Imaging and Molecular Biomarkers of Lung Cancer Prognosis

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- No other disclosures

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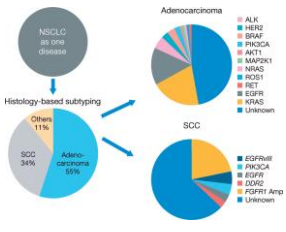
The Era of Precision Oncology

- Lung cancer is a heterogeneous disease.
- Molecularly targeted therapies exist according to the unique genetic makeup of each individual tumor.



Li T et al: J Clin Oncol 2013

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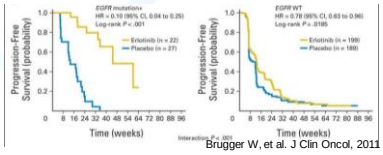
Biomarkers as a Pillar of Precision Oncology

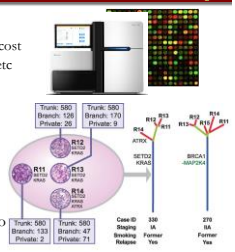
- Biomarkers can be used to inform diagnosis and prognosis, or to select appropriate therapy.
  - PSA level, Oncotype Dx recurrence score, EGFR activating mutation.
- Conventional: biological molecules measured in tissue, serum, or circulation, at DNA, RNA, or protein level.



Brugger W, et al. J Clin Oncol, 2011

Tissue-based Molecular Biomarkers

- Mainstay of current oncology practice
  - NGS: rapid, high-throughput profiling at reduced cost
  - Genome, transcriptome, proteome, metabolome, etc
  - Exquisite molecular detail, but…
- Invasive
  - requires biopsy or surgery
- Biased
  - samples a small portion of a tumor
- Incomplete
  - does not characterize tumor anatomy or in vivo physiology (e.g., blood flow)



Zhang et al: Science 2015

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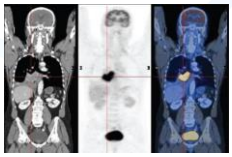
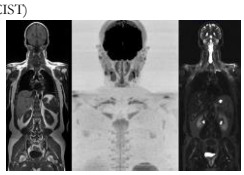
Imaging-based Biomarkers

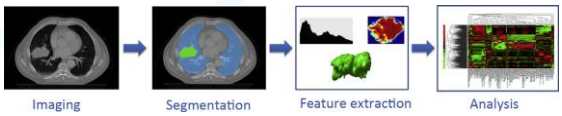
- The current FDA–NIH Biomarker Working Group definition includes radiographic characteristics.
- Routine, noninvasive, repeatable, whole tumor & surrounding tissue
- Currently based on radiologist's visual assessment
  - Subjective: inter-/intra-observer variations
  - Qualitative, not quantitative
  - Low-throughput (one or few: RECIST)





Radiomics: the Process

- Quantitative, high-throughput extraction of information from medical images
  - Converts pictures to 'omic' data
- Correlate with clinical outcomes: biomarkers
- Correlate with molecular data: potential driving biology



Lambin et al, Eur J Cancer, 2012

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Prognostic Biomarkers in Early-Stage NSCLC

- Excellent local control after SABR.
- Distant metastasis occurs in a significant proportion of patients.
- Most patients do not receive adjuvant systemic therapy.
- Need to accurately identify patients at highest risk of recurrence, who might benefit from additional therapy.

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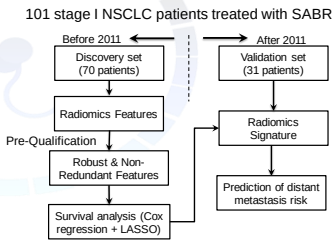
Identifying Prognostic Imaging Biomarker



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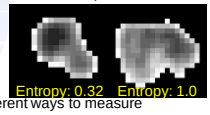
Wu et al, *Radiology*, 2016

Radiomic Analysis of PET/CT

- Our radiomic feature set includes:
  - 6 statistical (mean, max, variance, skewness, etc)
  - 5 SUV histogram
  - 2 morphology (CT)
  - 3 GLCM
  - 24 Wavelet
  - 30 Laws



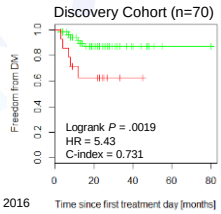
57 different ways to measure intra-tumor heterogeneity

- Total: 70 quantitative image features.

Wu et al, *Radiology*, 2016

Discovery of a Radiomic Signature

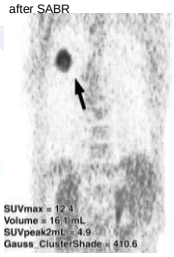
- The final radiomic signature was:
  - 2.1 x SUV_{peak_2cc} + 3.6 x Gauss_ClusterShade



Wu et al, *Radiology*, 2016

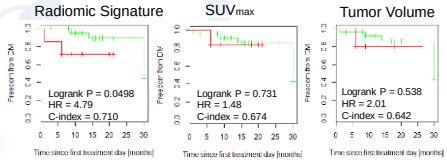
Pre-SABR PET images

Distant metastasis free 34 mo after SABR



Distant metastasis 9 mo after SABR

Independent Validation



Wu et al, *Radiology*, 2016

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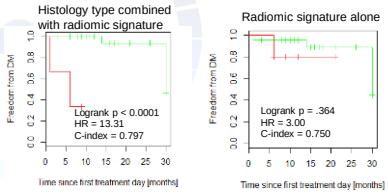
Histology Adds to Imaging



Wu et al, *Radiology*, 2016

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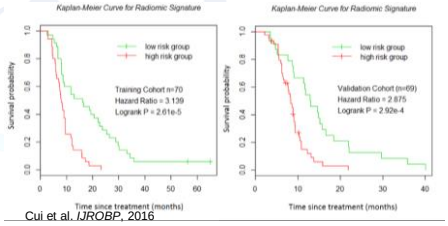
Prognostic Imaging Biomarker in Pancreatic Cancer

- A radiomic signature of FDG-PET improved upon SUV and tumor volume (C-index: 0.67 vs 0.58).



Cui et al, *IJROBP*, 2016
Basic/Translational Science Abstract Award, ASTRO 2015

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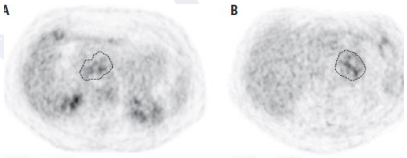
Pre-SRRT PET images



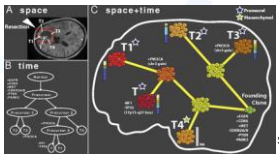
SUV_{max} = 5.58
Volume = 37.1cm³
Proposed Signature = -0.035
OS = 657days

SUV_{max} = 6.10
Volume = 35.9cm³
Proposed Signature = 0.526
OS = 248 days

Cui et al. IJROBP, 2016

Beyond Radiomics: Multi-Region Analysis

- Aggregate image features from the bulk tumor
  - Assuming tumor is well mixed
- Clonal evolution causes regional differences in a tumor.
- Habitat imaging to identify 'high-risk' subregions



Sottoriva, et al. PNAS, 2013

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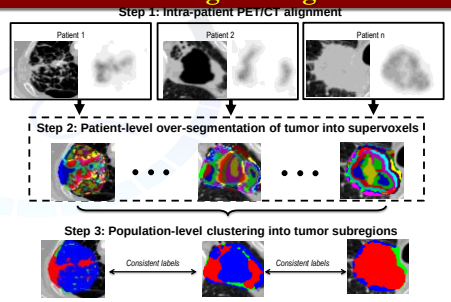
Intra-Tumor Partitioning of Lung Tumors



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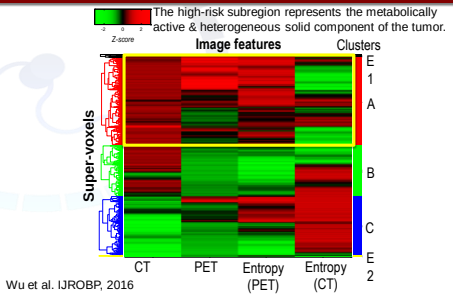
3 Distinct Intra-Tumor Subregions



The high-risk subregion represents the metabolically active & heterogeneous solid component of the tumor.

Wu et al. IJROBP, 2016

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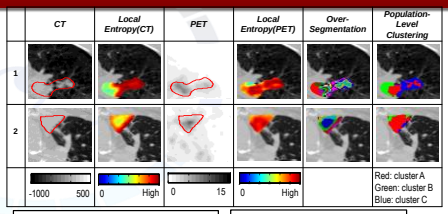
Two Patients with Stage IIIb NSCLC



Patient 1
Total Volume: 41.3 ml
SUV_{max}: 13.1
MTV_{50}: 5.8 ml
Tumor burden for cluster A: 8.9 ml
Alive after 4 years, no out-of-field progression

Patient 2
Total Volume: 39.1 ml
SUV_{max}: 8.7
MTV_{50}: 2.1 ml
Tumor burden for cluster A: 21.7 ml
Deceased after 3 months

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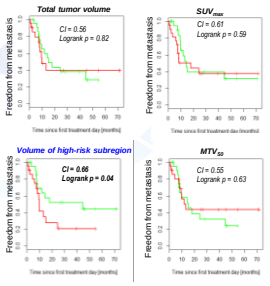
Prognostic Value in NSCLC (All Stage)



Tumor burden associated with the high-risk subregion predicts metastasis and overall survival better than conventional imaging metrics.
*CI: concordance index

Green: < median
Red: >= median

Wu et al. IJROBP, 2016

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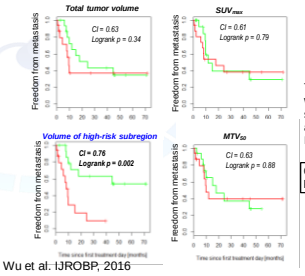
Stronger Prognostic Power in Stage III Patients



Tumor burden associated with the high-risk subregion strongly predicts metastasis and overall survival in stage III patients.

Green: < median
Red: >= median

Wu et al. IJROBP, 2016

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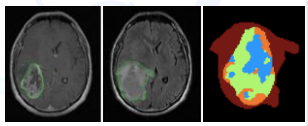
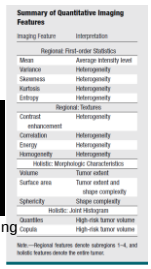
Combine Radiomics with Multi-Region Analysis

- Intra-tumor partitioning based on multi-parametric MRI
- Extract radiomic features for each subregion and gross tumor.



T1w T2w FLAIR Tumor Partitioning



Summary of Quantitative Imaging Features

Imaging Feature	Interpretation
Regional: First-order Statistics	
Mean	Average intensity level
Variance	Heterogeneity
Skewness	Heterogeneity
Kurtosis	Heterogeneity
Entropy	Heterogeneity
Regional: Textures	
Contrast enhancement	Heterogeneity
Correlation	Heterogeneity
Energy	Heterogeneity
Homogeneity	Heterogeneity
Holistic: Morphologic Characteristics	
Volume	Tumor extent
Surface area	Tumor extent and shape complexity
Sphericity	Shape complexity
Holistic: Joint Histogram	
Quantiles	High-risk tumor volume
Copula	High-risk tumor volume

Note.—Regional features denote subregions 1–4, and holistic features denote the entire tumor.

Cui et al, *Radiology*, 2016

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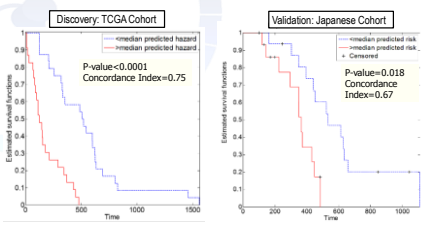
Prognostic imaging signature in GBM

- A 5-feature radiomic signature predicted overall survival, independent of age, gender, extent of resection.



Cui et al, *Radiology*, 2016

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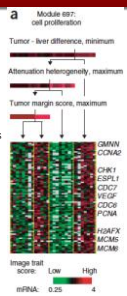
Initial Work on Radiogenomics

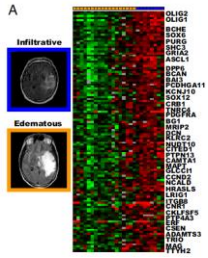
- Radiogenomics in HCC
  - First study to show that CT image features correlate with global gene expression.
  - 28 image features predicted the expression of 78% out of 6732 genes in 32 patients.



Segal et al, Nat Biotechnol 2007

Initial Work on Radiogenomics

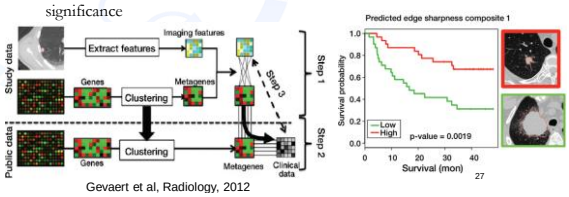
- Radiogenomics of GBM
  - Identified image features in brain MRI correlated with gene expression in 22 patients.
  - Tumor contrast enhancement and mass effect predicted hypoxia and proliferation gene expression programs.
  - Infiltrative imaging phenotype was correlated with clinical outcome.



Diehn et al, PNAS, 2008

Initial Work on Lung Cancer Radiogenomics

- Gene expression and CT image data from 26 NSCLC patients
- Linear models predict metagenes by 180 image features, vice versa
  - Accuracy: 59%–83%, or 65%–86%
- Tumor size, edge shape, and sharpness ranked highest for prognostic significance



Gevaert et al, Radiology, 2012

Limitations of Initial Work

- Proof of concept
- Small number of samples (~20-30)
- Large number of variables: false discovery
- Lack independent validation

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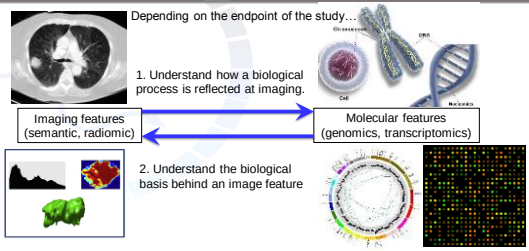
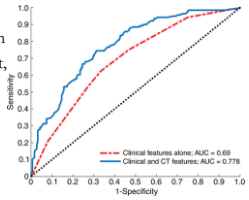
Current Paradigms of Radiogenomics



Type 1 Radiogenomic Association

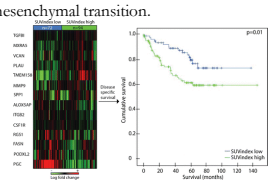
- What imaging features are associated with a biological process?
  - EGFR, KRAS mutation, ALK rearrangement in NSCLC
- Can imaging be used to predict genomic alternations?
  - 385 patients from a single institution
  - 30 CT features to assess EGFR mutation
  - smaller size, homogeneous enhancement, and pleural retraction
  - Good accuracy
  - Clinical value uncertain



Liu et al, Radiology, 2016

Type 2 Radiogenomic Association

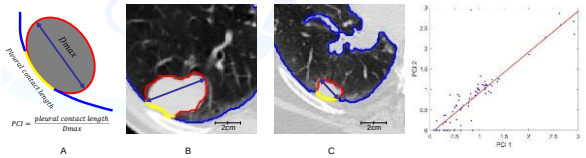
- What molecular pathways or biological processes are associated with a specific imaging phenotype?
  - Maximum SUV at FDG-PET prognostic of survival in NSCLC
  - 14 differentially expressed genes for SUV_{max} in 26 patients (FDR < 0.20)
  - Linked with survival and epithelial-mesenchymal transition.
  - Small, exploratory analysis
  - Additional validation required
  - No mechanistic evidence.



Yamamoto, et al, Radiology, 2016

Quantitative Pleural Contact Index in NSCLC

- Explicitly quantify relation of tumor and surrounding pleura
- PCI has a high degree of reproducibility for multiple contours (ICC = 0.87).



Lee et al. Eur Radiol, 2017. in press

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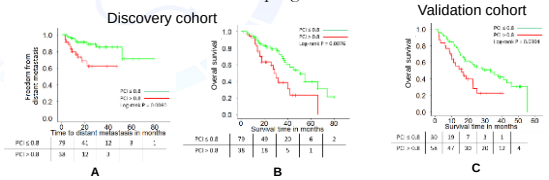
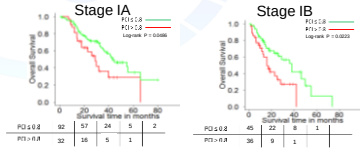
Prognostic Value of Pleural Contact in Stage I NSCLC

- PCI was significantly associated with overall survival in both discovery and validation imaging cohorts.
- PCI also stratified patients for distant metastasis.
- Pleural attachment was not prognostic.



Complementary Value PCI to Clinical Features

- PCI further stratified patients within clinical stage IA, IB subgroups.
- PCI was independently associated with survival beyond age, gender, tumor size, and histology.



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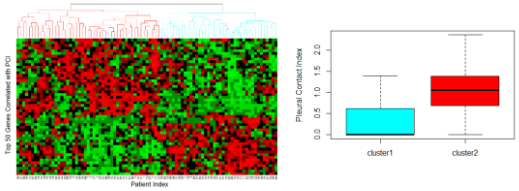
Molecular Correlates of Pleural Contact in NSCLC

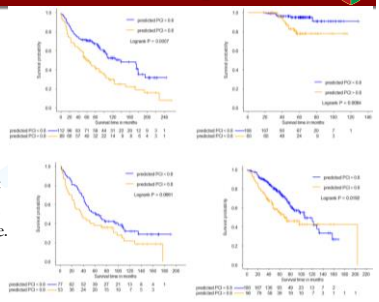
- In 89 patients, extracellular matrix (ECM) remodeling was enriched among genes correlated with PCI (FDR=0.005).
  - Role of ECM remodeling in cancer invasion and metastasis
- Built a genomic classifier for PCI (10-fold CV accuracy: 78%).



Validation of Prognostic Value of PCI in Stage I NSCLC

The genomic surrogate of PCI:

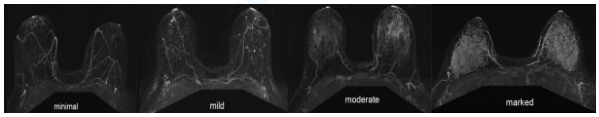
- stratified patients for overall survival in 4 cohorts (775 patients).
- remained a strong, independent prognostic factor adjusting for age, gender, and tumor stage.



Lee et al. Eur Radiol, 2017. in press

Radiogenomics of Breast Cancer Parenchyma

- Breast parenchyma enhances to various extents on DCE MRI.
- Background enhancement has been linked to breast cancer risk, but molecular mechanisms are poorly understood.
- Goal: determine biological underpinnings and assess *prognostic* relevance of parenchymal enhancement.



BI-RADS 2015

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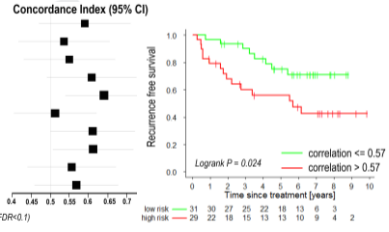
Discovery of Prognostic Parenchymal Image Features

Imaging features	Wald P†	FDR
dissimilarity	0.14	0.28
energy	0.56	0.62
entropy	0.41	0.52
homogeneity	0.07	0.18
correlation*	0.006	0.06
$Prop_{SER>0.5}$	0.82	0.82
$Prop_{SER>1.0}$	0.048	0.16
$Prop_{SER>1.5}$	0.037	0.16
$\overline{SER}_{1\%}$	0.34	0.49
$\overline{SER}_{100\%}$	0.22	0.37



* indicates statistical significant adjusted for multi-testing (FDR<0.1)
† value from Wald test in Cox regression model

Prognostic value independent of tumor imaging features

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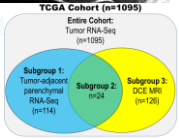
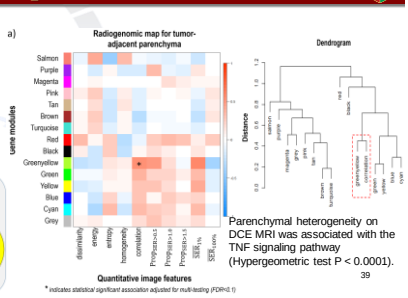
Wu et al. *Radiology*, 2017. in press

Radiogenomic Map

TCGA Cohort (n=1095)





Parenchymal heterogeneity on DCE MRI was associated with the TNF signaling pathway (Hypergeometric test P < 0.0001).

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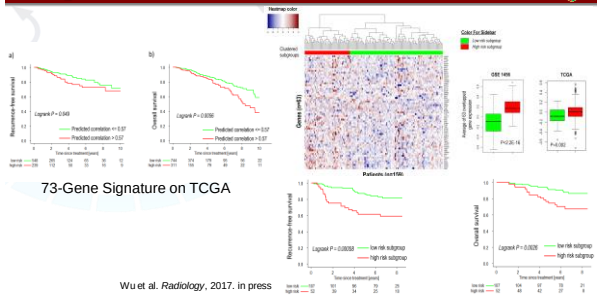
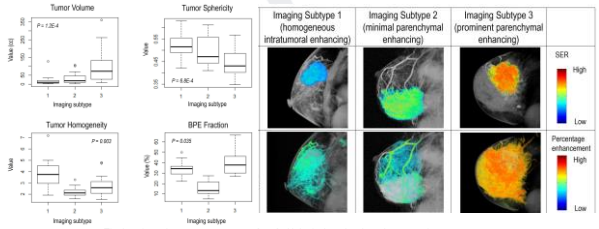
Independent Validation on Two Cohorts



73-Gene Signature on TCGA

Wu et al. *Radiology*, 2017. in press

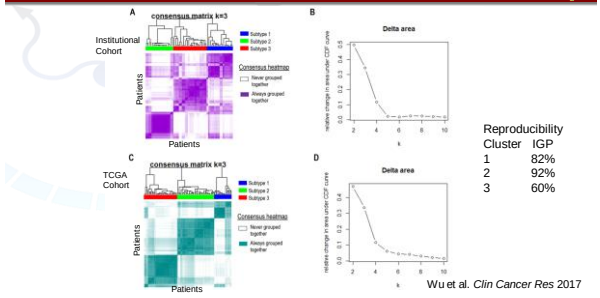
Breast Cancer Intrinsic Imaging Subtypes



The imaging subtypes were **not correlated** with intrinsic molecular subtypes such as luminal A, luminal B, basal-like, HER2-enriched (Person's Chi-squared test P = 0.87)

Wu et al. *Clin Cancer Res* 2017

Clustering of Image Features Revealed Three Subtypes



Reproducibility

Cluster	IGP
1	82%
2	92%
3	60%

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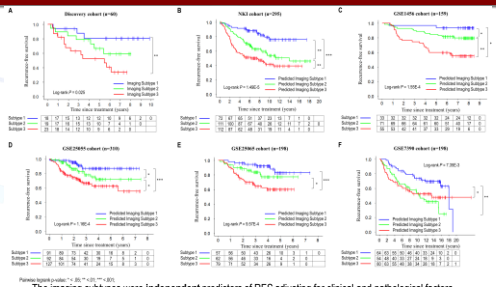
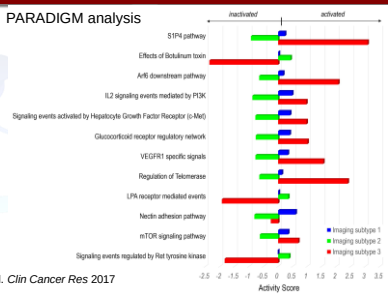
Imaging Subtypes Associated with Distinct Prognosis



The imaging subtypes were **independent** predictors of RFS adjusting for clinical and pathological factors.

Imaging Subtypes Associated with Distinct Molecular Pathways



Wu et al. *Clin Cancer Res* 2017

Challenges of Radiomics

- Reproducibility and robustness
  - Multi-center validation
- Statistical pitfalls
  - False discovery or over-fitting due to multiple testing.
- Biological interpretation difficult
  - Radiogenomics could help, with careful use.

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Conclusion

- Radiomics is a useful tool to discover new imaging biomarkers.
  - Gross tumor, intratumoral, peritumoral
- Integrating imaging with molecular data may improve biological understanding.
- Prospective validation is essential to truly establish the value of imaging in precision medicine.

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