Moving Radiomics Forward: Funding, Regulatory Issues, and Clinical Translation

Clinical Translation of Radiomics

Columbia University Medical Center
Discover. Educate. Care. Lead.

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Clinical Translation of Radiomics

Why the clinical community **needs** quantitative imaging biomarkers and radiomics?

- *Understanding* these needs
- *Adapting* our tools to the needs
- *Addressing* the needs

Engagement → Adoption → Clinical Acceptance

Role of Imaging in Oncology

- Detection
- Characterization
- Staging
- Assessing response to therapy

Problem statement

- Oncology drug development (and clinical care) is inefficient
  - 62.5% of phase III trials are negative
- Therapeutic progress has inherently made drug development more difficult
  - More active drugs leads to greater use of randomized phase II trials
  - However, trials continue to study traditional endpoints (ORR, PFS)
- Development of new, modern trial endpoints (including radiomics) is needed

Gan et al, JNCI, 2012

Problem statement

Two randomized trials in 1st-line NSCLC:

- Carbo/taxol plus placebo
- Carbo/taxol plus vorinostat

Ramalingam et al, JCO, 2010		Belani et al, ESMO, 2009	
NCI-supported consortia		Industry sponsored	
94 patients		253 patients	
Carbo/taxol:	12.5% RR 4.1m PFS	Carbo/taxol:	29.3% RR 5.5m PFS
& vorinostat:	34.0% RR 6.0m PFS	& vorinostat:	22.4% RR 4.3m PFS
A POSITIVE TRIAL		**A NEGATIVE TRIAL**	

PFS / OS as clinical trial endpoints

- Overall Survival (OS) has been considered the "gold standard"
  - Death is easy to define, is easily compared across disease sites
  - Not subject to investigator bias
  - However, as the available options for continuing therapy increase, the use of OS as a clinical trial endpoint has become problematic because of the increasing crossover and contamination of trials

PFS / OS as clinical trial endpoints

- Progression-free survival (PFS) is a more viable option for evaluating new therapies in metastatic and advanced carcinoma
- As with all endpoints, PFS has inherent biases, and those biases must be addressed to ensure that trial results are not compromised and that they will be accepted by regulatory authorities

Response and progression as distinct events in solid tumor oncology care and research

	Response	Progression
Timing of assessment:	Assessed early in treatment course	Assessed at intervals until change of therapy
Role in clinical practice:	Not normally used to determine whether to change therapy	Commonly used to determine when to change therapy
Role in clinical research:	Primarily used to calculate overall response rate	Primarily used to calculate time to progression endpoints

How can radiomics be integrated ?

Geoffrey R. Oxnard et al. JNCI J Natl Cancer Inst 2012;104:1534-1541

Assessing Response to Therapy

Used to evaluate *efficacy of a novel therapy* in a clinical trial

Used to determine *treatment decisions* for an individual patient

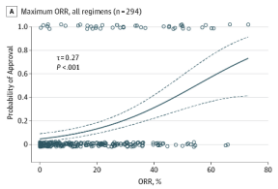
PROGRESSION RATHER THAN RESPONSE

Used for *correlative analysis* to develop predictive *tissue biomarkers*

Current Perspectives and Clinical Engagement

Response Rate and Progression-Free Survival as a primary endpoints

- Importance: ORR is an increasingly important end point for accelerated development of active anticancer therapies..
- Results From 1800 trials, 874 eligible arms in 578 trials were identified. Evaluation of ORR thresholds between 20% and 60% as potential trial end points demonstrated that ORR statistically exceeding 30% with a single agent had 98% specificity and 89% positive predictive value for identifying regimens achieving regulatory approval.



Oxnard Schwartz et al. JAMA Onc 2016; 2(6):772-779

Current Perspectives and Clinical Engagement

Response Rate and Progression-Free Survival as a primary endpoints


JAMA Oncology

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Invited Commentary | February 25, 2016

Response Rate as an Approval End Point in Oncology

Back to the Future ONLINE FIRST

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JAMA Oncol. Published online February 25, 2016. doi:10.1001/jamaoncol.2015.6352 Text Size:

- **"We at the FDA and other stakeholders are actively pursuing investigation into alternate metrics of response to better describe clinical benefit**. This will be critical for researchers and drug developers to assist in compound prioritization, optimization of combinatorial approaches, and to better inform "go/no-go" decision making. For regulators, **more sophisticated and refined response metrics will assist in identifying future breakthrough therapies and in developing better surrogates to predict long-term clinical outcome."**

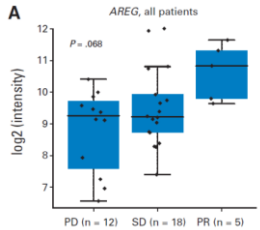
Used for *correlative analysis* to develop predictive *tissue biomarkers*

- Tissue analysis of responders is a fundamental way of identifying predictive biomarkers (e.g. EGFR mutations)
- For more complex biomarkers (IHC, gene expression, amplification), tissue characteristics from sensitive and resistant tumors must be compared to identify differences

Correlative Analysis to Develop Predictive Tissue Biomarkers

Tabernero et al (JCO, 2010) studied tissue from 35 patients with mCRC who received cetuximab

Nonsignificant difference in AREG expression by response category

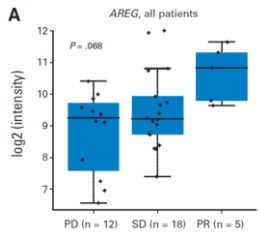


Correlative Analysis to Develop Predictive Tissue Biomarkers

Tabernero et al (JCO, 2010) studied tissue from 35 patients with mCRC who received cetuximab

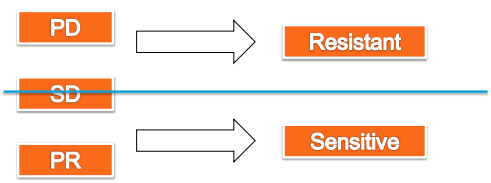
Nonsignificant difference in AREG expression by response category

Is there a better method for distinguishing resistant and sensitive tumors?

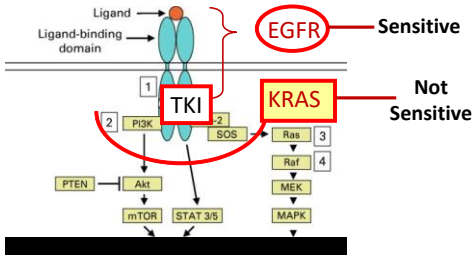


Correlative Analysis to Develop Predictive Tissue Biomarkers

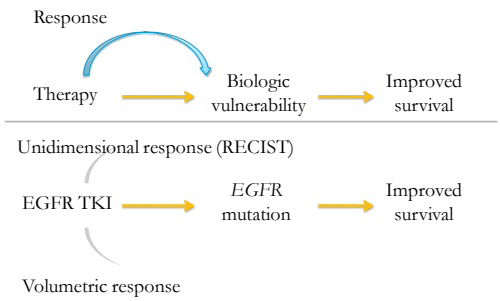
Can tumor biology be used to reclassify conventional response categories into biologically based groups?



Correlative Analysis to Develop Predictive Tissue Biomarkers



Correlative Analysis to Develop Predictive Tissue Biomarkers



Correlative Analysis to Develop Predictive Tissue Biomarkers

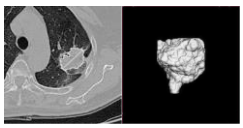
- 48 of 50 patients enrolled to the trial had imaging adequate for volumetric analysis
- 47 cases (98%) were adenocarcinoma

Mutation status	# Patients
EGFR mutant	21 (44%)
Exon 19 del	11
Exon 21 L858R	9
Exon 21 L861Q	1
KRAS mutant	5 (10%)
G12C	3
G12D	2
Wild type / wild type	22 (46%)

Correlative Analysis to Develop Predictive Tissue Biomarkers

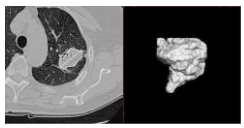
Patient with *EGFR* mutation

Baseline



Diameter = 4.1 cm
Volume = 163.4 cm^3

21 day follow-up

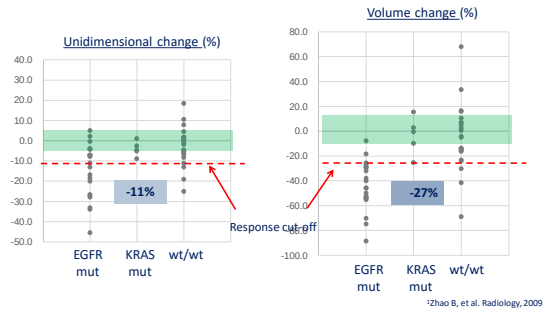


Diameter = 3.9 cm
Volume = 115.0 cm^3

Change in diameter = -3.8%
Change in volume = -29.6%

Correlative Analysis to Develop Predictive Tissue Biomarkers

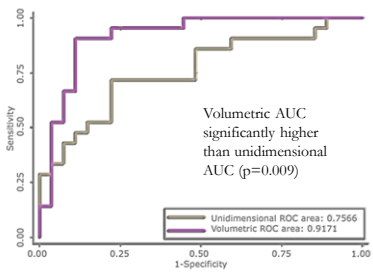
Measurement change after 21 days of gefitinib



[1]Zhao B, et al. Radiology, 2009

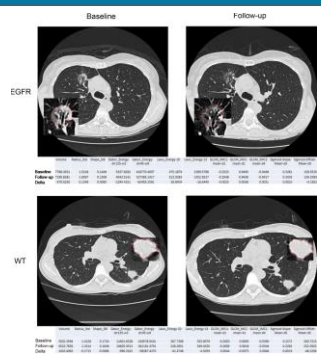
Correlative Analysis to Develop Predictive Tissue Biomarkers

Testing whether volume or unidimensional response is a better diagnostic test for EGFR mutation



Early volume response is better than early unidimensional response at predicting *EGFR* mutation after 21 days of gefitinib

Correlative Analysis to Develop Predictive Tissue Biomarkers



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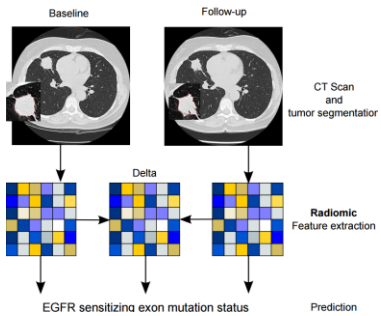

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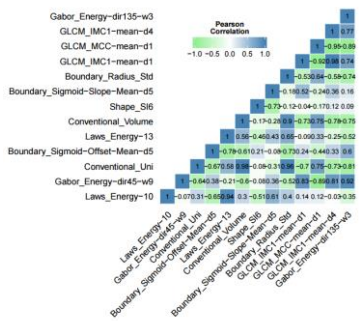


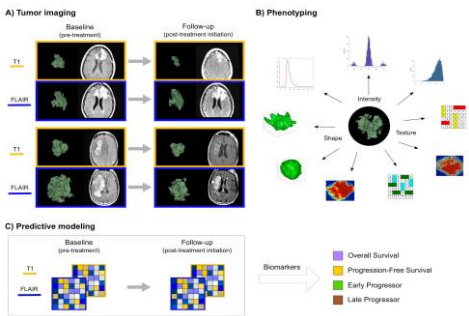
Used to evaluate efficacy of a novel therapy in a clinical trial

- Glioblastoma
  - Overall survival is poor; limited beyond 7 months
  - Bevacizumab, an inhibitor of VEGF developed to block angiogenesis is used at recurrence
  - Randomized multicenter, trial (AVF3708g) comparing bevacizumab plus irinotecan versus bevacizumab alone contributed to accelerated FDA approval.
  - However, negative Phase III clinical trials for newly-diagnosed glioblastoma in terms of OS
  - Given the demonstrated activity of bevacizumab evidenced by impact on imaging-based endpoints, and in recurrence – is their a subpopulation to benefit ?
  - The development of novel biomarkers is *critical*

Used to evaluate efficacy of a novel therapy in a clinical trial

- Glioblastoma
  - Analysis of prospectively acquired Phase II open-label, randomized, noncomparative BRAIN trial (AVF3708g)
  - Randomized 167 patients to receive either bevacizumab alone (n = 85) or in combination with irinotecan (n = 82).
  - MRI assessment every ~6 weeks on protocol. Post-contrast enhancing T1-weighted and FLuid-Attenuated Inversion Recovery (FLAIR) images of each study were transferred to off-line workstations, and tumor segmentation was performed semi-automatically using Slicer 3D

Used to evaluate efficacy of a novel therapy in a clinical trial



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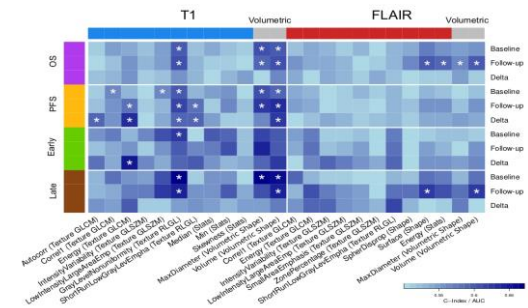

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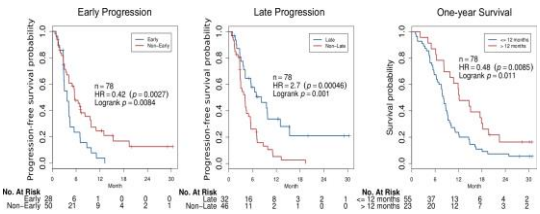
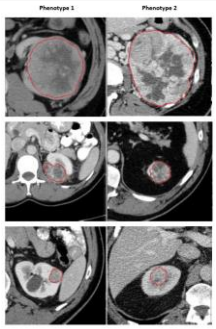


Treatment decisions for an individual patient

- The natural history of renal cell cancer is quite variable with some tumors exhibiting slow progression others demonstrating aggressive behavior
- No effective adjuvant treatment for RCC has been described, but research in this area is important since the 5-year relapse rate for intermediate- and high-risk early-stage RCC is 30%–40%
- Relapse risk reduction through adjuvant therapy is important goal in patients with intermediate- and high-risk early-stage RCC. However, despite significant efforts, no effective adjuvant therapy has been developed to date

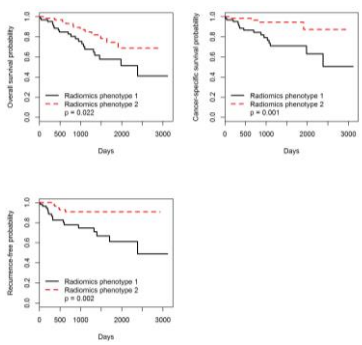
Treatment decisions for an individual patient



Treatment decisions for an individual patient

Model 1: Univariable Association						
	Overall Survival		Cancer-Specific Survival		Recurrence-Free Survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Radiomics Phenotype 1	2.25 (1.11-4.58)	0.025	5.00 (1.67-14.99)	0.004	4.23 (1.55-11.56)	0.005
Model 2: Multivariable Association Controlling for SSIGN Score						
	Overall Survival		Cancer-Specific Survival		Recurrence-Free Survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Radiomics Phenotype 1	1.26 (0.56-2.85)	0.581	2.12 (0.54-8.34)	0.282	3.17 (1.02-9.89)	0.047
Higher SSIGN Score	1.28 (1.15-1.42)	<.001	1.43 (1.25-1.64)	<.001	1.37 (1.15-1.63)	<.001
Model 3: Multivariable Association Controlling for SSIGN Score and ccA/ccB						
	Overall Survival		Cancer-Specific Survival		Recurrence-Free Survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Radiomics Phenotype 1	1.79 (0.76-4.22)	0.181	3.77 (0.78-18.22)	0.099	3.53 (1.14-10.97)	0.029
Higher SSIGN Score	1.20 (1-1.43)	0.046	1.50 (1.11-2.03)	0.009	1.33 (1.09-1.62)	0.005
ccA	0.42 (0.17-1)	0.050	0.21 (0.04-0.98)	0.047	0.34 (0.13-0.89)	0.029

Treatment decisions for an individual patient



Current Perspectives and Clinical Engagement

How do we engage and <u>what is the value proposition</u> ?

- Current imaging biomarkers are lacking
- OS is imperfect / flawed
- Tissue/Serum biomarkers are under evaluation but need validation (correlation)

Response Rate and Progression-Free Survival as a primary endpoints

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How do we engage and <u>what is the value proposition</u> ?

- Current imaging biomarkers are lacking
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Radiomics and Quantitative Imaging as a primary endpoints

The Complexities of Quantitative Radiomics

- Image standardization
- Image acquisition
- Data transfer and/or analysis
- Site versus central quantitative analysis
- Tool distribution
- **Tool validation**
- *Identify the biologically meaningful imaging biomarker to test*

The Complexities of Quantitative Radiomics

- Image standardization
- Image acquisition
- Data transfer and/or analysis
- Site versus central quantitative analysis
- Tool distribution
- Tool validation
- Identify the biologically meaningful imaging biomarker to test and
- Discover the need for quantification and radiomics

Grand Challenges – That answer research questions of response and progression with novel therapies

What imaging modality(ies) could solve the clinical question ?
What imaging technique(s) could answer the question ?
What tracer / contrast agent(s) will resolve the question ?
What quantitative technique(s) will provide a better biomarker ?
Which tool(s) will help in drug discovery and clinical care?

Clinical Engagement and Current Perspectives in Radiomics

Why the clinical community **needs** quantitative imaging biomarkers and radiomics?

Understanding needs
Adapting our tools to the needs
Addressing the needs

Engagement → Adoption → Clinical Acceptance