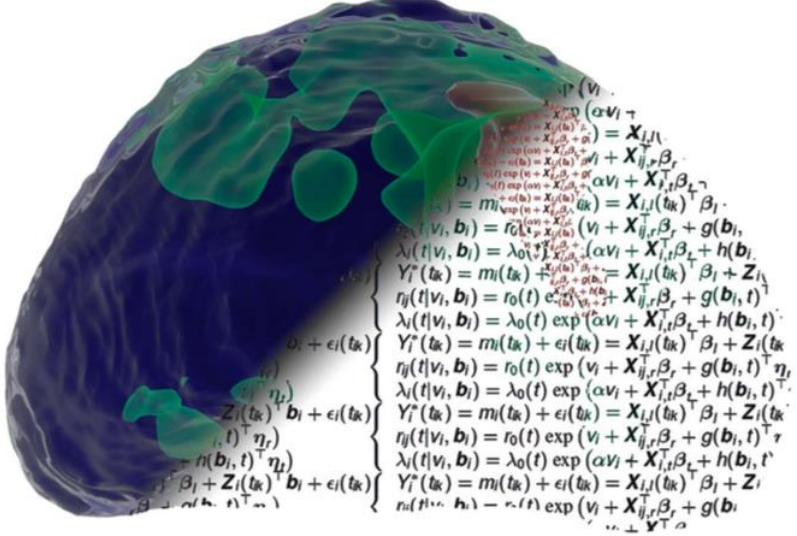


Statistical and biomathematical Models for imaging in cancer

What are the issues related to imaging in oncology?

M Kind, J Palussière

Institut Bergonié Bordeaux

Cancéropôle Grand Sud-Ouest

Bordeaux · Limoges · Montpellier · Nîmes · Toulouse

7-8 avril 2016 Bordeaux-ISPED

Institut Bergonié

While important in many practices, Cancer Imaging is becoming gradually more crucial in precision medecine

Tumor types

extent/ staging

aggressiveness

PRONOSTIC IMAGING

Biomarkers

QUANTITATIVE IMAGING

Treatment types and response criteria

cytotoxic / MTT/ antiangiogenic immunotherapy

PREDICTIVE IMAGING

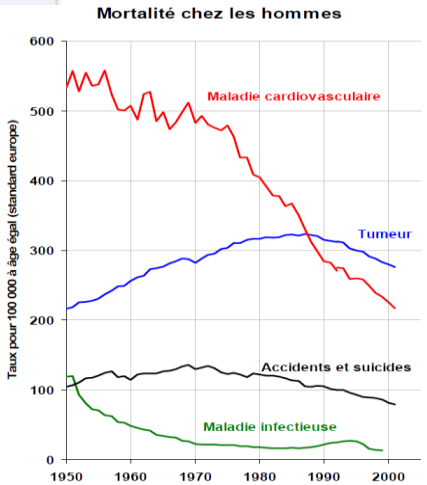
patient

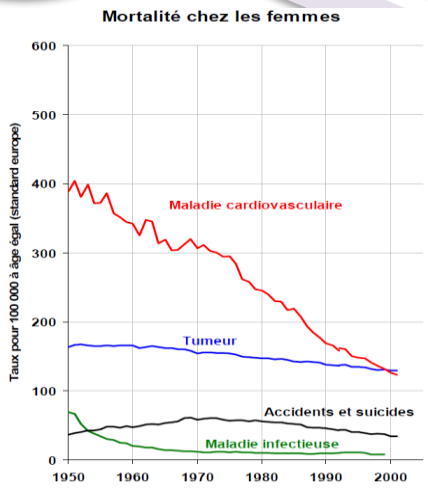
Side effects

Secondary resistance

Performance status

anemia sarcopenia





While important in many practices, Cancer Imaging is becoming gradually more crucial in precision medecine

Tumor types

extent/ staging

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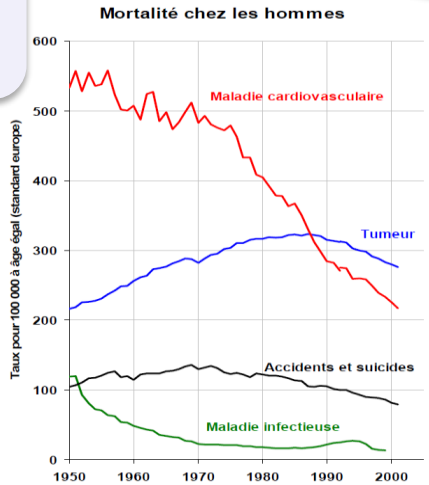
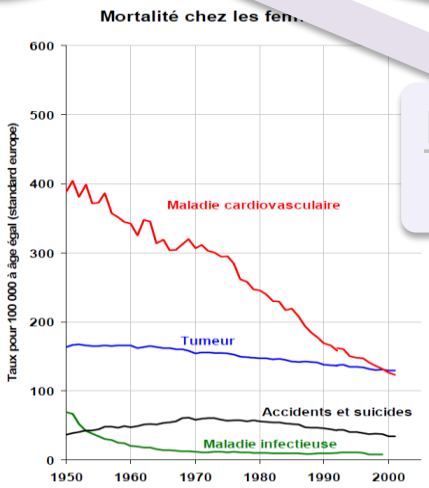




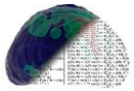
Images are not only pictures: they are data

R Gillies, Radiology 2016

Extract more information from medical images to facilitate decision making at the clinical level

Cancer Imaging challenges: modeling findings

- Understanding the biological substratum behind image phenotypes *(genes turned on/of with a particular phenotype)*
- Understanding **how a biological process is demonstrated** in imaging *(associated with hypoxia or angiogenic gene signature)*
- **Defining biomakers** or surrogates that outperform traditional criteria *(ie. survival)*



BEHIND THE NUMBERS: Decoding Molecular Phenotypes with Radiogenomic Kuo and Jamshidi

Radiology 2014; 270:320–325

1/ Tumor diagnosis : the challenges

As tumor diagnosis is moving from tissue-based approaches to the molecular level,

Traditional radiology-pathology correlations are no longer sufficient

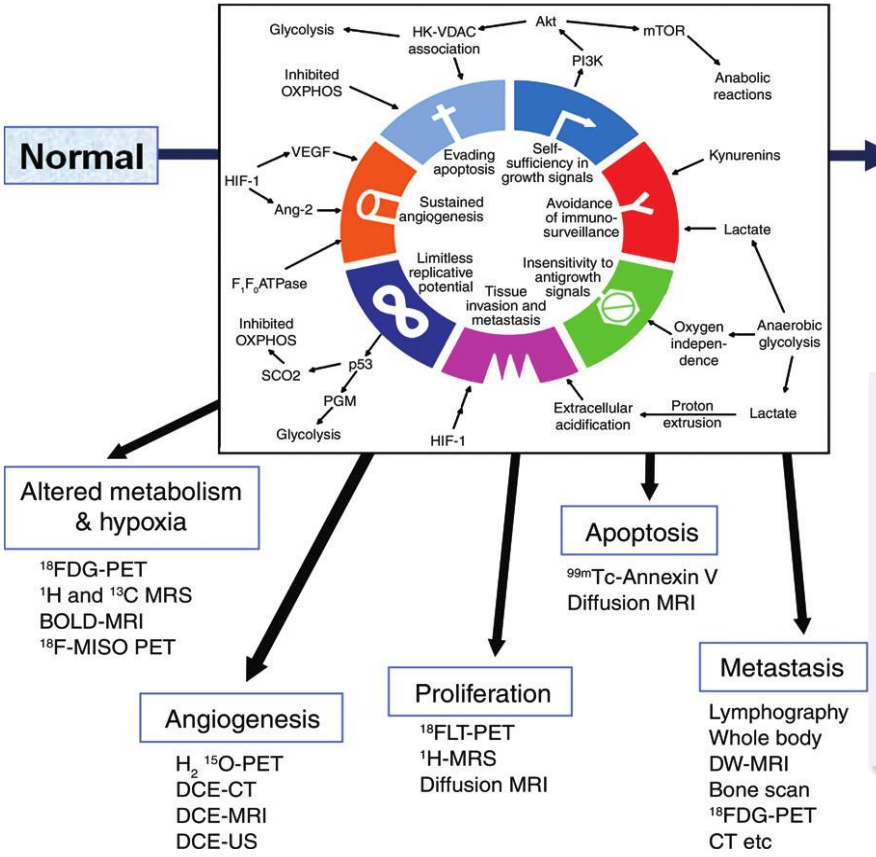
Switch from qualitative to quantitative imaging

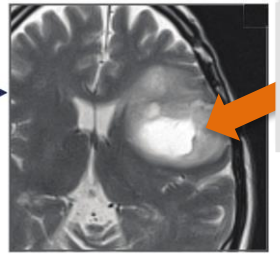
PRONOSTIC IMAGING

- Tumor phenotypes
- Tumor heterogeneity

- Decoding tumor phenotype
- Quantifying Tumor heterogeneity

Predicting T behaviour





Focus on a single tumor site

Tumor phenotypes (gene signature)
Angiogenic phenotypes
Hypoxia, habitats

Multimodality approach to integrate data

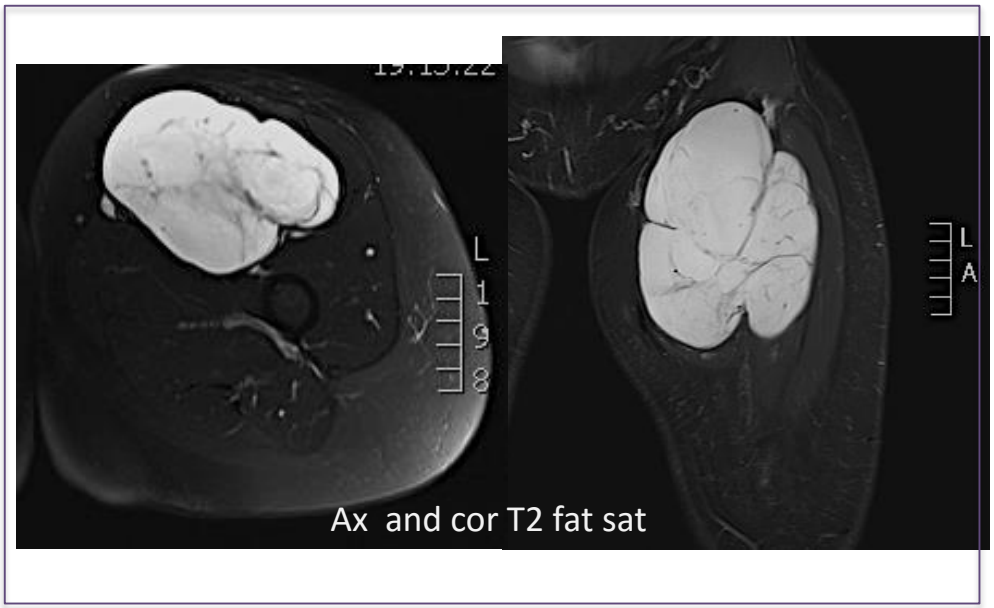
A Padhani and K Miles
Radiology 2010

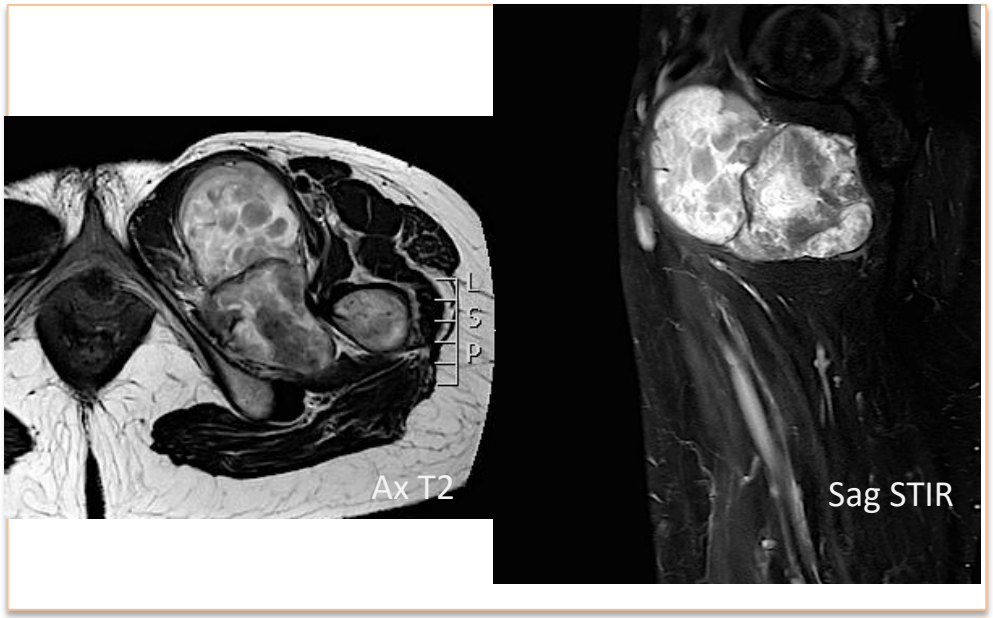
?

- How to model
- Which imaging biomarker is relevant
- How they are measured

In the same histological tumor type:

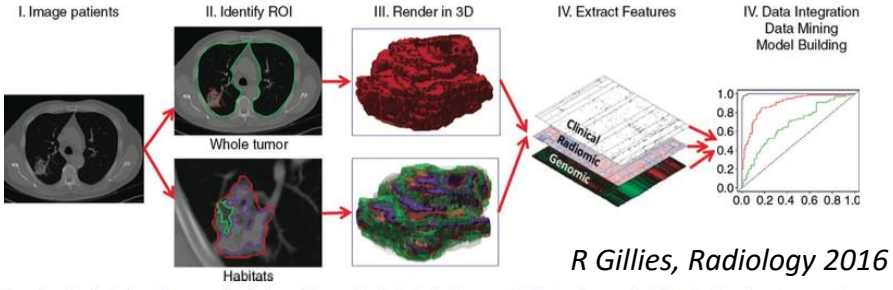
- Morphological differences discriminate subtypes with different behaviours
  (metastasis, overall survival)
- Impact therapeutic management





Myxoid Liposarcoma without and with subpopulation of round cells

a. Tumor phenotypes and imaging



R Gillies, Radiology 2016

Radiomics:

Association maps between Image features (phenotypes) and molecular markers

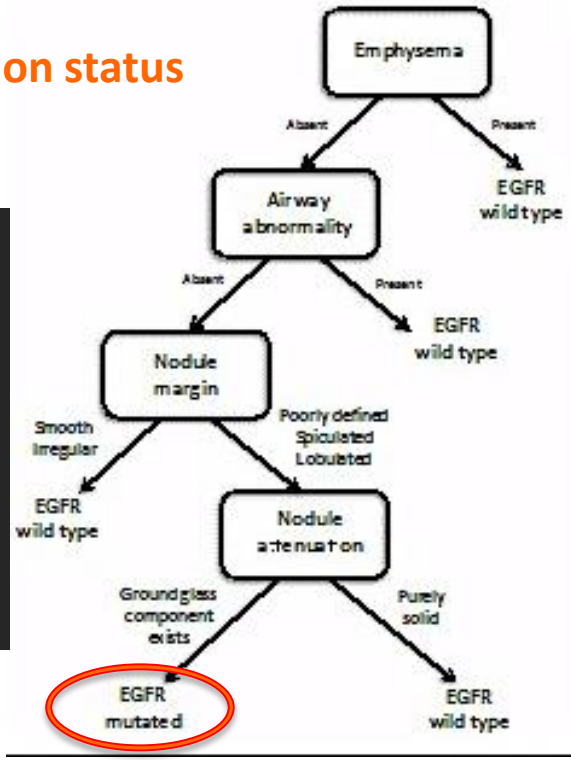
Radiogenomics mapping of non-small cell lung cancer identifies prognostic relationships between semantic image features and metagenes captured using RNA sequencing

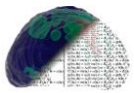
Lung K / 186 patients 82% adenoK
22% EGFR+
EGFR mutation status can be predicted using 4 features

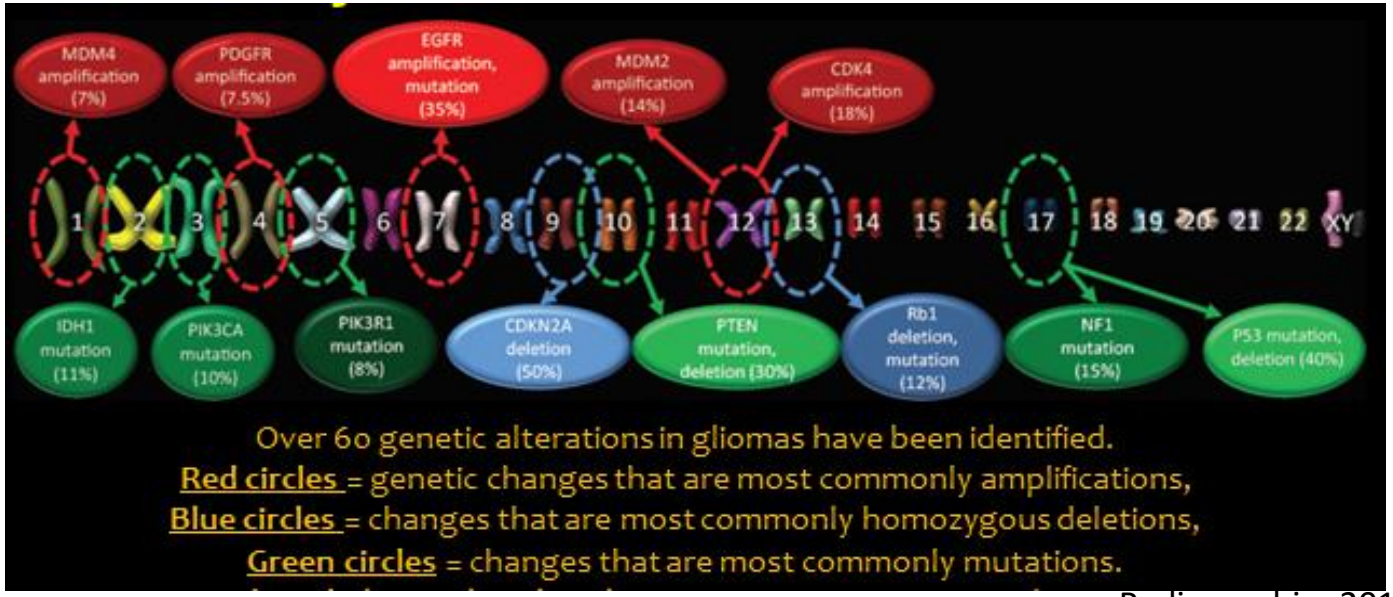
- Four features required
  - Emphysema => smoking
  - Airway abnormality
  - Nodule shape
  - Ground glass

O. Gevaert RSNA 2015

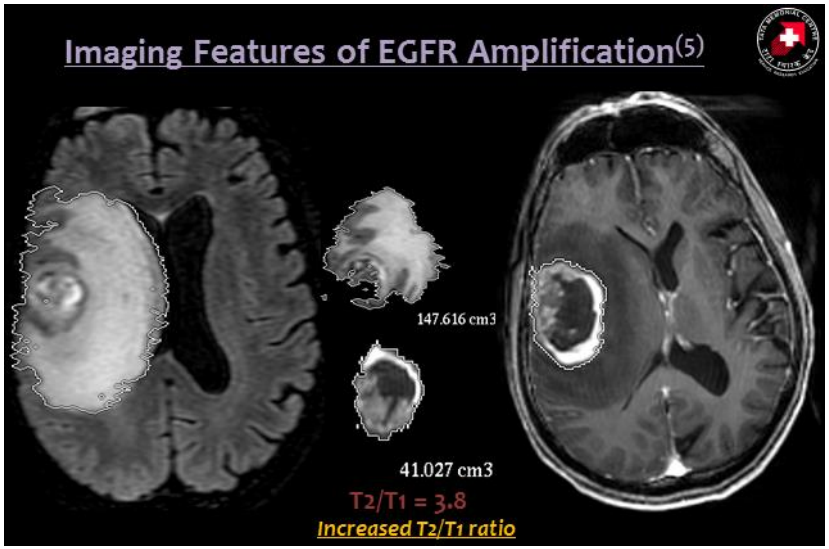
EGFR Mutation status



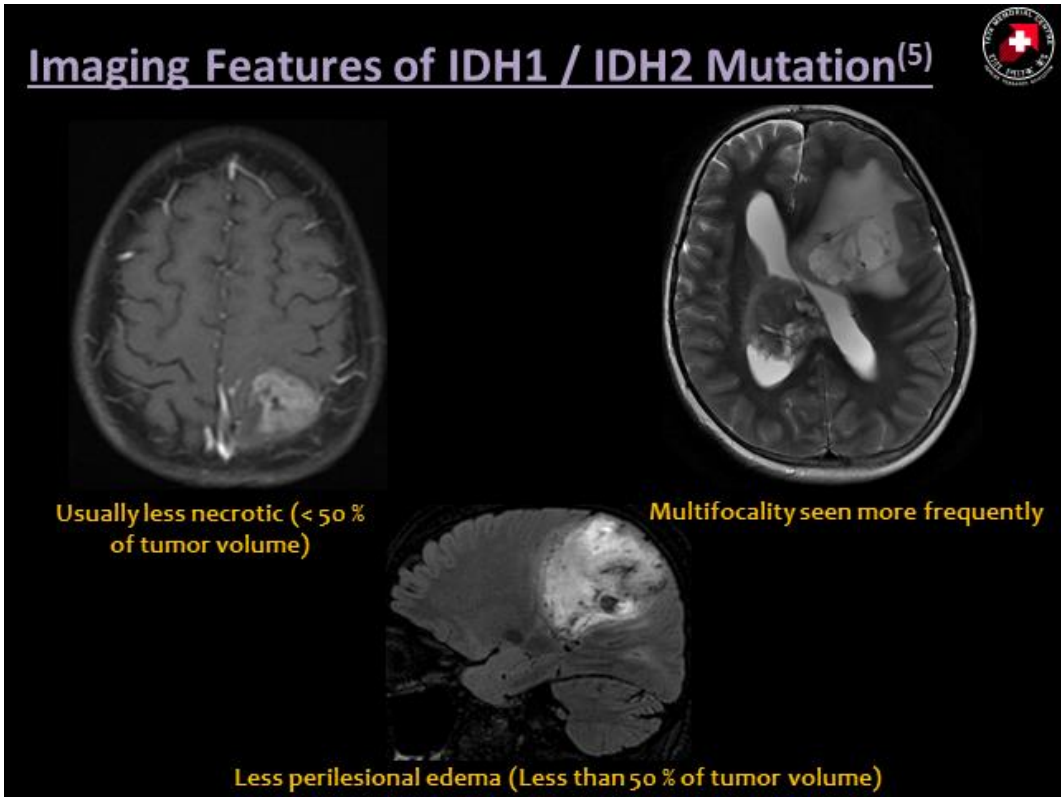




Radiographics 2011 Clifford J



S Singh RSNA 2015

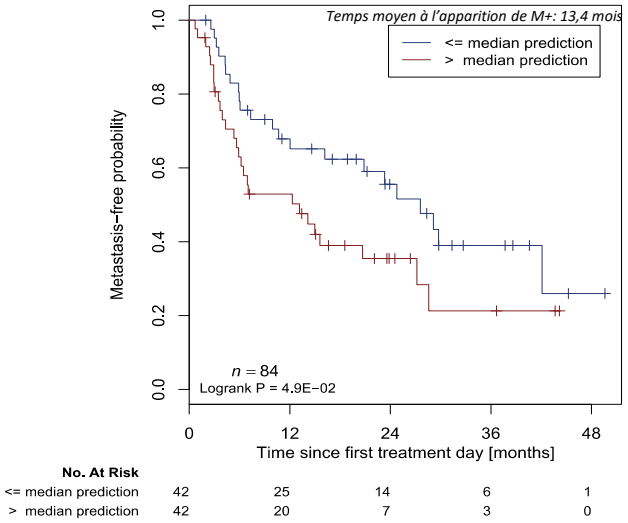


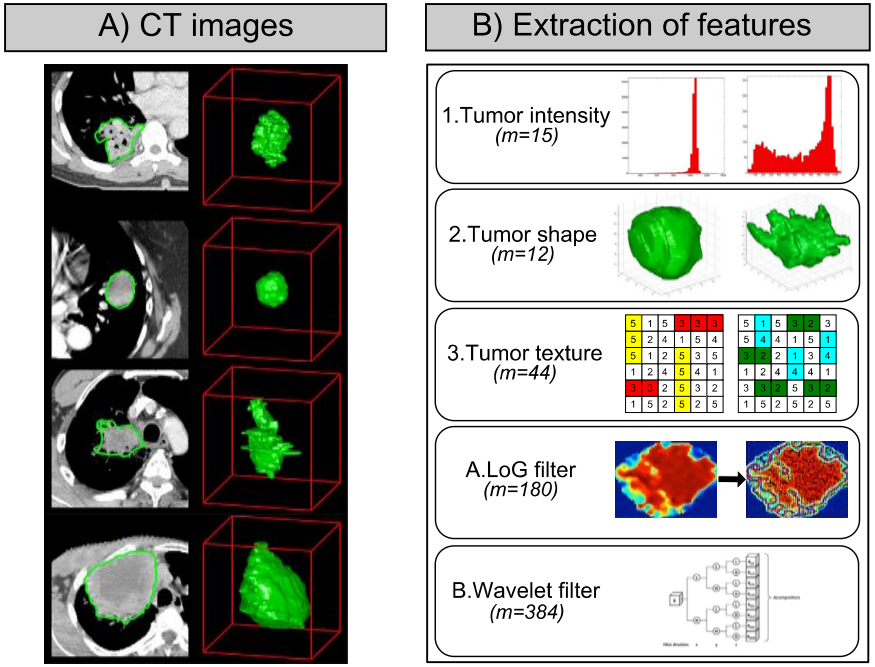
Radiomics:

Association maps between Image features (phenotypes) and outcome prediction

CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma

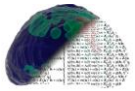
T.P. Coroller et al. / Radiotherapy and Oncology 114 (2015) 345–350



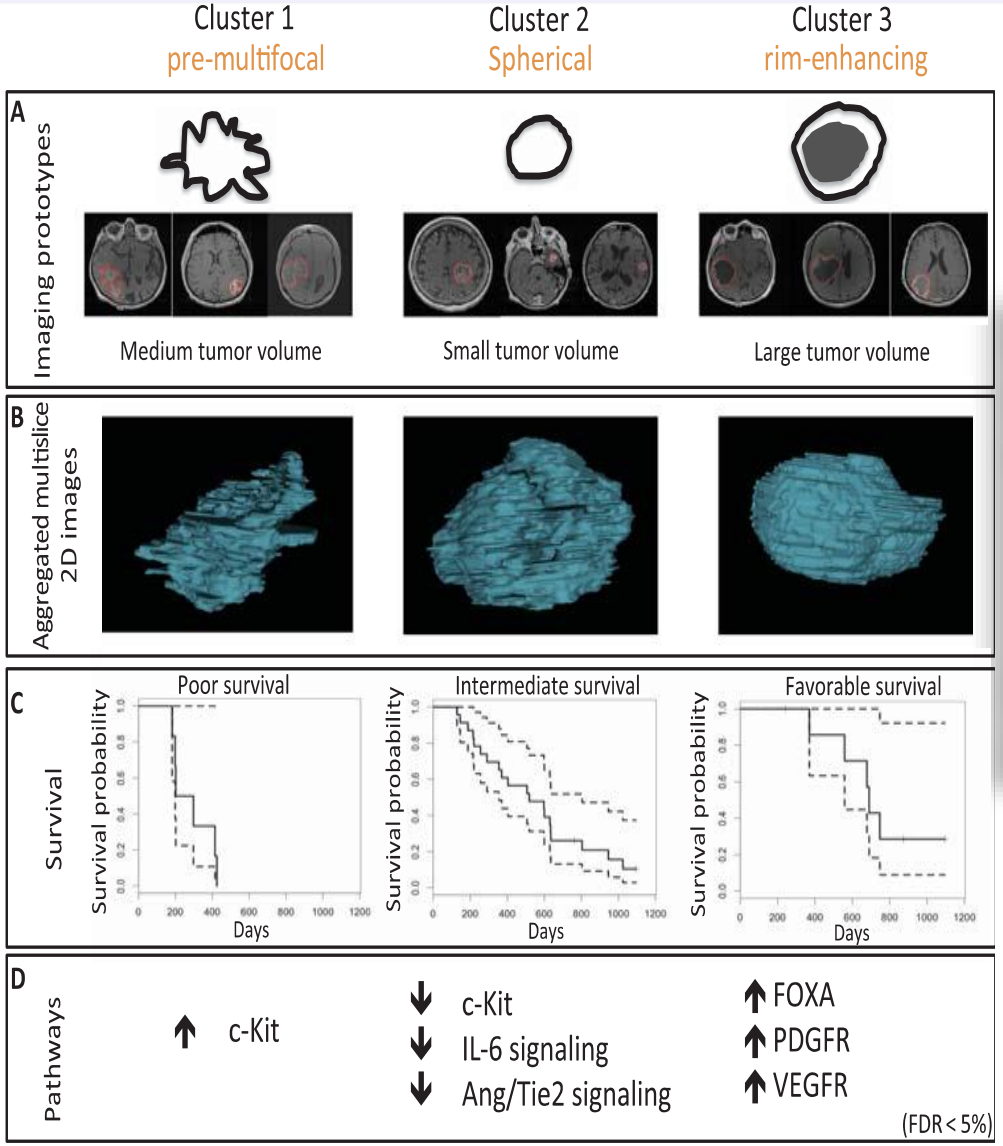


2 cohorts 98 and 84 P (validation) Lung cancer among identified features :

- 35 prognosis for Metastasis
- 12 prognosis for Overall Survival



Association maps between Image features (phenotypes) and molecular markers and outcome



Magnetic resonance image features identify glioblastoma phenotypic subtypes with distinct molecular pathway activities

Haruka Itakura,[1] Achal S. Achrol,[2] Lex A. Mitchell,[3] Joshua J. Loya,[2] Tiffany Liu,[1] Erick M. Westbroek,[4] Abdullah H. Feroze,[2] Scott Rodriguez,[2] Sebastian Echegaray,[5] Tej D. Azad,[2] Kristen W. Yeom,[3] Sandy Napel,[3] Daniel L. Rubin,[1,3] Steven D. Chang,[2] Griffith R. Harsh IV,[2]* Olivier Gevaert[1]*†

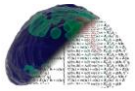
GlioBlastoma Cohort

144 Patients / multicentric validation

- Identify 3 classes:
  - Pre multifocal
  - Spherical
  - Rim enhancing

Linked with different molecular pathways and prognosis

www.ScienceTranslationalMedicine.org 2 September 2015



b. Heterogeneity and imaging

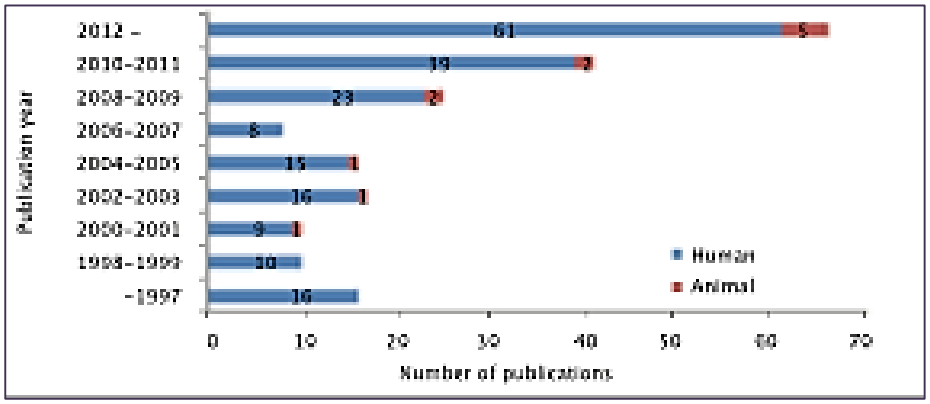
- High tumor heterogeneity is associated with poor prognosis

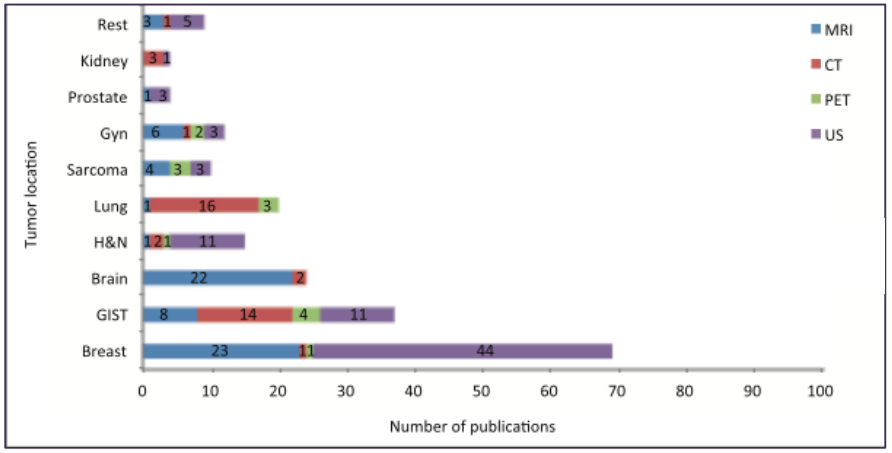
  (Brizel 1997, Davnall insights imaging 2012)

- Assessing heterogeneity with random sampling biopsy is difficult
  - 2/3 mutations found in single biopsy samples are not detected in all the sampled regions of the same tumor (Jaffe Radiol 2012)
  - Requirement for multiple biopsies is ethically challenging

bjcancer. R Fisher

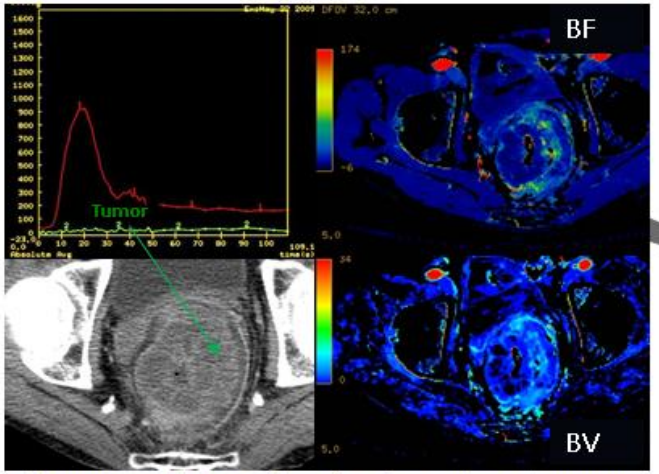
➡ **imaging can characterize variations in blood flow, cell density, and necrosis**



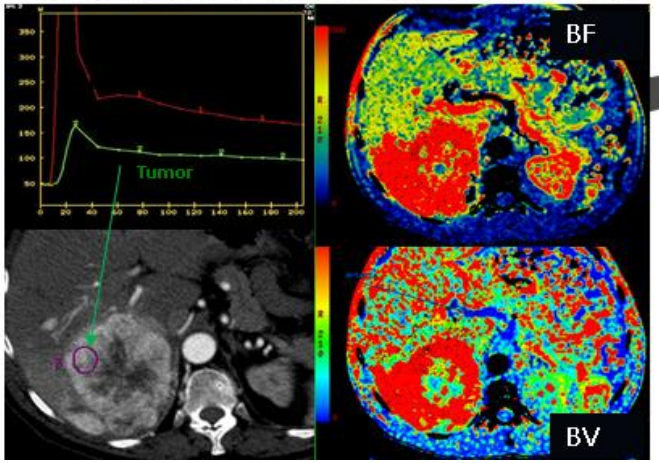


Alic L, Niessen WJ, Veenland JF (2014) Quantification of Heterogeneity as a Biomarker in Tumor Imaging: A Systematic Review. PLoS ONE 9(10): e110300. doi:10.1371/journal.pone.0110300

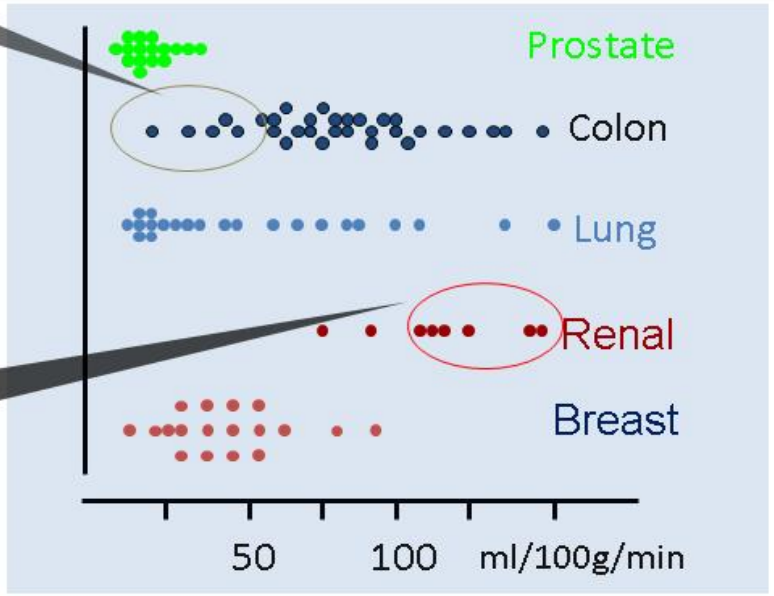
Tumor heterogeneity : is governed by **variation in blood flow**



Mucinous rectal tumor (above) vs Clear cell renal carcinoma



Angiogenic phenotype depends on tumor type and shows a wide individual variability

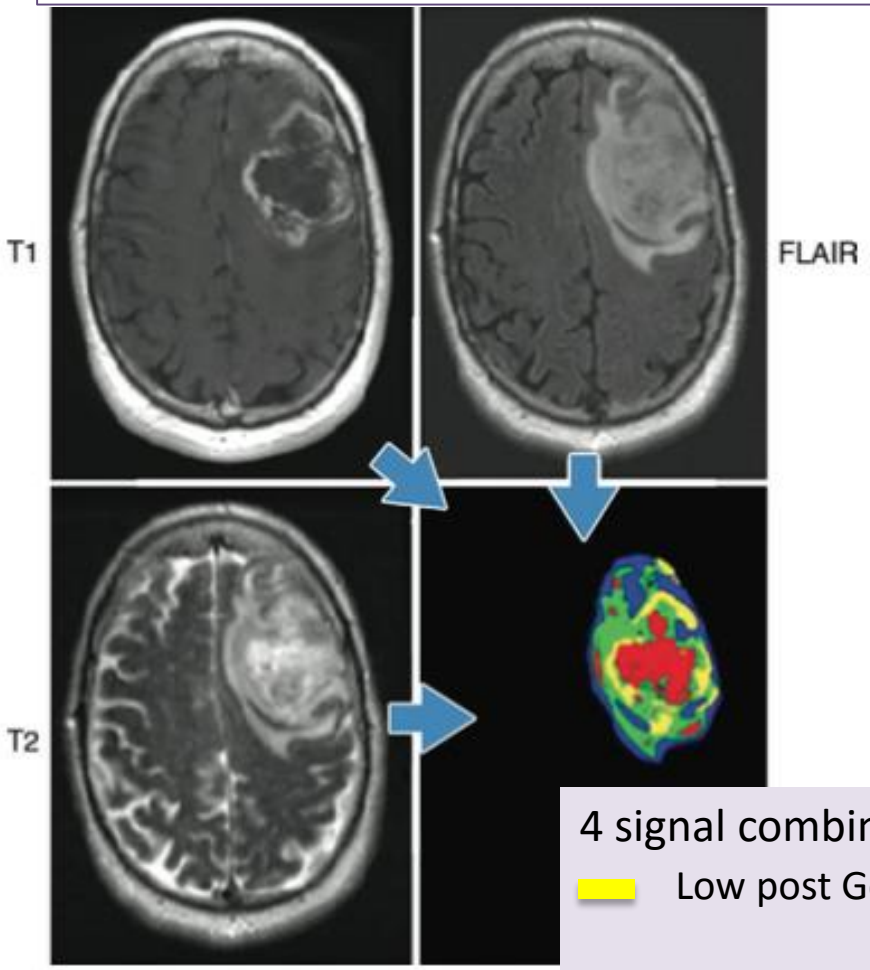


Blood flow (BF)

RSNA 2013

R Garcia-Figueiras, AR Padhani, AJ Beer, S Baleato-Gonzalez, DM Koh, JC Vilanova, A Luna

Non invasive imaging of heterogeneity might help to identify high risk patients



R Gatenby Radiol 2013
R Gillies Radiol 2016

Habitats in a patient with Glioblastoma
Acquisitions with different parameters are combined: define spatially explicit regions with a specific combination of blood flow, cell density, necrosis and edema
enable to discriminate different progression rates among glioblastoma subtypes (<400 days of survival versus indolent) *Zhou M Transl Oncol 2014*

4 signal combinations are significant for pronostic

Low post Gd T1 and low T2 = **low blood flow +high cell density**

(cells adapted to hypoxic acid conditions)

Tumor heterogeneity : is governed by **variation in blood flow**

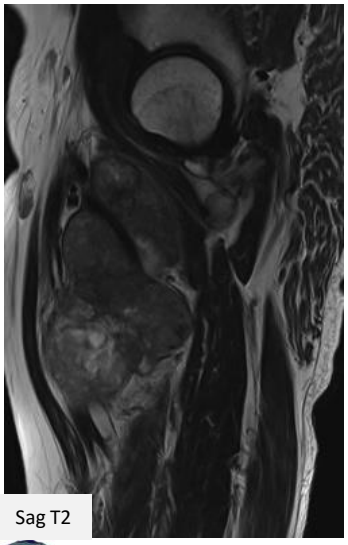
Poor perfusion is related to poor prognosis *(V. Goh Europ Radiol 2009)*

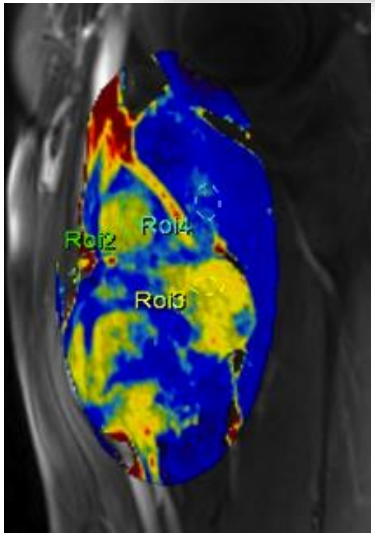
Poorly perfused regions are populated with cells adapted to low oxygen low glucose, high acid environment, that are likely resistant to treatment

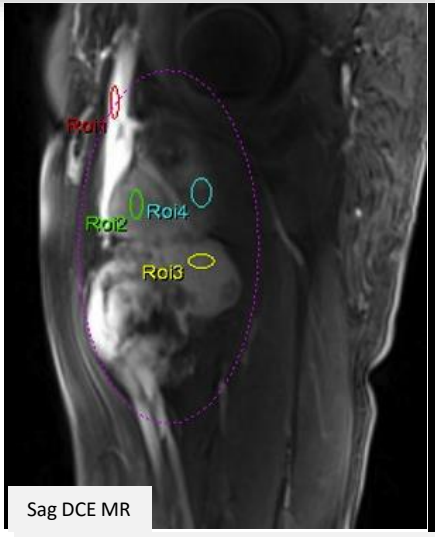
Perfusion: DCE IRM

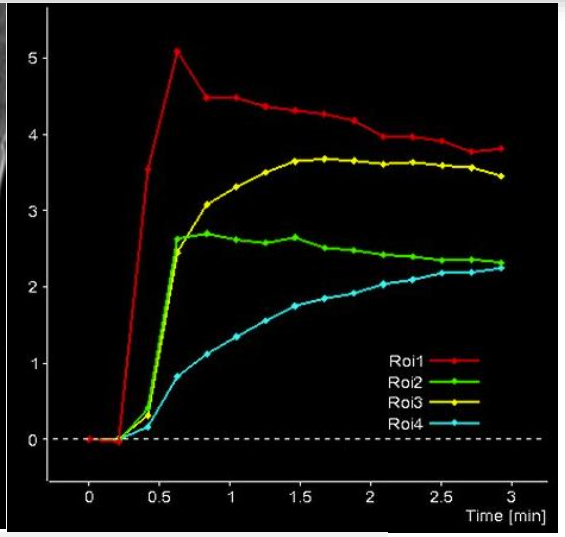
- *Signal Time-intensity course is related to contrast agent concentration* (Blood Flow , Blood Volume, permeability)
- Imaging describes tumor environment properties that give rise to adaptative phenotypes

  (hypoxia, glucose, acidosis represent selection forces)

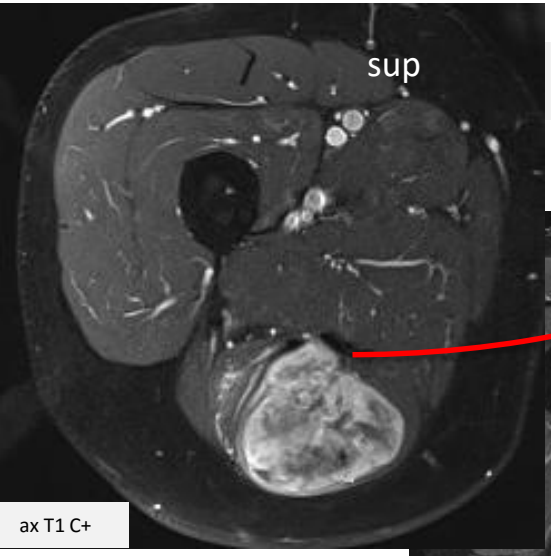




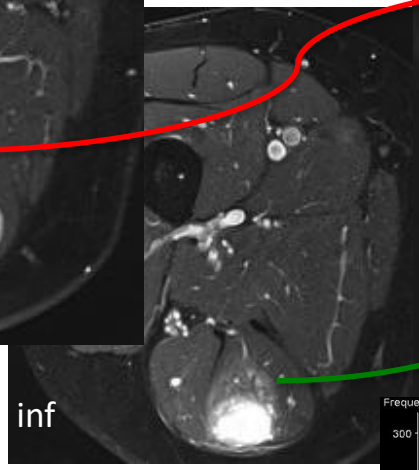


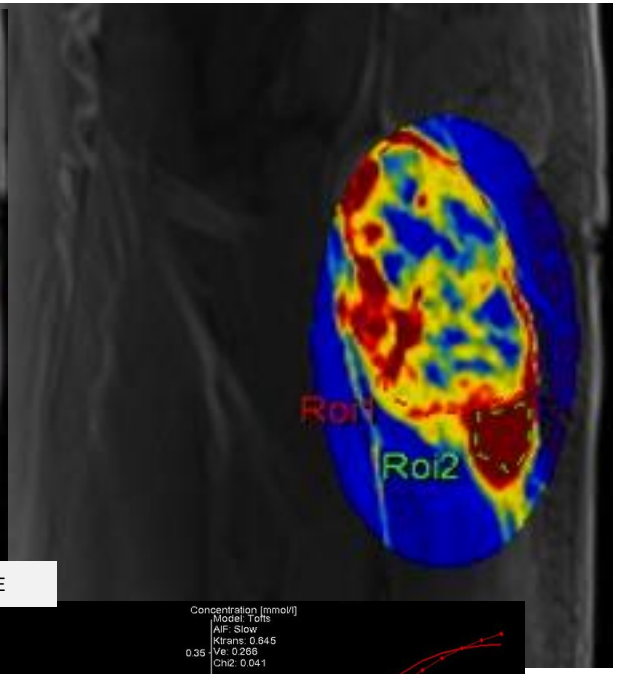


M/ LeiomyoS gr 2/ High heterogeneity

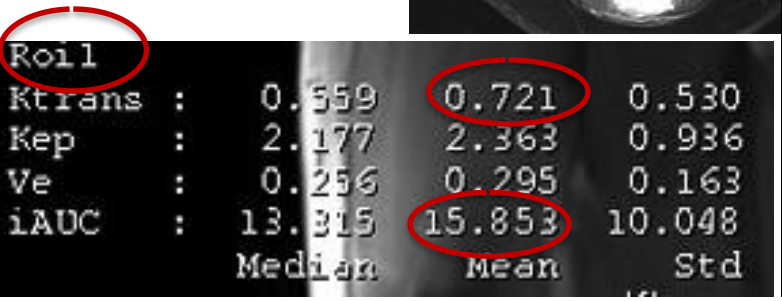


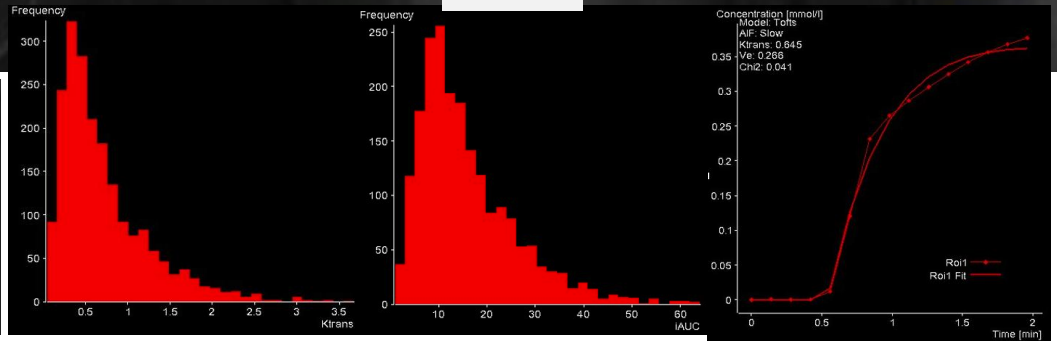
M / UPS gr 2

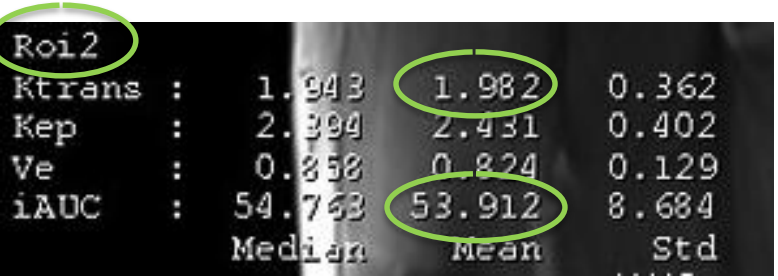


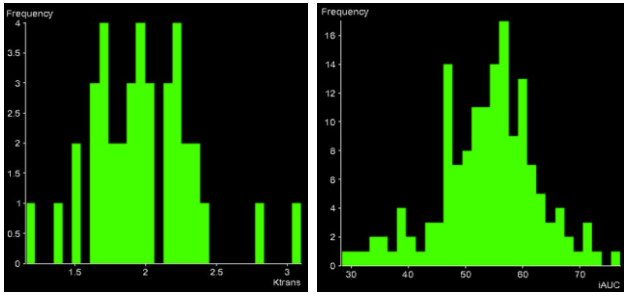


Sag DCE



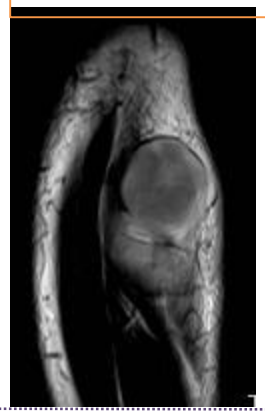


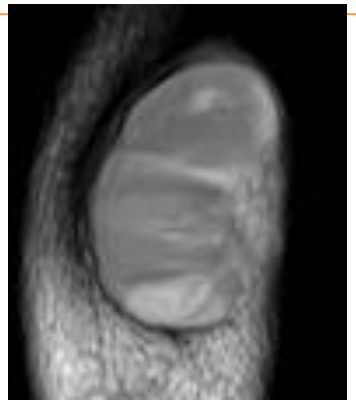


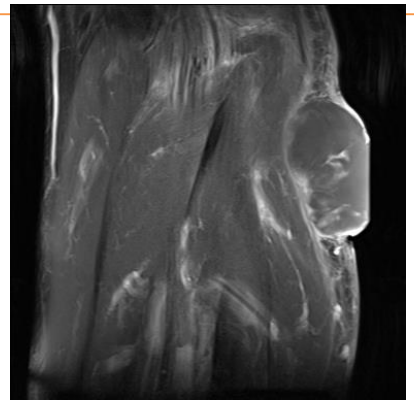


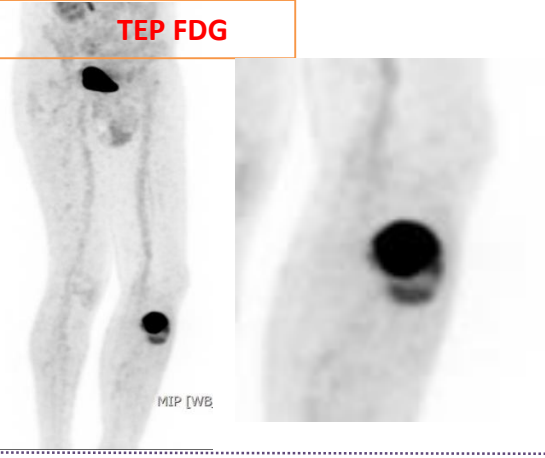
- *How to model?*
- *How to measure?*

High initial tumor heterogeneity / patchwork of habitats

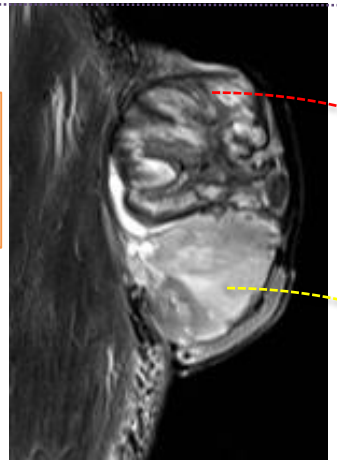


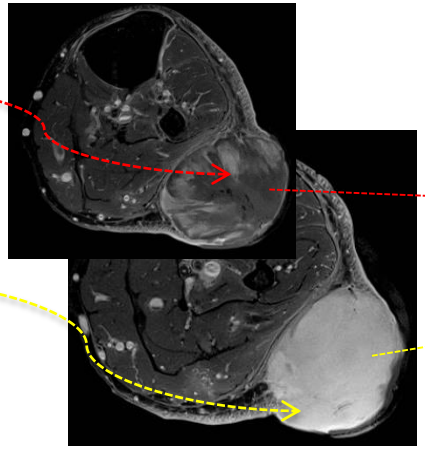


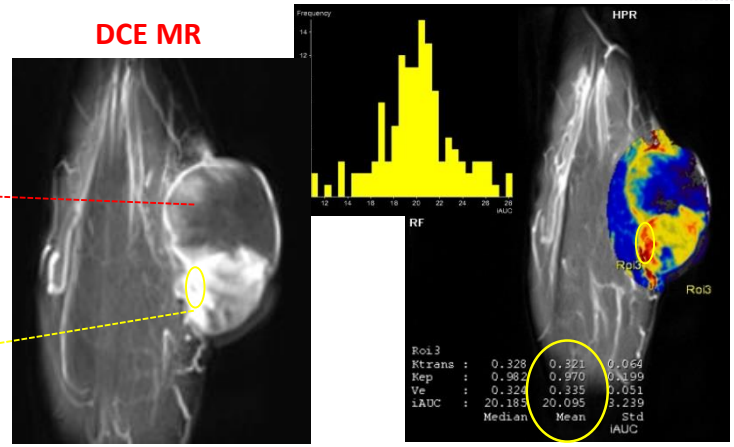




Post C2
RECIST: PD
Decision: new Trt

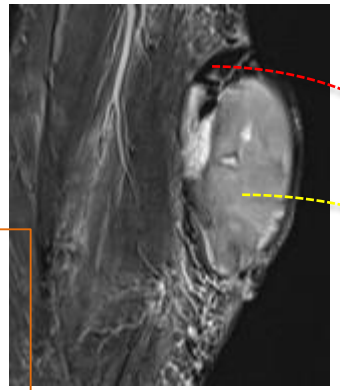


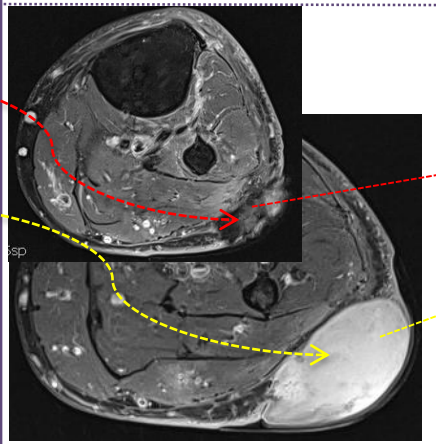


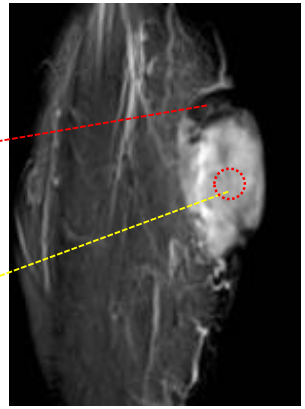


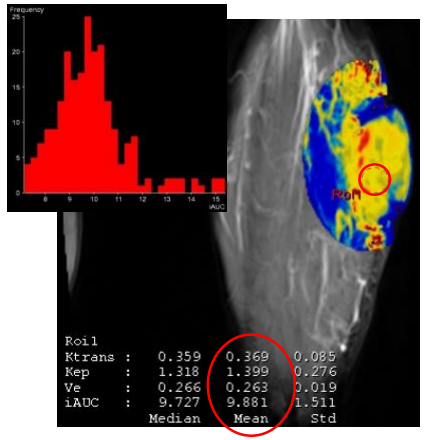
Post C4
PRE SURGERY
RECIST: SD (-14%)

Histology:
Necrosis:0
Viable T cells: 100%
Mitotic index:3



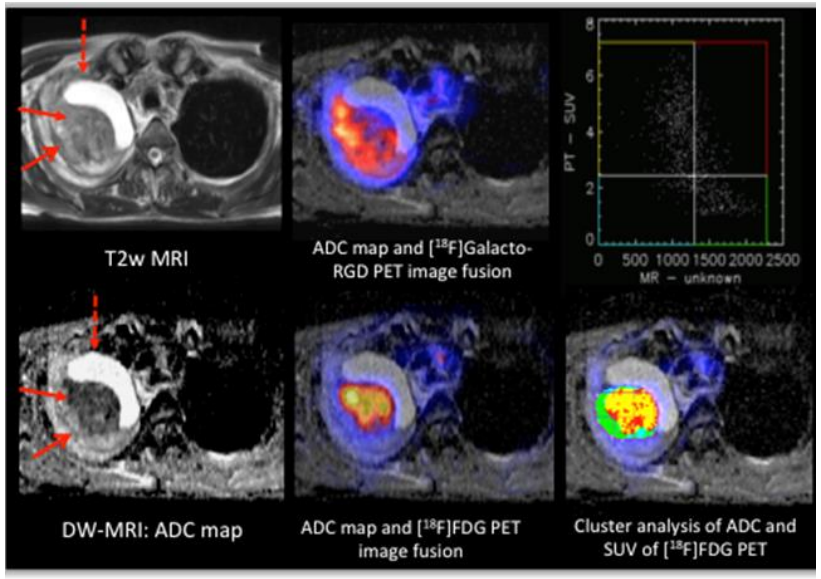






Multiparametric imaging to better understand biological processes: discord between perfusion and Glucose metabolism

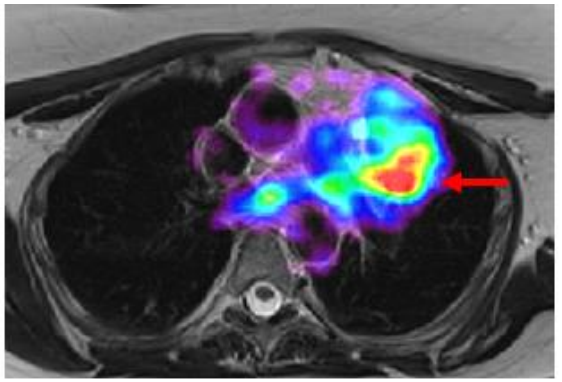
Combining Functional and Molecular imaging: Hybrid Techniques



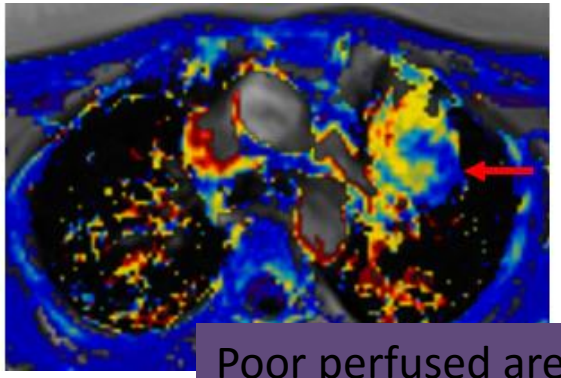
Imaging of a lung cancer combining anatomy, glucose metabolism, angiogenesis (αvβ3 expression), and cellularity (ADC). Fusion images allow for evaluation of mismatch between different biological characteristics

- *How to model?*
- *Which imaging biomarker is relevant?*
- *How they are measured?*

Complementary role of Functional and Molecular imaging: Discrepancies



[18F]Galacto-RGD PET/MRI - image fusion



DCE MRI - K

Images show that avid uptake of RGD in PET occurs in tumor areas of low K^{trans}

Poor perfunded areas with high angiogenic activity

Poor perfused area with high metabolism= adaptation to hypoxia

R Garcia-Figueiras, AR Padhani, AJ Beer

RSNA 2013

2/ Response assessment : the challenges

- Even highly targeted cancer therapies sometimes fail:

  Due to the capacity of malignant cells to show effective adaptations multiple genetic populations coexist in the same tumor

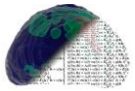
Imaging criteria

- Each imaging metric has its own set of applications for which it is designed:
  - CT/ PET-CT / Whole Body MR: extent M+ disease
  - PET-CT/ DCE MR ou DCE CT: single tumor site

- Types of treatment
- Biomarker qualification
- Side effects of new Trt
- Clinical trials

- Randomised trials: 1954
- First utilisation of imaging as surrogate (WHO): **1979**

  present size-based morphological criteria: **2000**
  - RECIST 1.0 & 1.1 (2000 et 2009)
  - CHESON (1999 et 2007)
- **Progression towards other criteria 2010**
  - CHOI et mCHOI
  - mRECIST, EASL
  - IRRC



Response prediction: international RECIST criteria

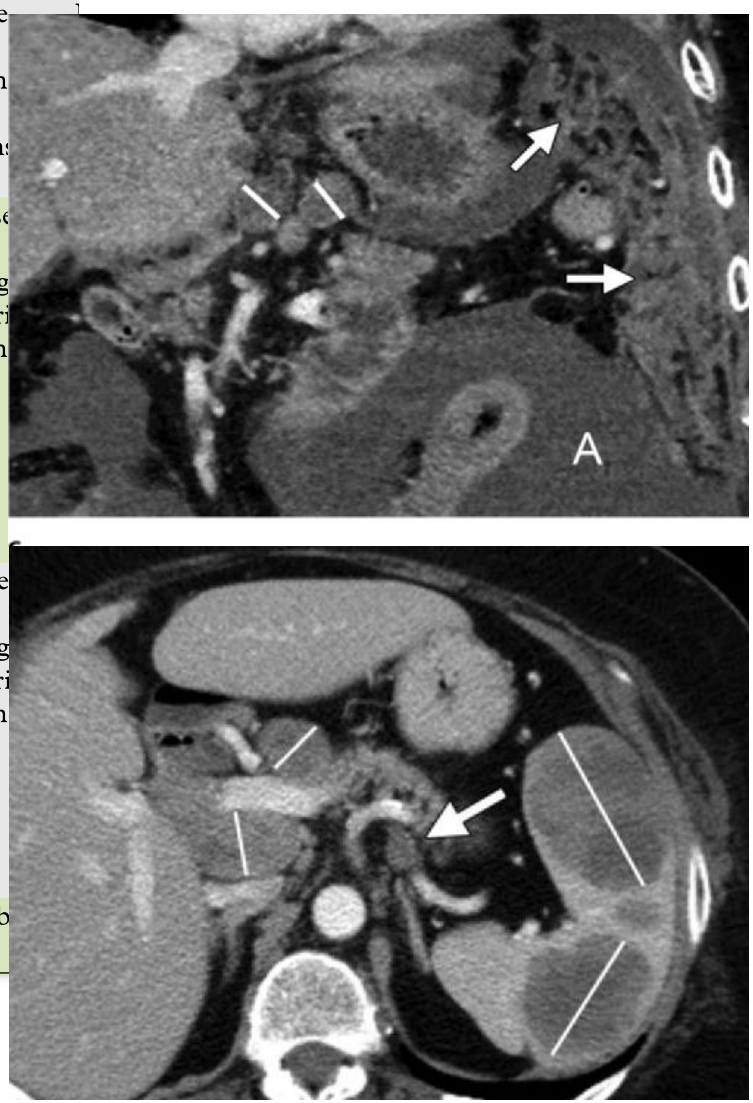
Response	WHO*	RECIST 1.1	Choi†	mRECIST‡
Complete response	No lesions detected for at least 4 weeks	Disappearance of all target lesions or lymph nodes <10 mm in the short axis		Disappearance of arterial phase enhancement in all target lesions
Partial response	≥50% decrease in SPD (confirmed at 4 weeks)	>30% decrease in sum of longest diameters (SLD) of target lesions		>30% decrease in SLD of "viable" target lesion (arterial phase enhancement)
Progressive disease	≥25% increase in SPD in one or more lesions; new lesions	>20% increase in SLD of target lesions with an absolute increase of ≥5 mm; new lesions		>20% increase in SLD of "viable" target lesion (arterial phase enhancement)
Stable disease	None of the above	Not above		None of the above

RECIST 1.1

-Strict rules with well defined cut off

>30% decrease in sum of longest diameters (SLD) of target lesions

>20% increase in SLD of target lesions with an absolute increase of ≥5 mm; new lesions



Tirkes

RadioGraphics 2013; 33:1323–1341

Comparison of WHO, RECIST 1.1, Choi, mRECIST, and PERCIST Tumor Response Criteria

Response	WHO*	RECIST 1.1	Choi†	mRECIST‡
Complete	No lesions	Disappearance	Disappearance of all	Disappearance

Only size based criteria is used to define Objective response

Cytotoxic treatment

RECIST Limits (1):

inter - intra observer reproducibility

- % discrepancies between response groups:
  - interObserv: 29% Prog D et 13% Partial Resp
  - intraObserv: 9.5% PD et 3% PR ***ref JCO 2003***
- Study 33p NSLCC
  - 84% measurement variation +/-10%
  - 3% misclassified in PD ***ref JCO 2011***
- interobserv liver analysis discrepancy is greater ***Krajewshi et al, Cancer 2014***

Erasmus JJ, Gladish GW, Broemeling L, et al. Interobserver and intraobserver variability in measurement of non-small-cell carcinoma lung lesions: implications for assessment of tumor response.
J Clin Oncol 2003;21(13):2574–2582.

RECIST Limits (2)

Disconnect ? between PFS and OS for cytotoxic therapies

- **JCO 2008 Burzykowski and breast cancer**

Objective Response is an acceptable surrogate
3953 patients / meta-analyse 11 randomised trials

- **JCO 2012 R Jain**

570p / 24 phases I Strong correlation between size and OS

- **Clin Cancer Res 2014 C ferté**

250p / 20 phases I lesion regression rate is associated with PFS

- **The Oncologist 2014 Krajewski**

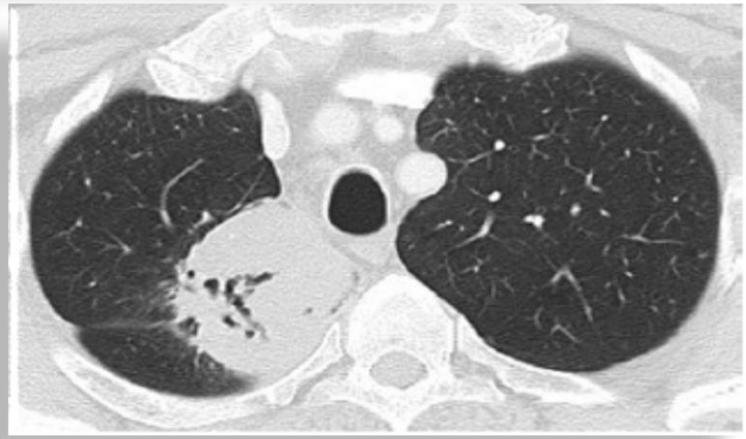
Anti angiogenic trt and renal cell carcinoma: 10% regression rate is associated with OS

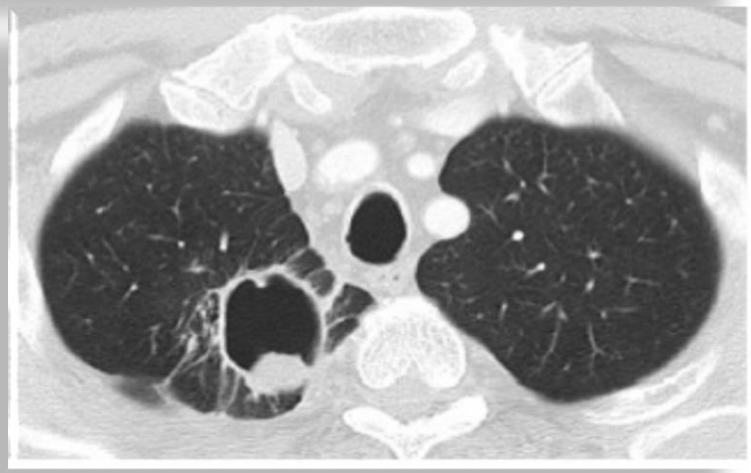
Temel Tirkes

RadioGraphics 2013; 33:1323–1341

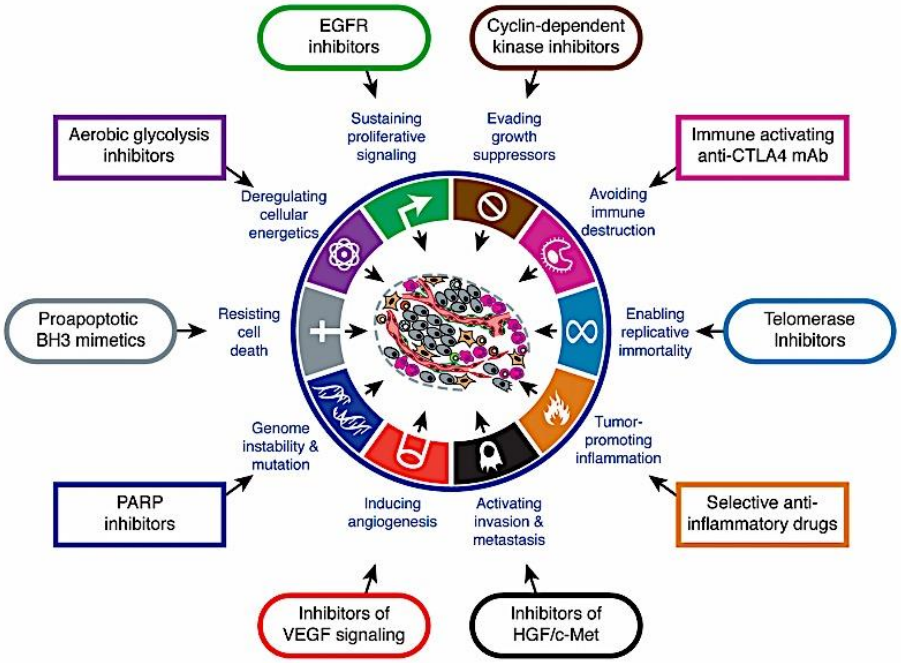
RECIST Limits (3)

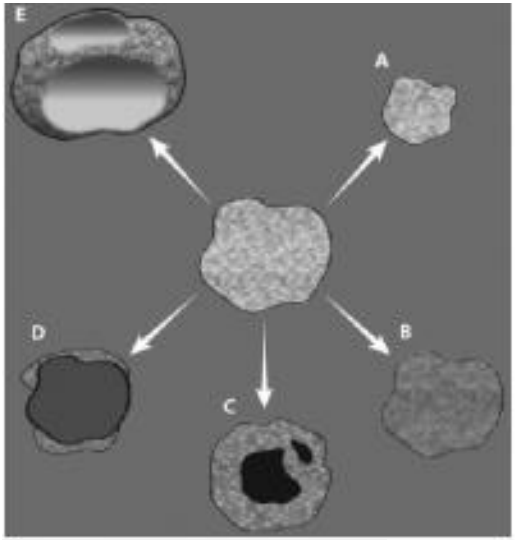
Targeted therapies





Douglas Hanahan[1,2,*] and Robert A. Weinberg[





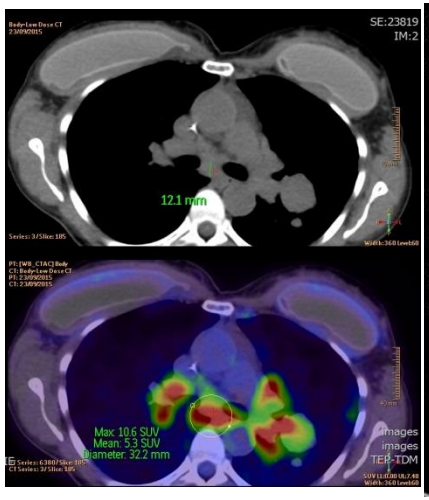
Temel Tirkes
RadioGraphics 2013

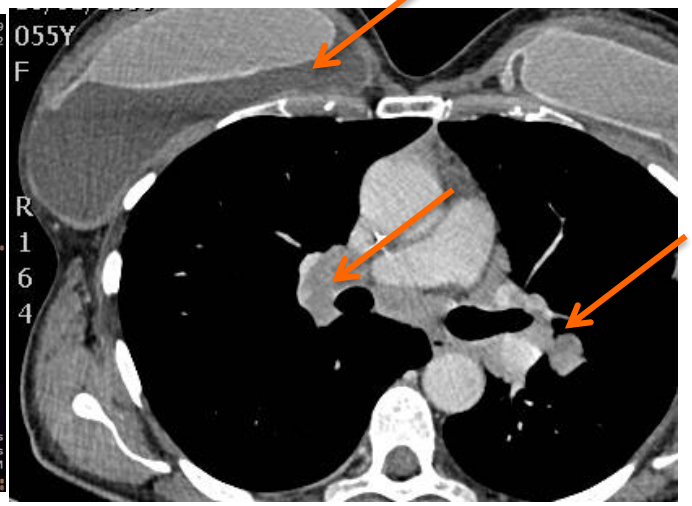
RECIST Limits (3)

Targeted Trt and secondary side effects

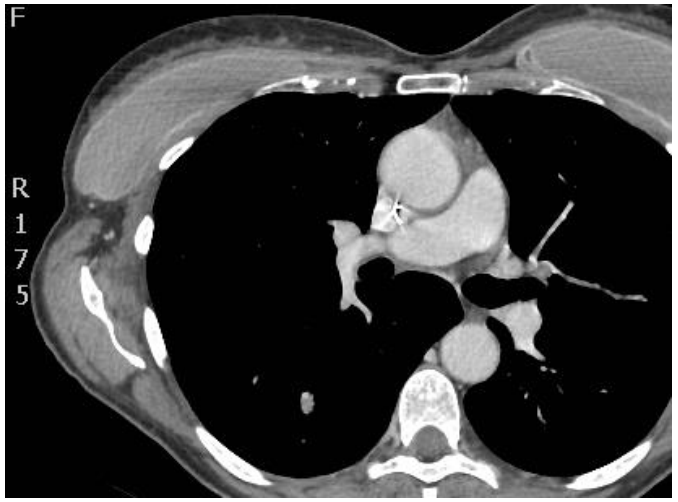
F 56y metastatic leimyosarcoma
ph II trial

Sept 2015





Mai 2015



CHOI criteria

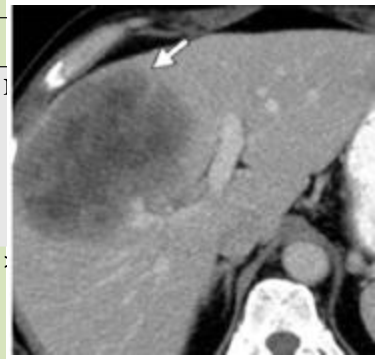
Comparison of WHO, RECIST 1.1, Choi, mRECIST, and PERCIST Tumor Response Criteria

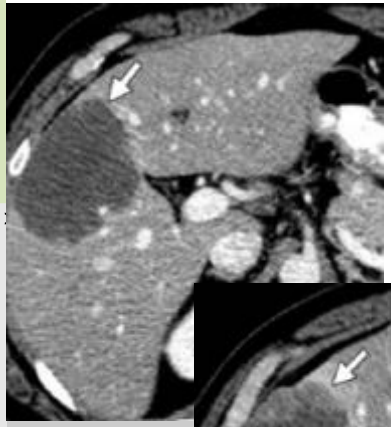
Response	WHO*	RECIS	Choi†	RECIST‡
	No lesions detected for at least 4 weeks	Disappe of all t lesions lymph <10 m the sh		ppearance arterial ase enhance- nt in all get lesions
Partial response	≥50% decrease in D (con- firm t 4 week	>30% d in sum longes eters (of targ sion	≥10% decrease in tumor size or ≥15% decrease in tumor attenuation at computed tomography (CT); no new lesions	% decrease SLD of able" target ion (arterial ase enhance- nt)
Progressive disease	≥25% increase in SPD in one or more lesions; new sions	>20 in S target with a lute in of ≥5 new le	≥10% increase in SLD of lesions; does not meet the criteria for partial response by virtue of tumor attenuation, new intratumoral nodules, or an increase in the size of the existing intratumoral nodules	% increase SLD of able" target ion (arterial ase enhance- nt)
Stable disease	None of the above	e of		e of the above

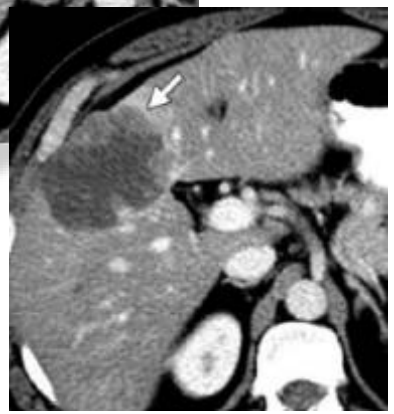
Choi†

GIST

10% size regression **or** - 15UH cut off







GIST: CHOI criteria limits
Is 10% variation size reliable ?

>>>mCHOI renal carcinoma

Tl Tirkes

RadioGraphics 2013; 33:1323–1341

J Clin Oncol 25:1760-1764. © 2007

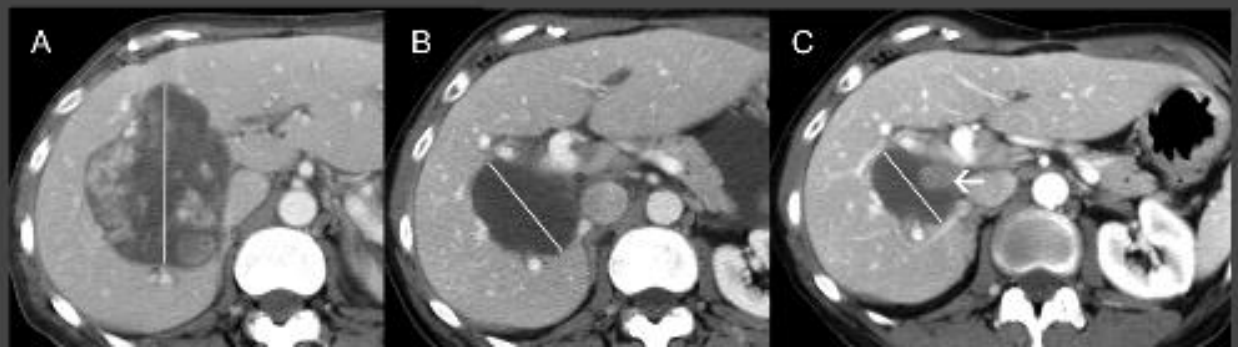
We Should Desist Using RECIST, at Least in GIST

Robert S. Benjamin, Haesun Choi, Homer A. Macapinlac, Michael A. Burgess, Shreyaskumar R. Patel, Lei L. Chen, Donald A. Podoloff, and Chuslip Charnsangavej

Tirkes
RSNA 2014

Choi's Criteria- Response Categories in comparison with RECIST

A) Baseline scan for a metastatic GIST
B) Post-treatment scan shows 61% decrease in tumor density and >30% decrease in size
RECIST: Partial response Choi's Criteria: Partial response
C) A follow-up scan after the treatment shows further decrease >40% in size but there is a new internal enhancing nodule, and only 7% decrease in density.
RECIST: Partial Response Choi's Criteria: Progressive disease



Absence of progression predicts Survival in GIST

VOLUME 27 · NUMBER 24 · AUGUST 20 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Absence of Progression As Assessed by Response Evaluation Criteria in Solid Tumors Predicts Survival in Advanced GI Stromal Tumors Treated With Imatinib Mesylate: The Intergroup EORTC-ISG-AGITG Phase III Trial

Axel Le Cesne, Martine Van Glabbeke, Jaap Verweij, Paolo G. Casali, Michael Findlay, Peter Reichardt, Rolf Issels, Ian Judson, Patrick Schoffski, Serge Leyvraz, Binh Bui, Pancras C.W. Hogendoorn, Raf Sciot, and Jean-Yves Blay

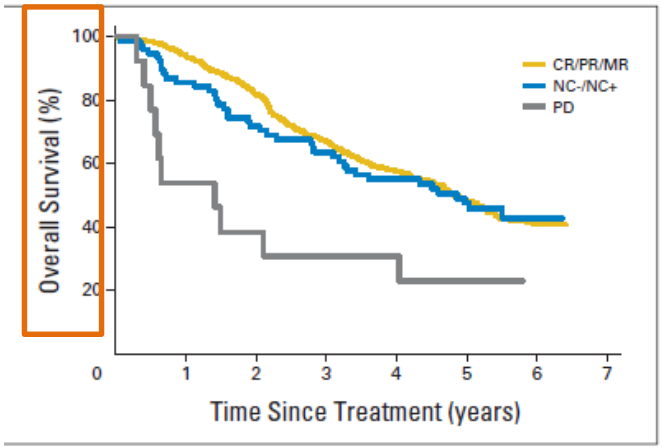


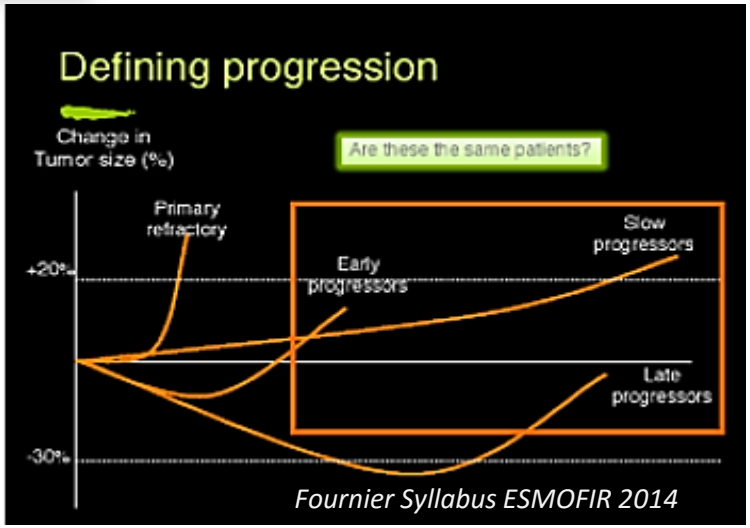
Fig 3. Overall survival according to grouped categories of response at 6 months

Tumor Growth Rate and renal cell carcinoma

EUROPEAN UROLOGY 65 (2014) 713–720

Tumor Growth Rate Provides Useful Information to Evaluate Sorafenib and Everolimus Treatment in Metastatic Renal Cell Carcinoma Patients: An Integrated Analysis of the TARGET and RECORD Phase 3 Trial Data

Charles Ferté[a,b,c], Serge Koscielny[b,d], Laurence Albiges[a,b], Laurence Rocher[e], Jean-Charles Soria[a,b], Roberto Iacovelli[a], Yohann Loriot[a,b], Karim Fizazi[a,b], Bernard Escudier[a,b,]*



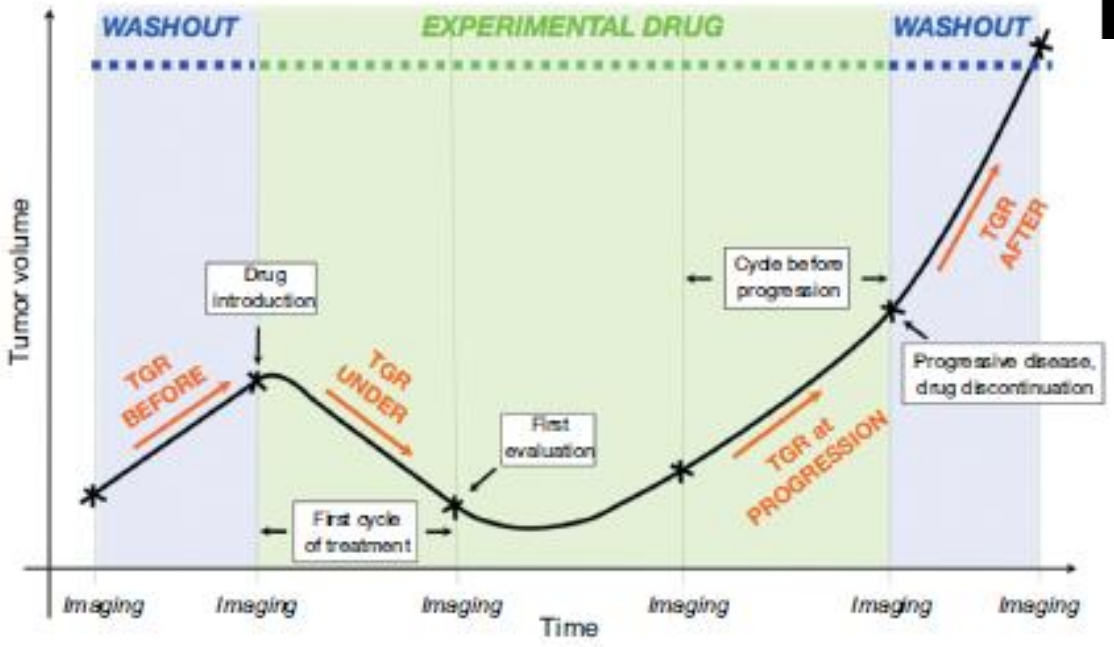
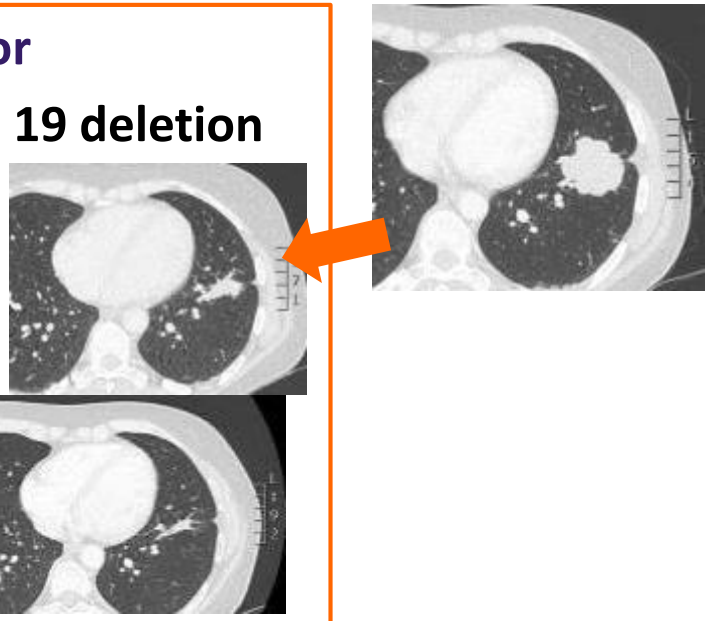


Fig. 1 – Hypothetical representation of tumor growth rate (TGR) across specific treatment periods.

Mrs R. 37y non smoker: Left inferior lobe Tumor

Lung Adenocarcinoma **EGFR mutation with exon 19 deletion**



Good response with cytotoxic chemotherapy

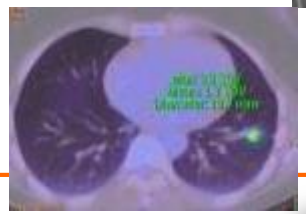
But recurrent para neoplastic sd

2nd line of TRt with **Géfitinib**

Good responder 18 months / RadioFr decision

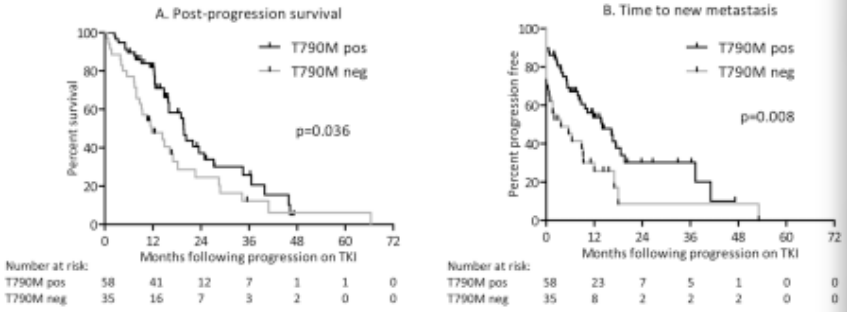
Positive PET pre RF

Biopsy : 2nd mutation T790M exon 20



Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation

Oxnard[1] *Clin Cancer Res.* 2011 March 15; 17(6): 1616–1622.



Strategy after progression

Slow Progression (new mut T790M +)

➡ keep TKI

Fast Progression (T790M –)

➡ back to cytotoxic Chemoth

TGR modeling can help to avoid 2nd biopsy and define strategy after progression

RECIST limits (4)

Clinical Trials

- **Lessons learned from trials** (R Ford EJC 2009)

9% enrolled patients do not have measurable disease

10-13% missing imaging data

Reported rate of discrepancy for PD: 24 -29% (local site/ central review)

Main reasons for local site/ reviewer discord

Selected target Lesions

Inter/ intra- reader variability (up to 38%)

Understanding response criteria

Failure to compare prior studies (baseline or Nadir as references)

Perception of new lesions

Subjective assessment of Non Target Lesions

Workflow process: structured review process in trials

- **The components of progression** (S Sitière EJC 2014)

13 randomised trials 3758 patients (breast, lung, colorectal K)

Progressive disease:

36% new lesions

28% NTL progression

49% TL progression

Images of imaging utilization for mass data: logistic challenges

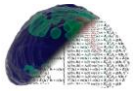
Sistrom AJR 2015

- Large portions of medical **data are unstructured**
- Needs of Human translator with **medical expertise**

  to validate segmentation (3 hours processing per patient)
  - Missing data?
  - Meaning information lost in extraction process?
- Modeling: approaches tailored to a specific **medical context**
- Needs of **sharing data** to make analystics possible: **interoperability?**
  - Gathering data from different databases may over-represent a population (patient nomadism)

Yankeelov,
Clin Cancer Res; 22(2) January 15, 2016

Logistic and scientific infrastructures:
Select imaging modality tailored to the study
Process of site qualification
De-identification: is challenging with advanced imaging methods
Changes to analysis software during the data collection period ?



Images of imaging utilization for large data: logistic challenges

- Large portions of medical data are unstructured
- Needs of Human translator with medical expertise
  to validate segmen
  - Missing data?
  - Meaning inform
- Modeling: appro
- Needs of sharing
  - Gathering data fr
    nomadism)

- Curation of **high quality** data by radiologists
- Incentive for **standard lexicon** to be used

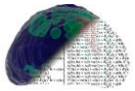
(massive data exist in PACS but inaccessible because of lack of standard lexicon)

- Collecting prospectively high quality image data requires expertise

Education and information need to be shared with the radiologist community

Logistic and

Select imaging modality tailored to the study
Process of site qualification
De identification: is challenging with advanced imaging methods
Changes to analyse software during the data collection period ?



Size-based imaging does not reflect the complexity of T behavior

Changes in measures are not predictive of therapy benefit
(disconnect between PFS and OS for cytotoxic therapies)

Hypothesis: link between variation in environmental properties and cellular adaptative strategies permit **quantitative imaging** to describe intratumoral dynamics during treatment

PET CT (Glucose metabolism and others tracers….)

DCE MRI or CT (perfusion) / **Diffusion weighted MRI** (cell density)

Bold MRI (hypoxia)

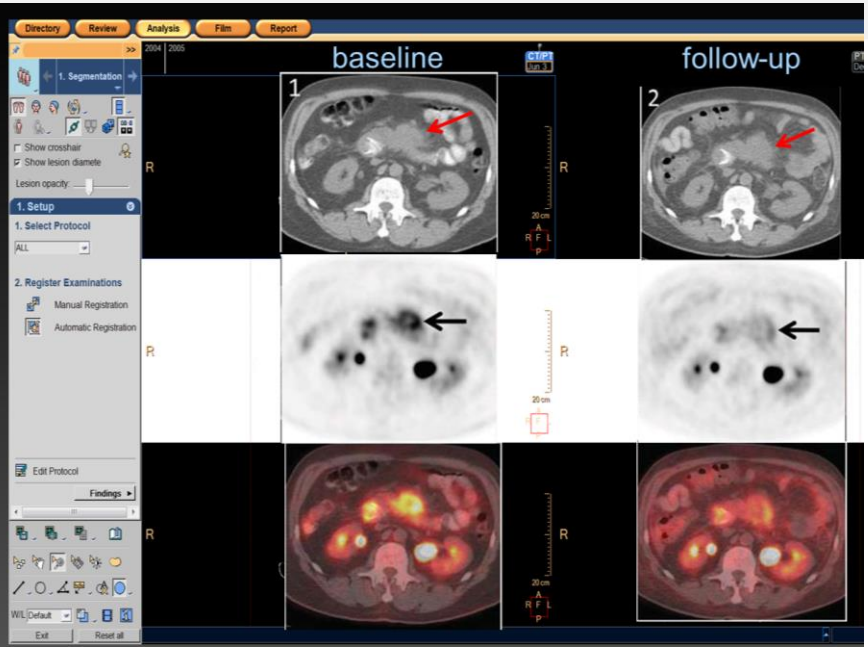
PERCIST

T Tirkes RSNA 2014

59-year-old patient with pancreatic cancer.

- RECIST: No change in size (red arrows)
  - stable disease
- PERCIST: 41% decrease in SUL (black arrows)
  - partial response

If no metabolically active lesions, refer to RECIST



Size-based imaging does not reflect the complexity of T behavior

Changes in measur
(disconnect betwee

Hypoth: link between v
adaptative strategies pe
dynamics during treatm

PET CT (Glucose

DCE CT or MR (p

- How to model
- Which imaging biomarker is relevant
- How are they measured
- What is their role
- How to store

PERCIST

T Tirkes RSNA 2014

59-year-old patient with pancreatic cancer.

- RECIST: No change in size (red arrows)
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