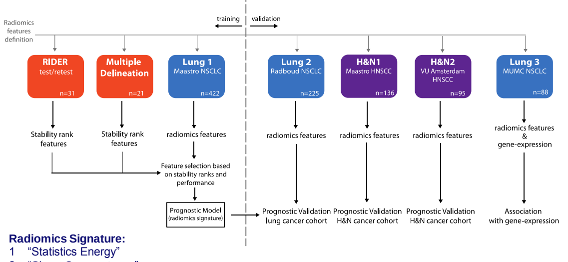
*Aerts *et al.* Nature Comm. 2014

- Radiomics analysis on CT imaging of >1000 patients with Lung or H&N cancer
- Developed and validated a prognostic radiomics signature that can be applied across cancer types
- Imaging-Genomics analysis showed strong correlations between radiomics and genomics data

Lung1 Dataset
422 NSCLC Patients MAASTRO Clinic



Radiomics CT Workflow

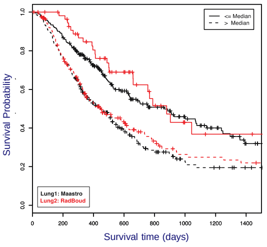


Radiomics Signature:
1 “Statistics Energy”
2 “ShapeCompactness”
3 “Gray Level Nonuniformity”
4 Wavelet “Gray Level Nonuniformity HLH”

7 datasets with a total of 1018 patients

Radiomics CT Signature Performance

Lung cancer cohorts



Performance Model:
- CI = 0.65 on the Lung2 Validation Dataset (n=225)

*Aerts *et al.* Nature Comm. 2014

Radiomics CT Signature Performance

Extended Data Table 1 | Prognostic performance in validation datasets (Concordance Index CI)

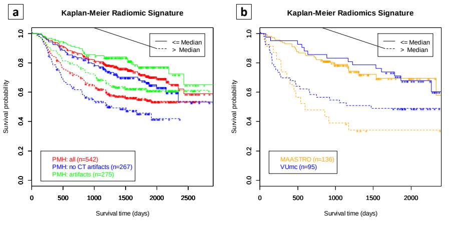
Dataset	TNM	Volume	Radiomics	TNM-Radiomics	Volume-Radiomics	TNM vs. Radiomics	Volume vs. Radiomics	TNM vs. TNM-Radiomics	Volume vs. Volume-Radiomics
Lung2	0.60	0.63	0.65	0.64	0.65	$1.42x10^{-04}$	$6.29x10^{-07}$	$1.40x10^{-05}$	$7.52x10^{-08}$
H&N1	0.69	0.68	0.69	0.70	0.69	0.12	$1.70x10^{-02}$	$3.79x10^{-04}$	$8.55x10^{-03}$
H&N2	0.66	0.65	0.69	0.69	0.68	$6.48x10^{-08}$	$3.72x10^{-10}$	$3.06x10^{-10}$	$2.52x10^{-10}$

Prognostic performance in validation datasets (Concordance Index CI)

- Signature performed significantly better compared to volume in all datasets.
- Signature performance was better than TNM staging in Lung2 and H&N2, and comparable in the H&N1 dataset.
- Combining the signature with TNM showed significant improvement in all datasets.

Additional Validation of Prognostic Signature

542 Oropharyngeal squamous cell carcinoma (OPSCC) treated at Princess Margaret Hospital (PMH) in Toronto.

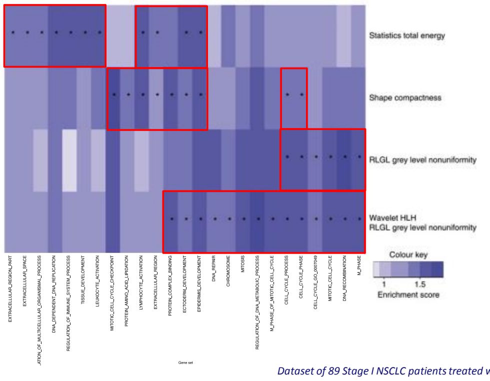


C-index was: PMH1: 0.628 (P<2.72e-9), PMH2: 0.634 (P<2.7e-6) and PMH3: 0.647 (P<5.35e-6)

Radiomics signature could be validated in an additional large OPSCC cohort

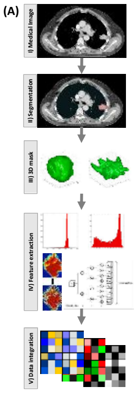
*Leijnaar *et al.* Acta Onco 2015

GSEA of Prognostic Radiomics Signature

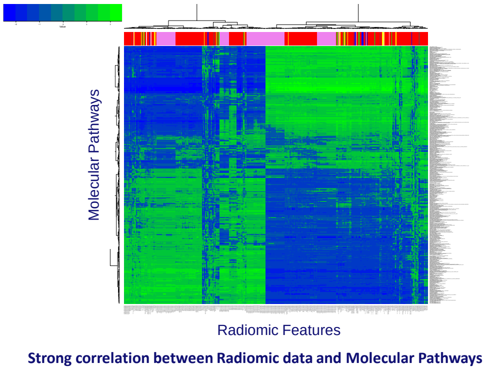


Dataset of 89 Stage I NSCLC patients treated with surgery

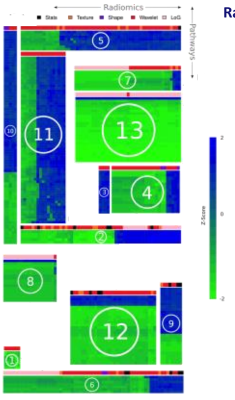
Radiomics-Genomics in NSCLC



Association Heatmap Radiomics-Genomics



Strong correlation between Radiomic data and Molecular Pathways



Radiomics-Genomics association modules

13 association modules were identified and independently validated

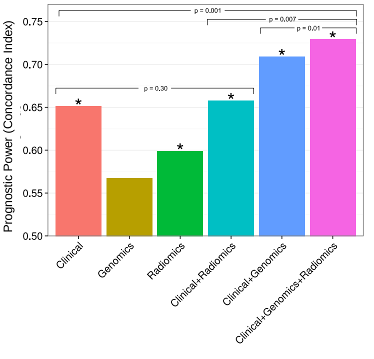
Radiomics Modules associate with distinct biological processes

Modules are significantly associated with clinical parameters:
survival (3), histology (5), stage (10)

Clinical-Radiomics-Genomics Prognostic Signatures

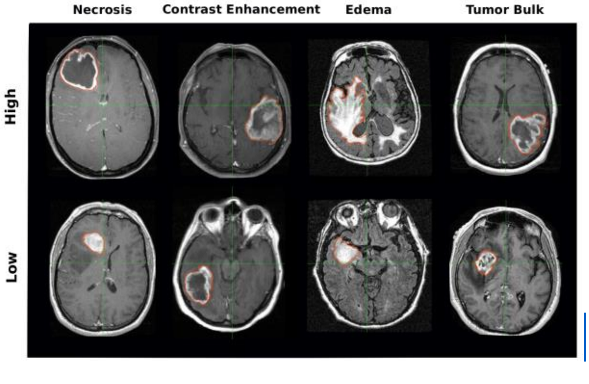
Genomic Signature:
Hou et al., 2010
17 genes for
Post-treatment survival

Radiomics Signature:
Aerts et al., 2014
(I) Statistics Energy
(II) Shape Compactness
(III) Grey Level Nonuniformity
(IV) Wavelet Grey Level
Nonuniformity HLH

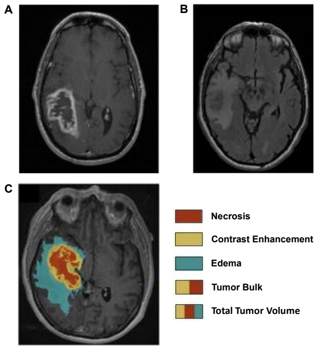


Radiomics significantly adds to prognostic gene-signatures

Imaging-Genomics in GBM



Methods: Manual delineations



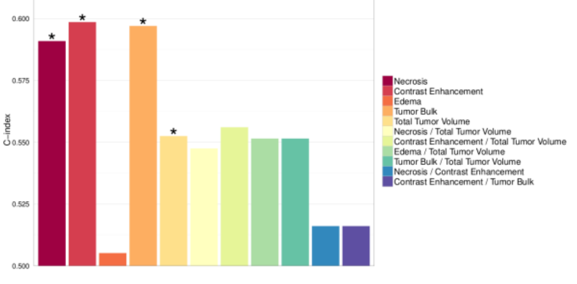
Manual slice-by-slice contouring of the abnormal signal on T1c and FLAIR images

FAST algorithm to segment contrast-enhancing and necrotic sub-volumes on T1c

Final contours were all manually reviewed and edited by expert neuro-radiologists

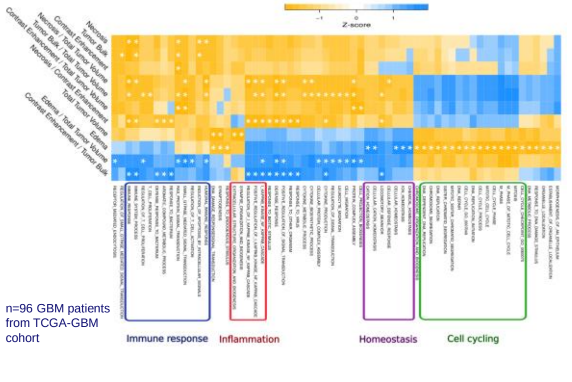
*Grossmann *et al.* Submitted

Prognostic value of volumetric features



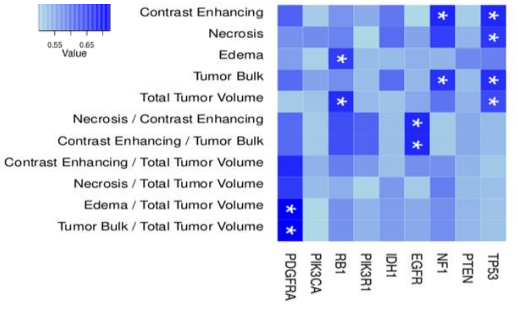
*Grossmann *et al.* Submitted

Imaging-Genomics Pathway Analysis of MRI Derived Volumetric Tumor Phenotype Features in Glioblastoma



n=96 GBM patients from TCGA-GBM cohort

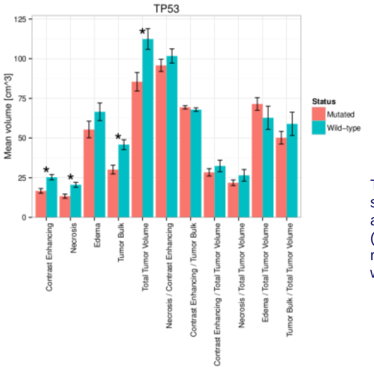
Volumetric features predict mutational status in GBM patients



N=76 GBM patients from TCGA-GBM cohort

*Gutman *et al.* Submitted

TP53 positive/negative



TP53 mutated tumors had significantly smaller CE and necrotic volumes (*p*=0.012 and 0.017, respectively) compared to wild-type.

*Gutman *et al.* Submitted

Quantitative Imaging: Current Status & Outlook

- Imaging moves towards a computational data science (bioinformatics)
- Due to advances in imaging, quantitative imaging is currently possible
- Large retrospective and prospective potential

- Large number of imaging features defined & successfully implemented
- Robust feature extraction pipeline implemented in 3D-Slicer (Python / Matlab)
- Radiomics signatures are prognostic across cancer types
- Radiomics data is strongly association with driving biological processes

- Ongoing: “Delta radiomics” change of image features
- Ongoing: Preclinical models with tumor models having inducible KO
- Ongoing: Radiomics in clinical trial data

Take home message

The field of Forensic Bioinformatics (Keith Baggerly, MD Anderson)
Investigating the reproducibility and methodology of scientific studies in retrospect. They request the data from the investigators, they assess the used statistics, methods, results, and conclusions.
They find a large number of studies that are wrong or even fraud

Duke Scandal (Anil Potti)
Accused of falsifying data regarding the use of microarray genetic analysis for personalized cancer treatment. Publications in various prestigious scientific journals were retracted (including PNAS, Lancet Oncology, Nature Medicine, JAMA, JCO, NEJM).

Forensic Radiology

PLOS | ONE

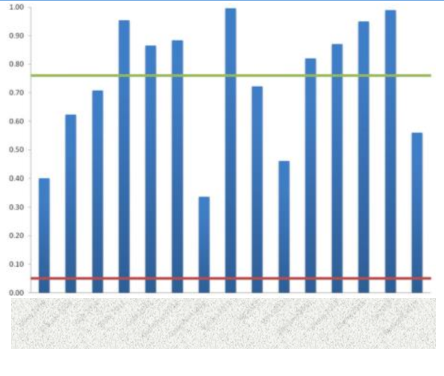
RESEARCH ARTICLE

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

Forensic Radiology



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