Imaging biomarkers in oncologic liver disease

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Imaging biomarkers

- Imaging characteristics that are objectively measured as indicators of pathogenic processes or pharmacologic responses to therapeutic interventions: **quantitative imaging**

- Advantages of imaging biomarkers relative to serum or tissue biomarkers
  - Non invasive
  - Spatially and temporally resolved

- Diagnostic biomarkers: cross-sectional relationship between predictor and outcome
- Prognostic biomarkers: longitudinal relationship between predictor and outcome

Biomarkers Definition Working Group, 2001
Collins GS et al. Ann Intern Med 2015

Imaging biomarkers: RECIST criteria

- RECIST: response evaluation criteria in solid tumors
- Measurement of tumor diameter at CT
    - Complete response: disappearance of the lesions
    - Objective response: decrease ≥ 30%
    - Stable disease
    - Progressive disease: increase ≥ 20%
- Used since more than 10 years to assess response to treatment in drug development studies
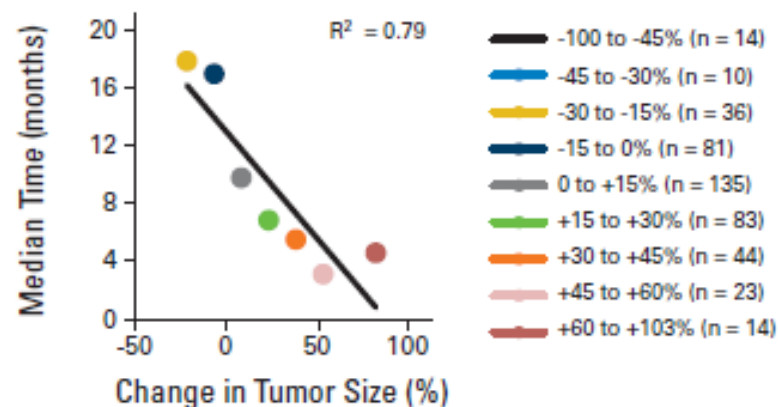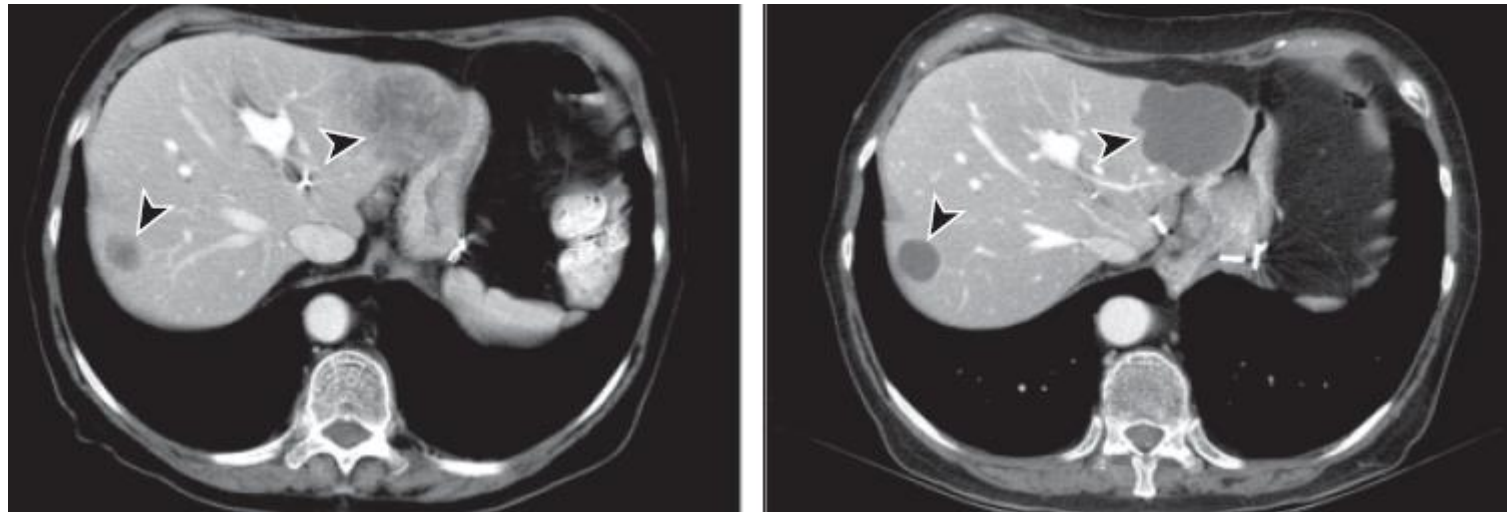
Therasse P et al. JNCI 2000; 92: 205-216
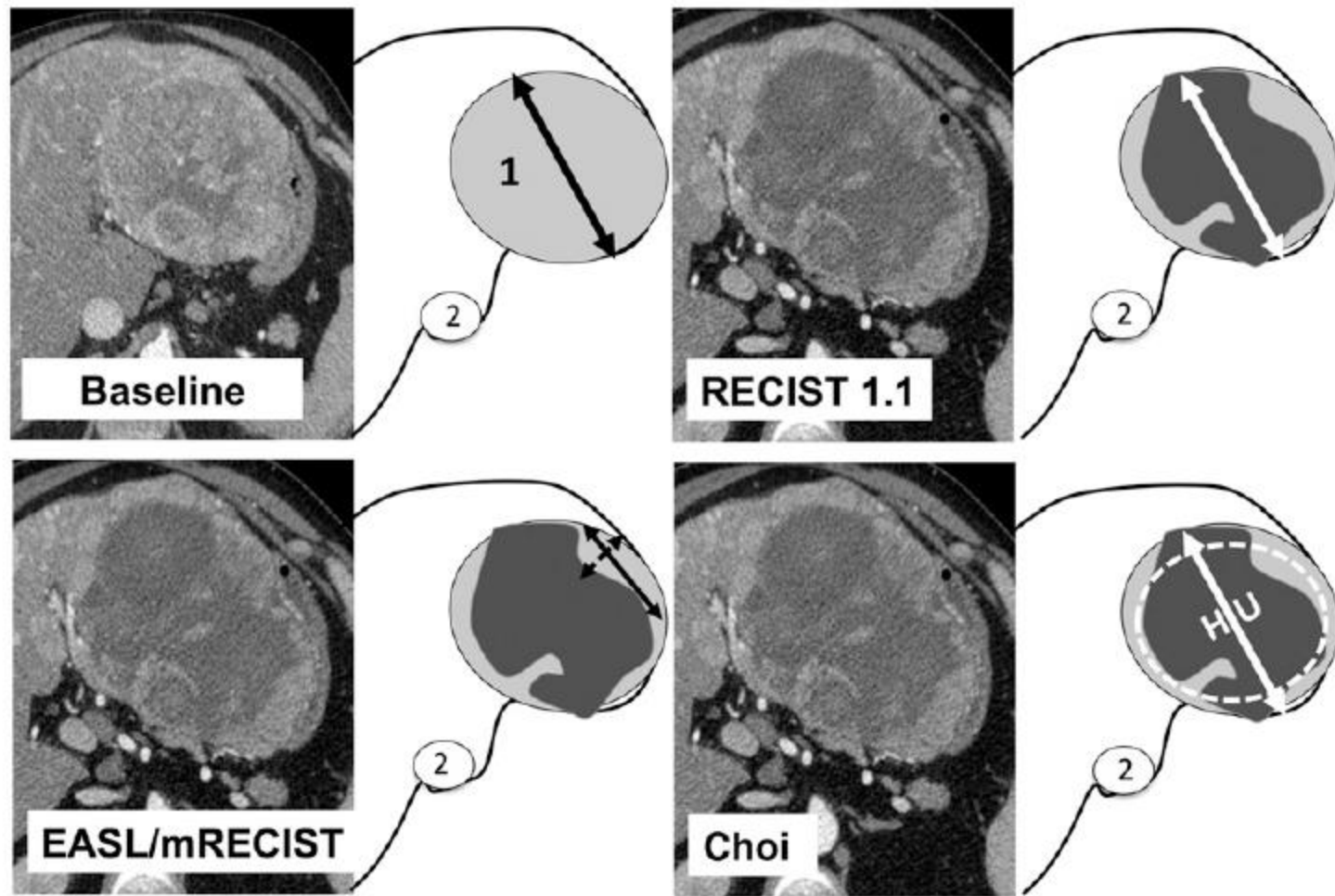Jain RK et al. J Clin Oncol 2013; 266: 812-821

Limitations of RECIST criteria

- RECIST : semi-quantitative score with arbitrary cutoffs

- Decrease in size is not always observed because tumor tissue may be completely replaced with necrosis or fibrosis, especially when targeted treatments are used

Colorectal liver metastases treated with chemotherapy and bevazucimab

Chun YS et al. JAMA 2009; 302: 2338-2344

Size criteria in HCC treated with sorafenib

Ronot M et al. Oncologist 2014; 19: 394-402

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Ronot M et al. Oncologist 2014; 19: 394-402
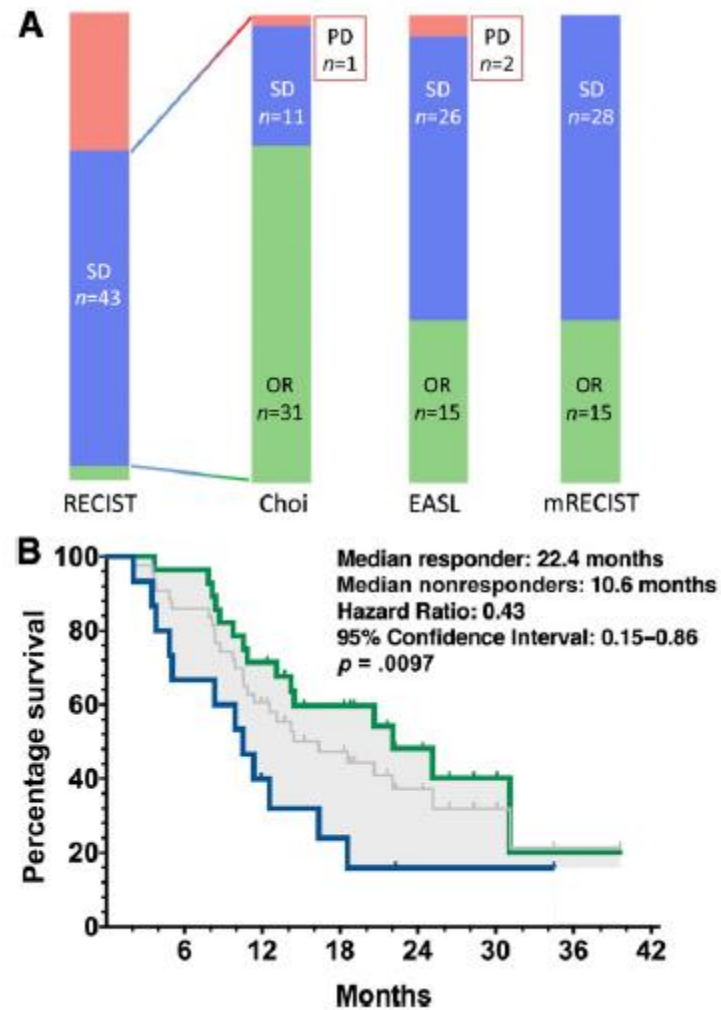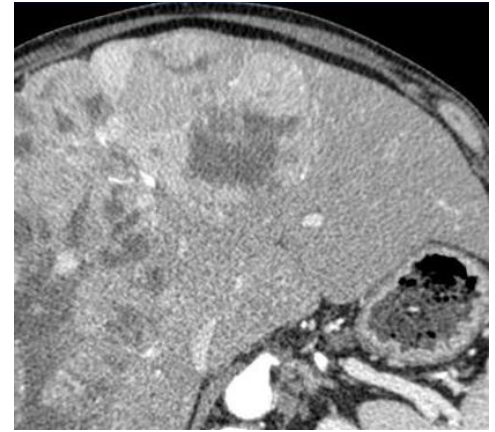
Limitations of mRECIST/EASL

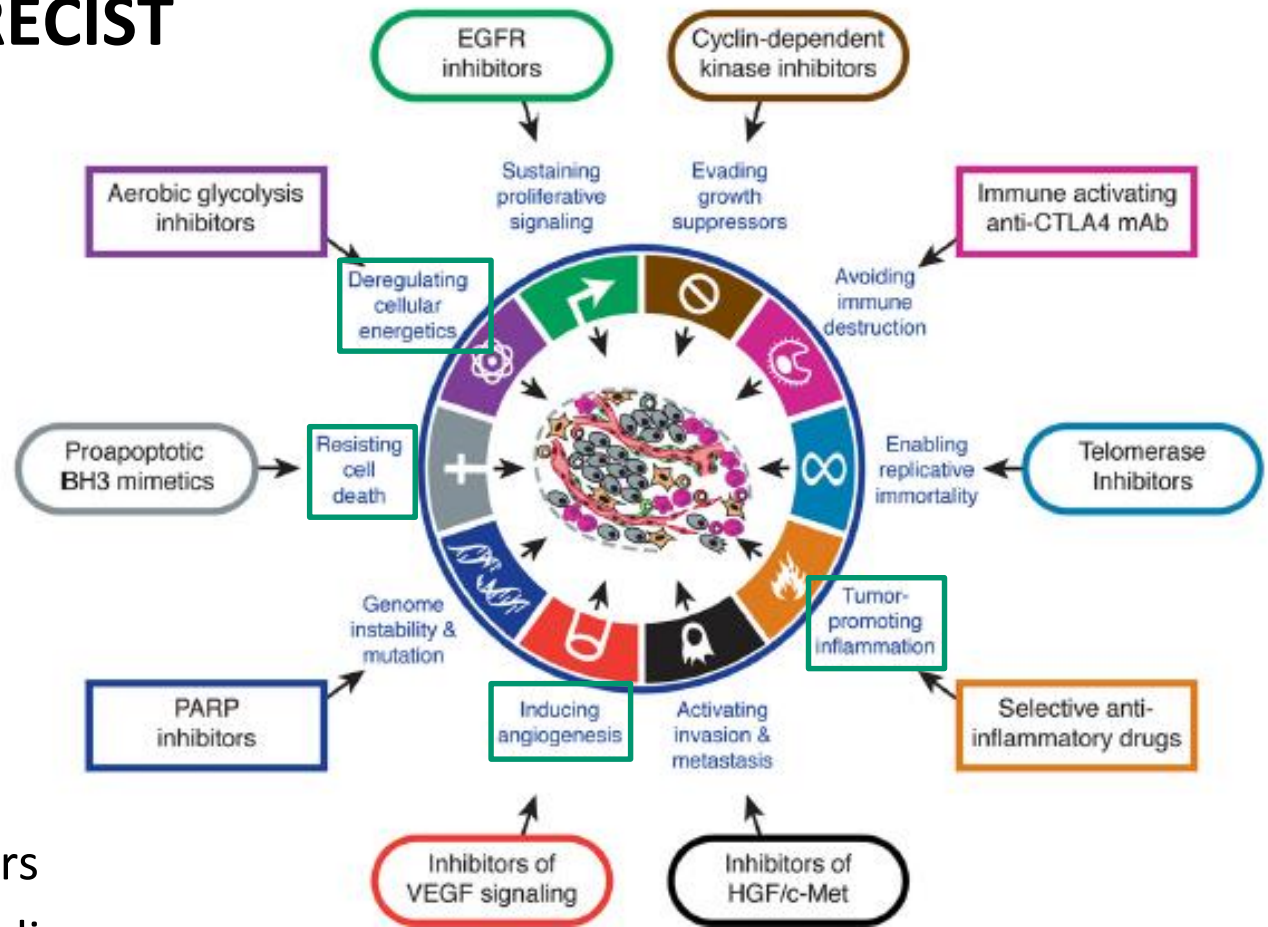- 2D measurements in very heterogeneous tumors
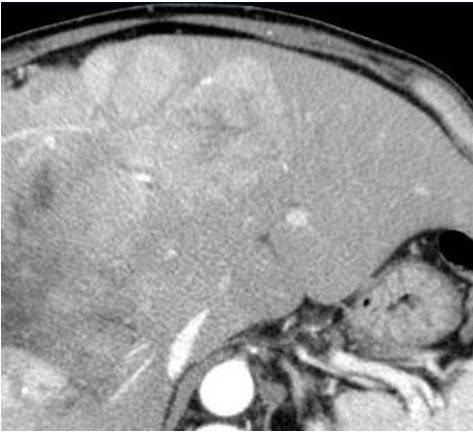
| March | April | June |

Beyond RECIST

- Functional biomarkers
  - FDG PET: metabolism
  - Dynamic contrast-enhanced CT/MRI: angiogenesis
  - Diffusion MRI: cellularity
  - MR elastography: visco-elasticity

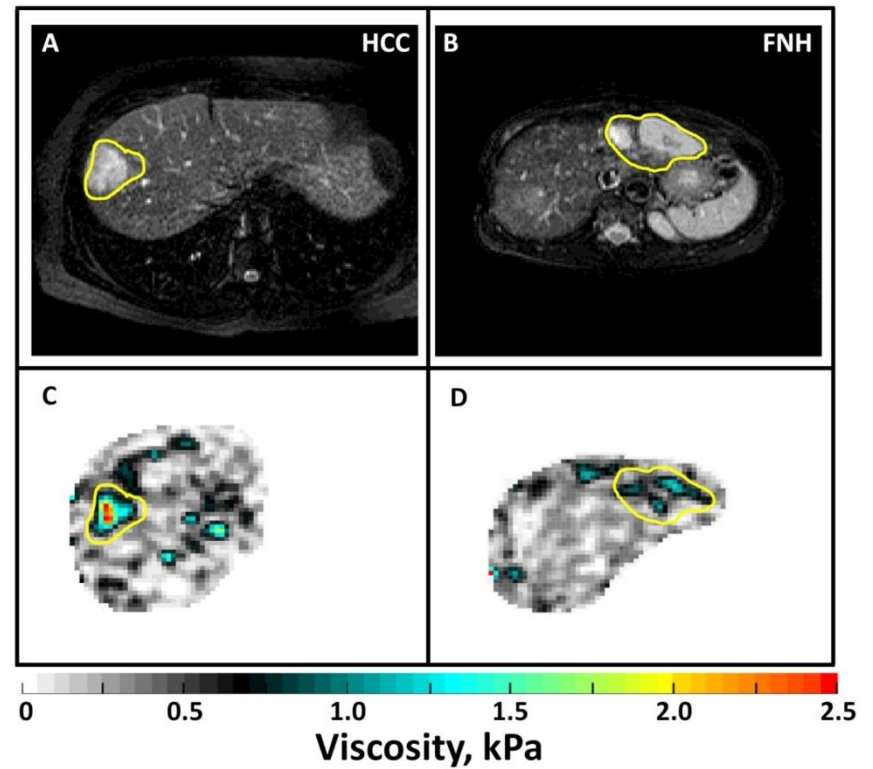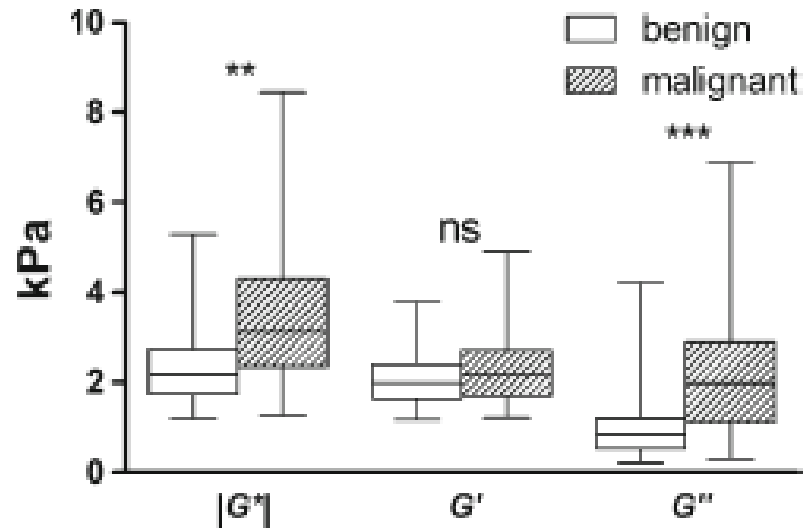Hanahan D et al. Cell 2011; 144: 646-674

ADC: distinction between benign and malignant lesions

- High ADC in benign lesions with high fluid content such as hemangiomas

- No significant difference in ADC between benign hepatocellular lesions and malignant tumors
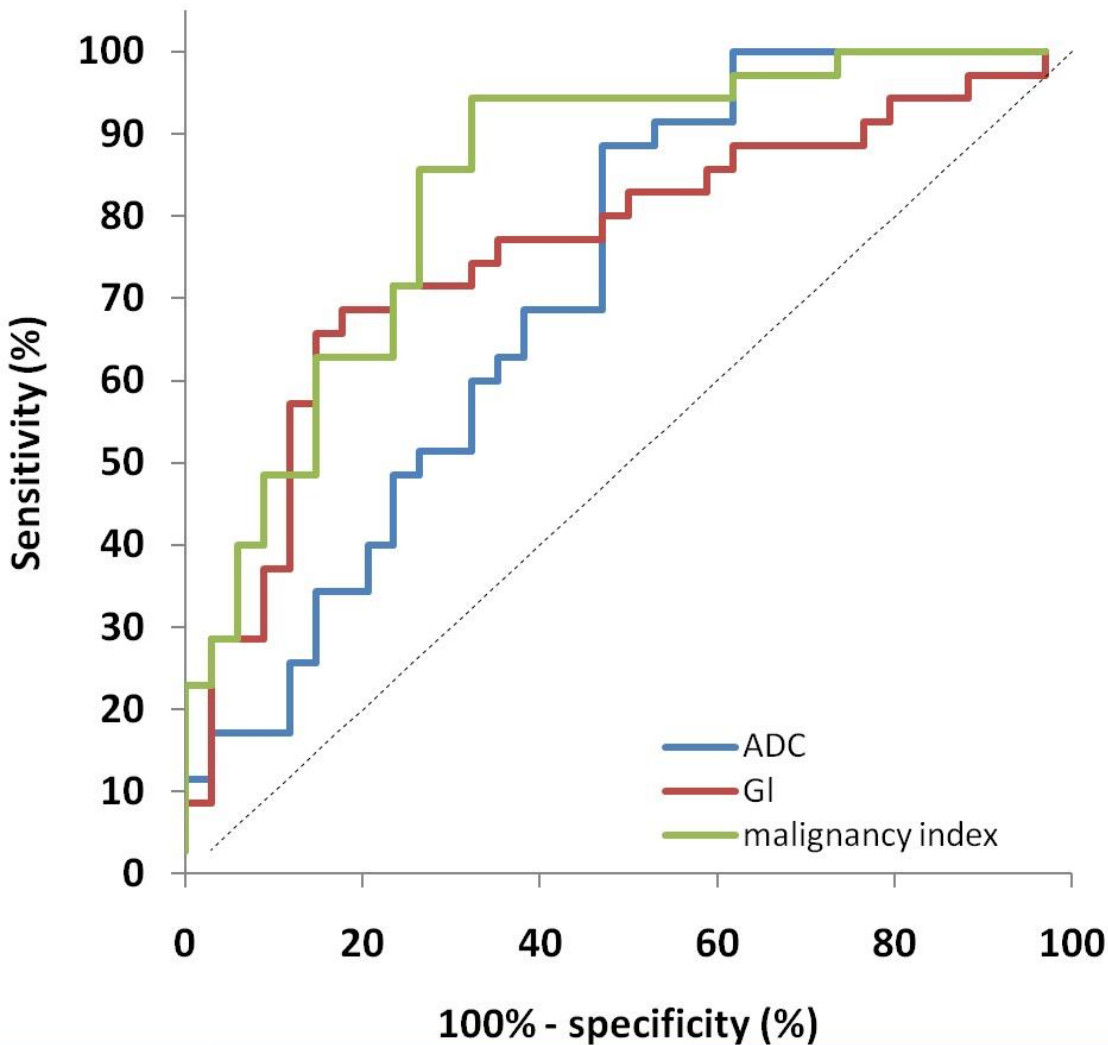

Doblas S et al. Invest Radiol 2013;48: 722-728
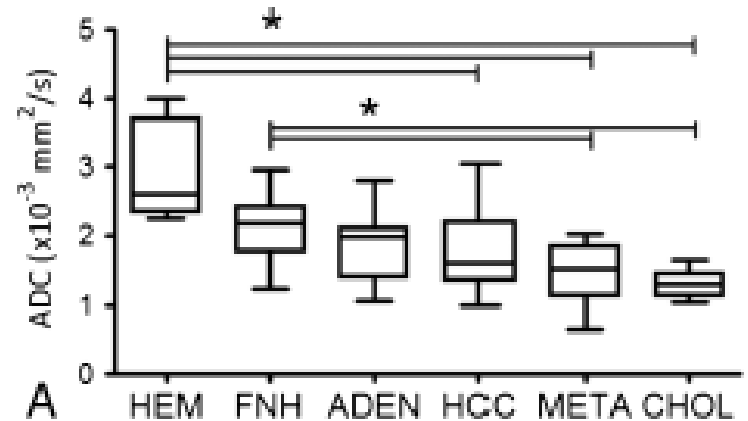
Visco-elastic properties

Garteiser P. et al. Eur Radiol 2012; 22: 2169-2177

Areas under ROC curves

AUROC$_{ADC}$ = 0.71

AUROC $_{Gl}$ = 0.76

AUROC $_{malignancy\ index}$ = 0.84

FDG PET for tumor aggressiveness

- Meta-analysis: high pretreatment FDG PET activity is predictive of poor survival in colorectal liver metastases

- High $SUV_{HCC/liver}$ is predictive of HCC aggressiveness (microvascular invasion, poor cellular differentiation)

- No correlation between SUV and ADC
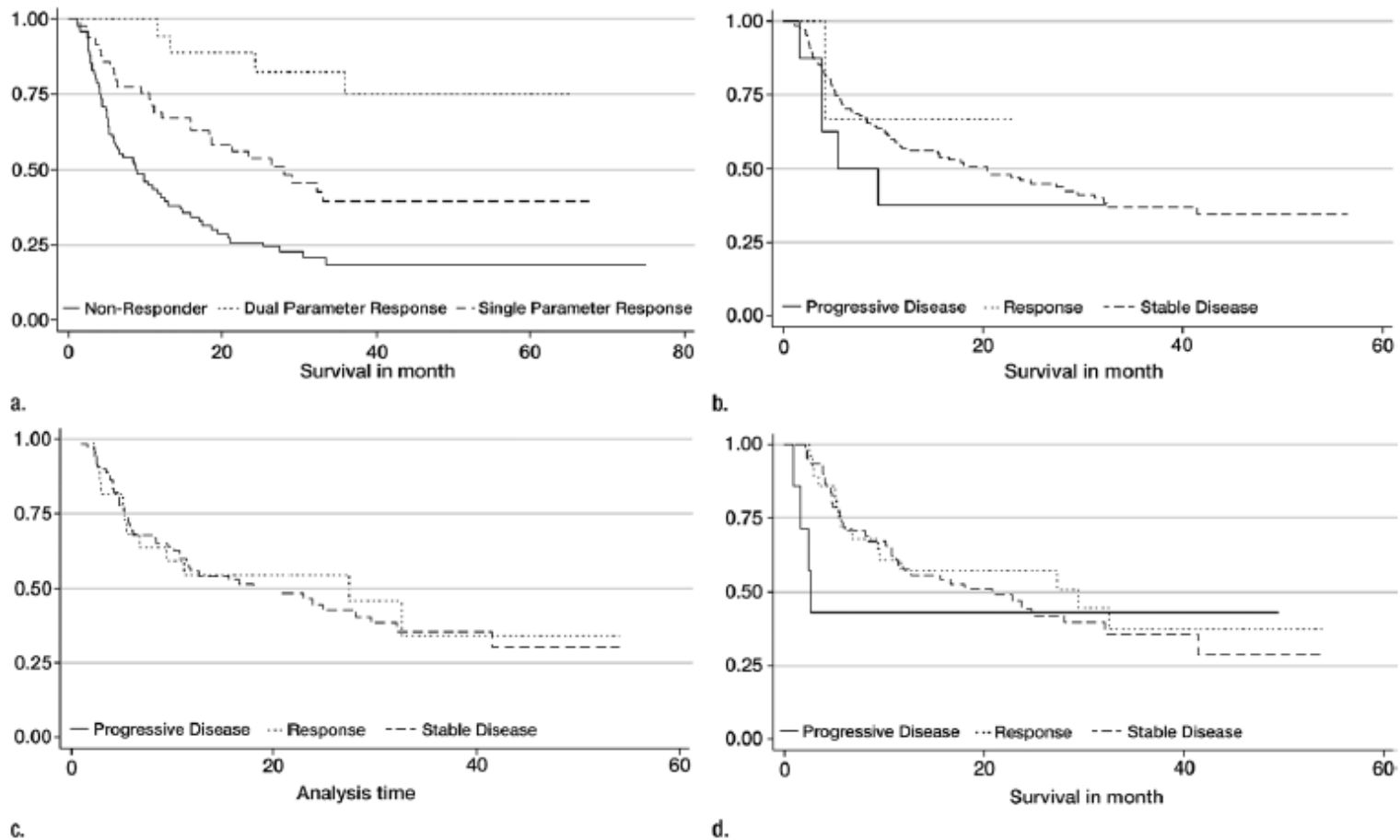- No correlation between SUV and K_{trans}

Xia Q et al. Cancer Imaging 2015
Boussouar S. et al. Cancer Imaging 2016

Response to treatment: volumetric assessment of ADC and enhancement
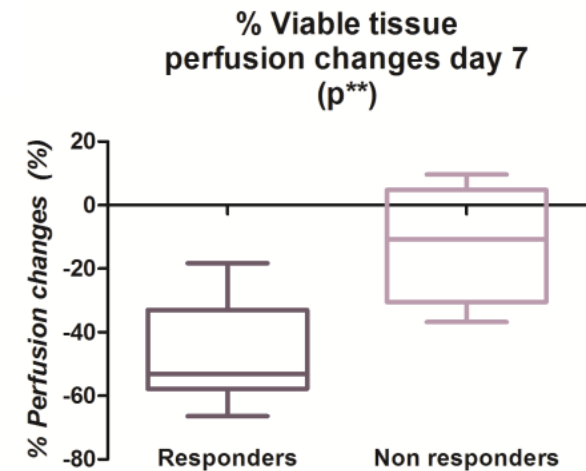
Bonekamp S et al: Radiology 2013; 268: 431-439
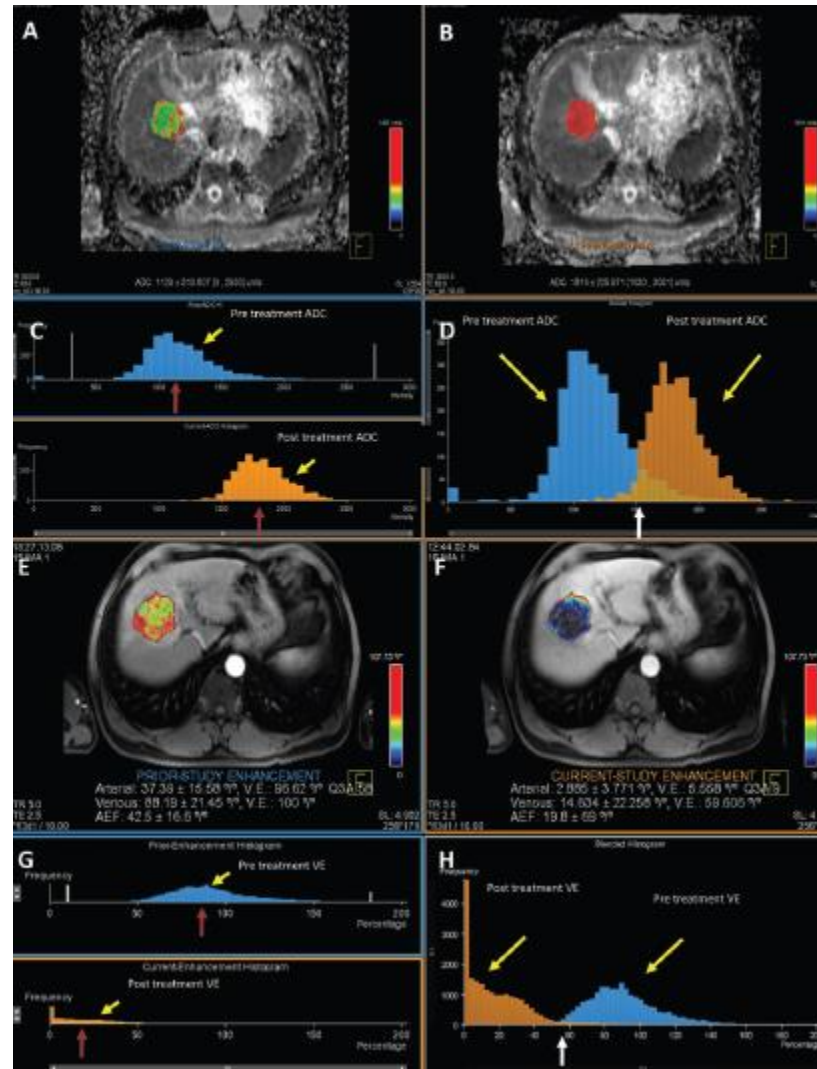
HCC after TACE
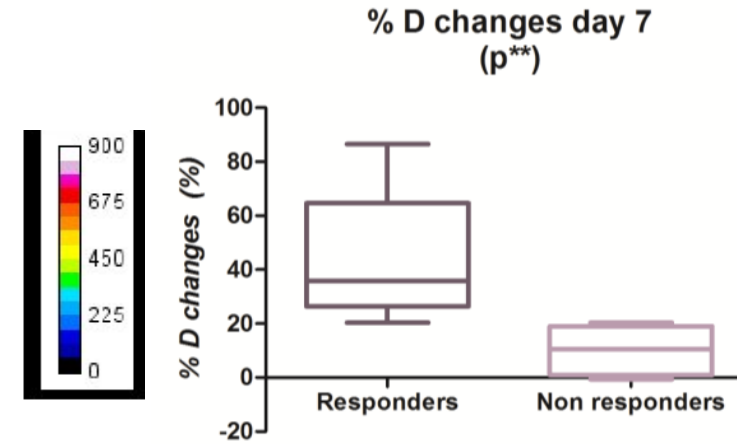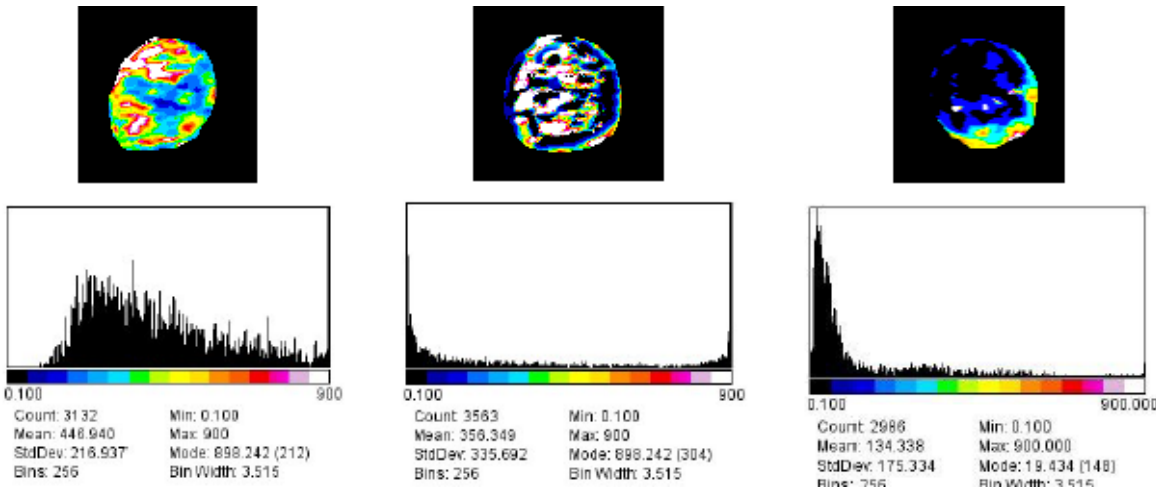

Volumetric ADC increase ≥ 25% and portal venous enhancement increase ≥ 65% 3 – 4 weeks after TACE are better predictors of survival than RECIST, mRECIST and EASL criteria

Bonekamp S et al: Radiology 2013; 268: 431-439

Early diffusion and perfusion changes after TACE of HCC

Diffusion and perfusion changes are already observed at MR imaging one week after TACE

Boustany G et al. 2015

Perfusion MRI changes after treatment in liver metastases
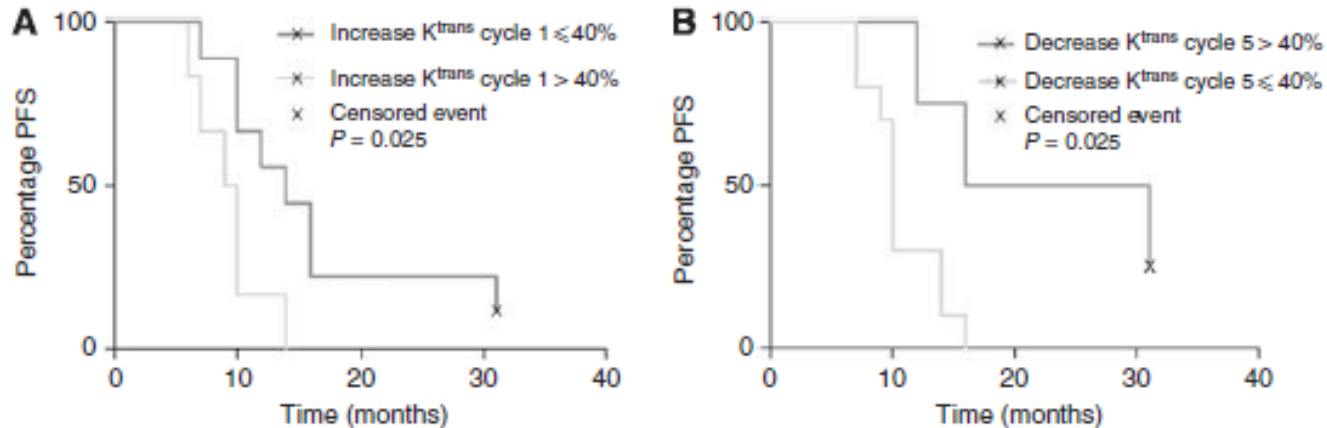
Improvement of disease free survival in patients with liver colorectal metastases treated with chemotherapy and bevacuzimab when perfusion increase < 40% after one week and perfusion decrease > 40% after 10 weeks

De Bruyne S et al. Br J Cancer 2012

FDG PET as predictor of survival
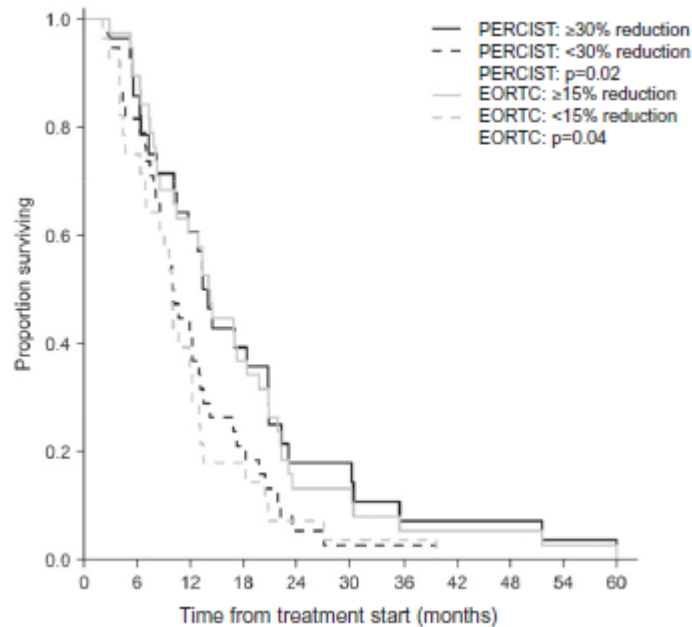
- Reduction of FDG uptake after one treatment (irinotecan and cetuximab) of metastatic colorectal cancer is predictive of survival
- However, diagnostic performance not strong enough to support implementation in daily practice

Skougaard K et al. Acta Oncol 2016

Improvement of diagnostic performance with functional MRI relative to RECIST

- Shift from morphological to functional parameters

- Shift from manual one-dimensional to automatic three-dimensional approach
  - Tumor heterogeneity is better taken into account
  - Reproducibility is improved

Bonekamp D et al. Eur J Radiol 2014
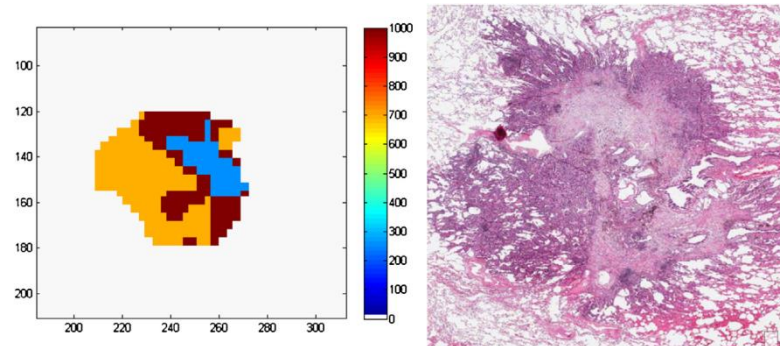
Radiomics

- Radiomics is defined as the conversion of images to higher dimensional data and the subsequent mining of these data for improved decision support

- Three characteristics

  - Shape

  - Signal intensity

  - Texture: spatial variations of voxel intensity related to tumor heterogeneity

Tumour intensity

Tumour shape

Tumour texture

Aerts H. et al. Nat Commun 2014
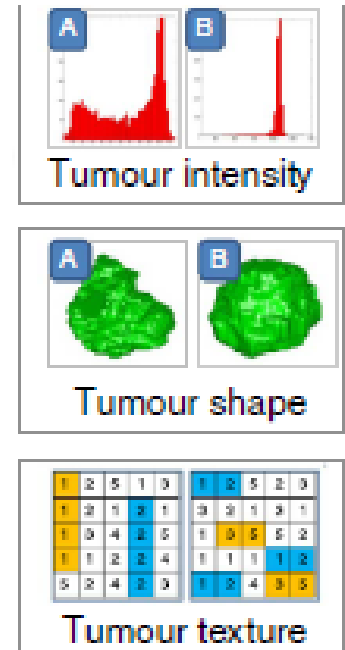
Tumor heterogeneity

- Spatial and temporal tumor heterogeneity that creates local habitats
    - Random genetic mutations
    - Importance of microenvironment
- Genomic heterogeneity within tumors is a major cause of treatment failure
- Correlations between radiomics and histopathological phenotype
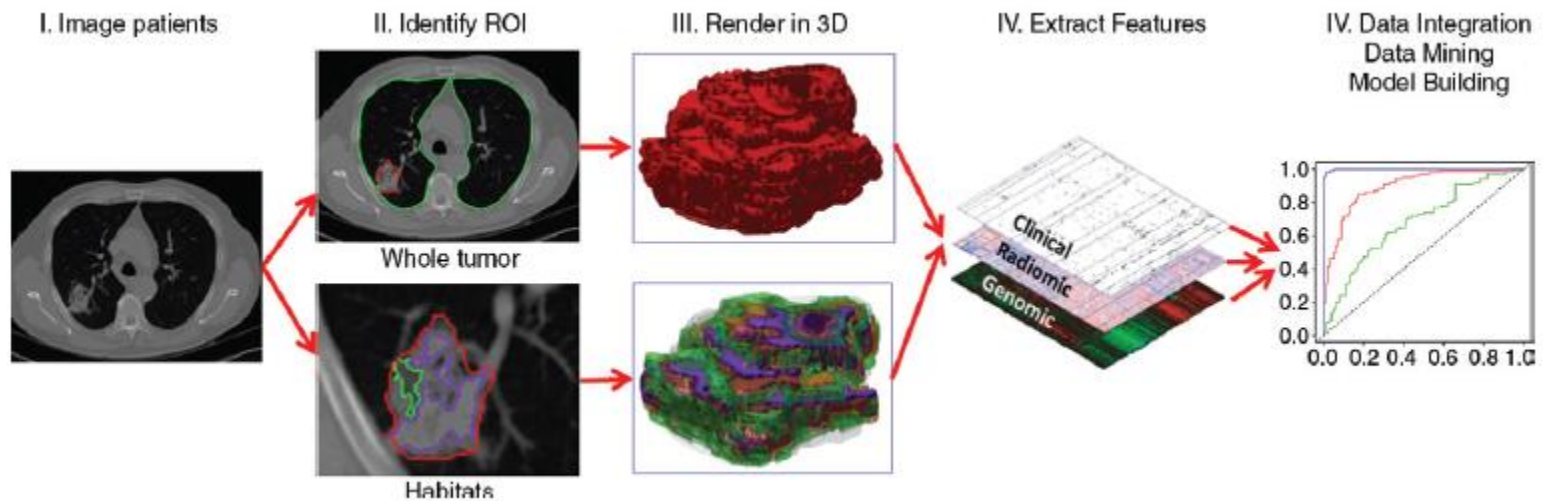- Correlations between radiomics and genomics: radiogenomics

Gatenby RA et al. Radiology 2013
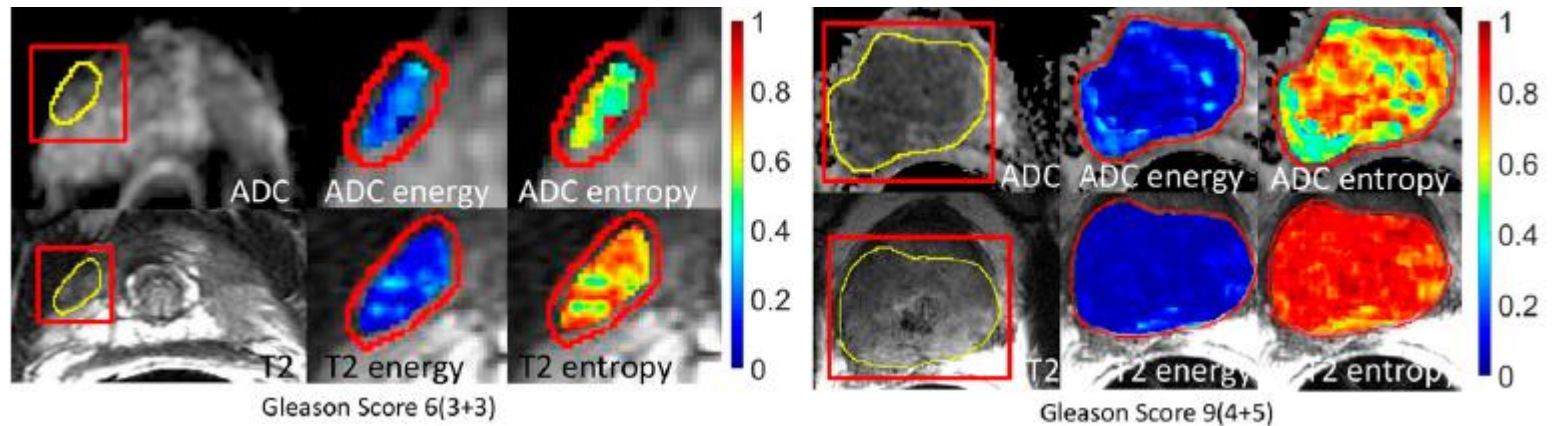Lee G et al. Eur J Radiol 2016

Radiomics

- Standardized acquisition
- Segmentation
- Feature extraction
- Feature selection
- Data analysis: statistical (logistic regression) or machine learning methods

I. Image patients   II. Identify ROI   III. Render in 3D   IV. Extract Features   IV. Data Integration Data Mining Model Building

Gillies RJ et al. Radiology 2016

Diagnostic value of radiomics


Gleason Score 6(3+3)

Gleason Score 9(4+5)

- In HCC, combinations of 28 imaging traits at CT can reconstruct 78% of the global gene expression profiles, revealing cell proliferation, liver synthetic function, and patient prognosis

- T2-weighted MRI and diffusion MRI in prostate cancer
  - Radiomics: accuracy of 93% for diagnosing Gleason 6 versus ≥ 7
  - ADC $_{mean}$: 63%
- More validation studies are needed

Segal E. et al. Nature Biotech 2007
Fehr et al. PNAS 2015

Advanced method: oscillating gradient DW imaging

- Very short diffusion times
- Sensitive to intracellular changes
- Characterization of high dysplastic nodules and early HCC

Wagner M et al. 2015
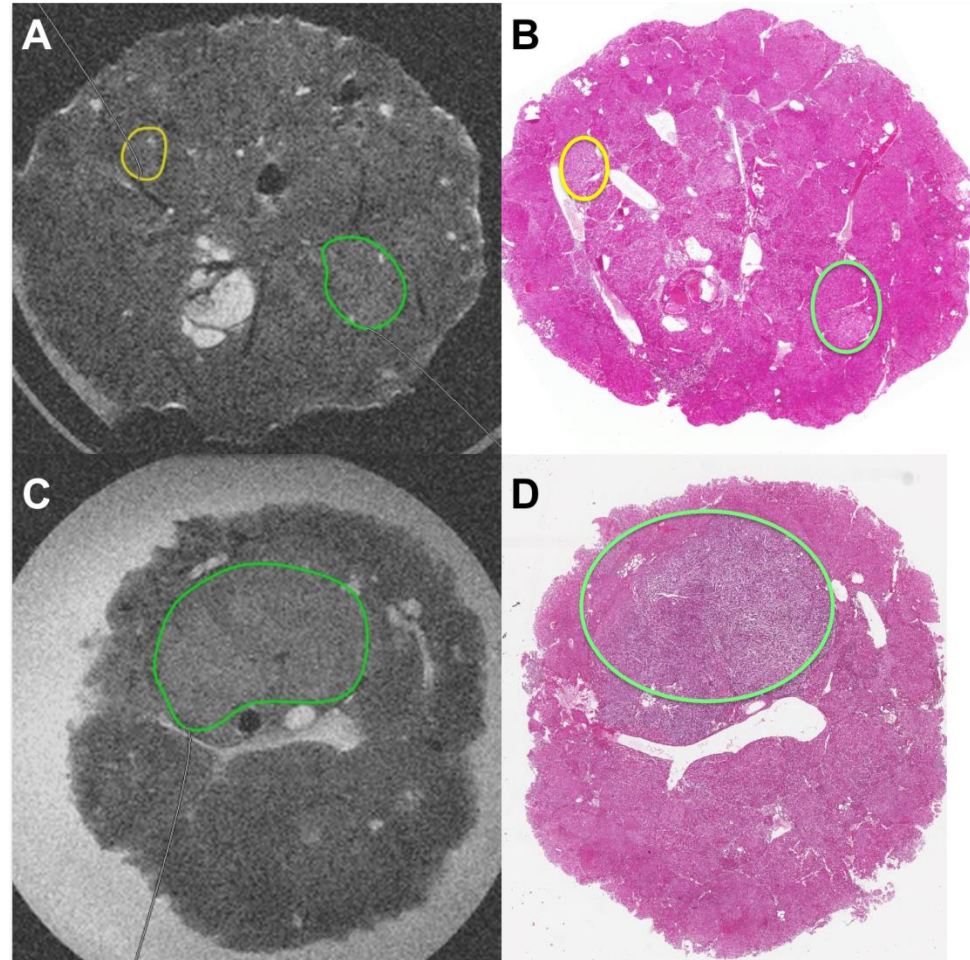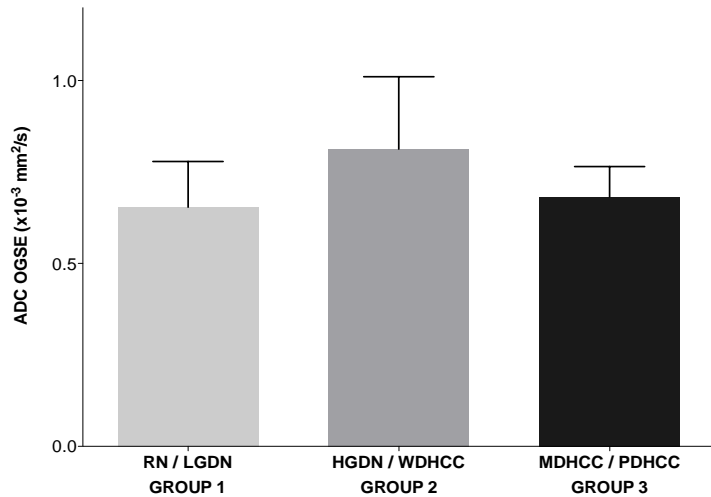
Advanced method: MR force elastography
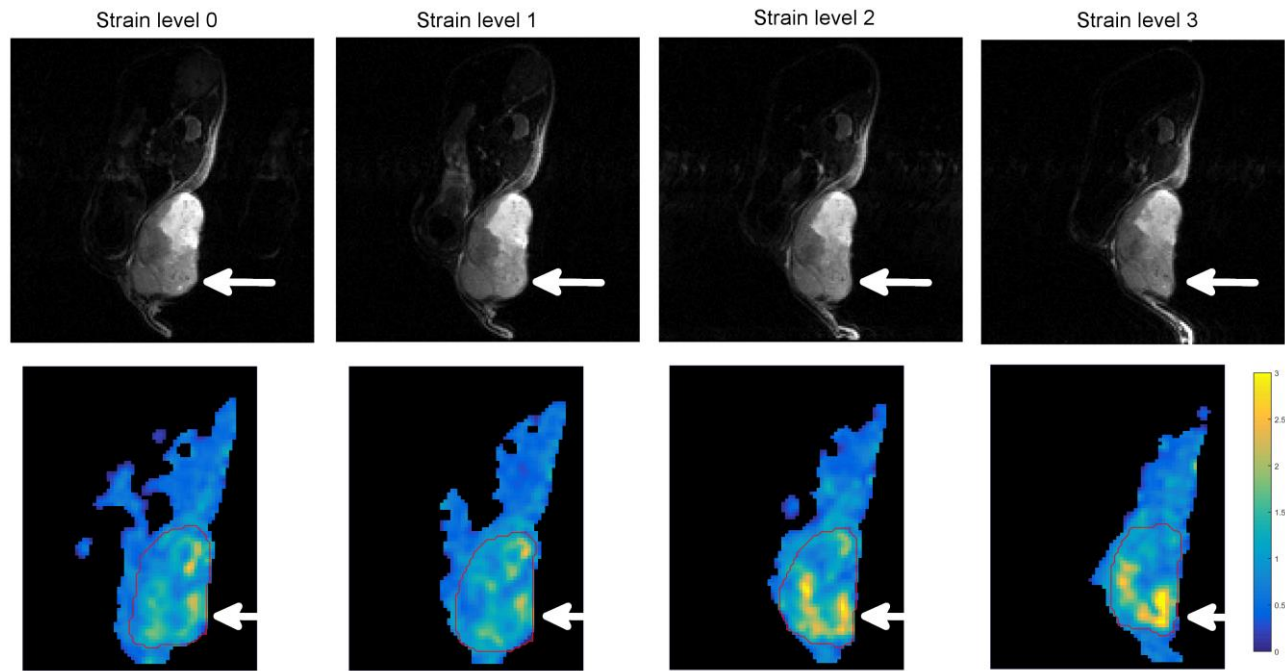
- MR elastography under increasing strain conditions
- Measurement of interstitial fluid pressure: marker of both prognosis and response to treatment

Tardieu M.et al. 2016

Conclusions

- Imaging biomarkers, especially functional imaging biomarkers, help in liver tumor characterization and assessment of treatment response
- Integration of multiple predictors
  - Multiparametric MR imaging
    - DW MR imaging
    - Perfusion MR imaging
    - MR elastography
  - Multimodal approach
    - PET-MRI
  - Radiomics
    - Regional assessment of tumors
  - Data integration
    - Radiomics
    - Genomics, metabolomics
    - Clinical data
- Development of new biomarkers
- Need for validation (reproducibility, accuracy) and standardization
- Increasing need of biostatistics