What are the issues related to imaging in oncology?
M Kind, J Palussière
Institut Bergonié Bordeaux

Statistical and biomathematical Models
for imaging in cancer
While important in many practices, Cancer Imaging is becoming gradually more crucial in precision medicine.

- **Tumor types**
  - extent/staging
  - aggressiveness

- **Biomarkers**
  - QUANTITATIVE IMAGING

- **Treatment types and response criteria**
  - cytotoxic / MTT/
  - antiangiogenic
  - immunotherapy

- **PREDICTIVE IMAGING**
  - Side effects
  - Secondary resistance
  - Performance status
  - anemia sarcopenia

**Patient**
While important in many practices, Cancer Imaging is becoming gradually more crucial in precision medicine.

- **Patient**
  - Treatment types and response criteria
  - Cytotoxic / MTT / Antiangiogenic immunotherapy
  - PREDICTIVE IMAGING
  - Side effects
  - Secondary resistance
  - Performance status
  - Anemia
  - Sarcopenia

- **Biomarkers**
  - Quantitative Imaging
  - Pronostic Imaging

- **Tumor types**
  - Extent / staging
  - Aggressiveness

**Graphs**
- Mortality changes over time with different causes.
Images are not only pictures: they are data

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/off with a particular phenotype)*
- Understanding **how a biological process is demonstrated** in imaging *(associated with hypoxia or angiogenic gene signature)*
- **Defining biomarkers** or surrogates that outperform traditional criteria *(ie. survival)*
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
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

a. Tumor phenotypes and imaging
Over 60 genetic alterations in gliomas have been identified.

Red circles = genetic changes that are most commonly amplifications,
Blue circles = changes that are most commonly homozygous deletions,
Green circles = changes that are most commonly mutations.

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**Imaging Features of EGFR Amplification**

- Increased T2/T1 ratio
- Usually less necrotic (< 50% of tumor volume)
- Less perilesional edema (less than 50% of tumor volume)

**Imaging Features of IDH1 / IDH2 Mutation**

- Usually less necrotic (< 50% of tumor volume)
- Multifocality seen more frequently

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S Singh RSNA 2015
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
Glioblastoma Cohort
144 Patients / multicentric validation

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

Linked with different molecular pathways and prognosis

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,5 Scott Rodriguez,2 Sebastian Echegaray,5 Tej D. Azad,2 Kristen W. Yeom,7 Sandy Napel,3 Daniel L. Rubin,1,5,6 Steven D. Chang,7 Griffith R. Harsh IV,2* Olivier Gevaert1*
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

Imaging can characterize variations in blood flow, cell density, and necrosis

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SMAC 7 avril 2016
Tumor heterogeneity: is governed by variation in blood flow

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

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

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)
High initial tumor heterogeneity / patchwork of habitats

- How to model?
- How to measure?
Baseline T2

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**

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

**Complementary role of Functional and Molecular imaging: Discrepancies**

Images show that avid uptake of RGD in PET occurs in tumor areas of low $K_{trans}$ Poor perfused areas with high angiogenic activity

Poor perfused area with high metabolism= adaptation to hypoxia

Imaging of a lung cancer combining anatomy, glucose metabolism, angiogenesis ($\alpha\beta_3$ expression), and cellularity (ADC). Fusion images allow for evaluation of mismatch between different biological characteristics.
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.

- 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

<table>
<thead>
<tr>
<th>Response</th>
<th>WHO*</th>
<th>RECIST 1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>No lesions detected for at least 4 weeks</td>
<td>Disappearance of all target lesions or lymph nodes &lt;10 mm in the short axis</td>
</tr>
<tr>
<td>Partial response</td>
<td>≥50% decrease in SPD (computed at 4 weeks)</td>
<td>&gt;30% decrease in sum of longest diameters (SLD) of target lesions</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>≥25% increase in SPD in one or more lesions; new lesions</td>
<td>&gt;20% increase in SLD of target lesions with an absolute increase of ≥5 mm; new lesions</td>
</tr>
<tr>
<td>Stable disease</td>
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### 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

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*Tirkes

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

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<th>mRECIST‡</th>
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<tr>
<td>Complete</td>
<td>No lesions</td>
<td>Disappearance</td>
<td>Disappearance of all</td>
<td>Disappearance</td>
</tr>
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</table>

**Only size based criteria is used to define Objective response**

*Cytotoxic treatment*

**RECIST Limits (1):**

- % 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*

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RECIDIST 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
RECIST Limits (3)

Targeted therapies

Temel Tirkes
RadioGraphics 2013
F 56y metastatic leiomyosarcoma ph II trial

Sept 2015

Mai 2015

Targeted Trt and secondary side effects

RECIST Limits (3)
## CHOI criteria

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<td>Partial response</td>
<td>≥50% decrease in size (confirmed at 4 weeks)</td>
<td>10% size regression or -15UH cut off</td>
<td></td>
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<tr>
<td>Progressive disease</td>
<td>≥25% increase in SPD in one or more lesions</td>
<td>≥10% decrease in tumor size or ≥15% decrease in tumor attenuation at computed tomography (CT); no new lesions</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>None of the above</td>
<td>≥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</td>
<td></td>
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### GIST: CHOI criteria limits

Is 10% variation size reliable?

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mCHOI renal carcinoma

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* Tl Tirkes

RadioGraphics 2013; 33:1323–1341

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We Should Desist Using RECIST, at Least in GIST

Robert S. Benjamin, Hae soo Choi, Homer A. Macapinlac, Michael A. Burgesson, Shreyas Kumar R. Patel, Lei L. Chen, Donald A. Podoleff, and Ghuslip Charmsangavej
Absence of progression predicts Survival in GIST
Tumor Growth Rate and renal cell carcinoma

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\textsuperscript{a,b,c}, Serge Koscielny\textsuperscript{b,d}, Laurence Albige\textsuperscript{a,b}, Laurence Rocher\textsuperscript{e}, Jean-Charles Soria\textsuperscript{a,b}, Roberto Lacovelli\textsuperscript{a}, Yohann Loriot\textsuperscript{a,b}, Karim Fizazi\textsuperscript{a,b}, Bernard Escudier\textsuperscript{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

2\textsuperscript{nd} line of TRt with **Géfitinib**
Good responder 18 months / RadioFr decision

**Positive PET** pre RF
**Biopsy** : 2\textsuperscript{nd} mutation T790M exon 20

**Strategy after progression**

**Slow Progression** (new mut T790M +) ➔ keep TKI
**Fast Progression** (T790M −) ➔ back to cytotoxic Chemoth

TGR modeling can help to avoid 2\textsuperscript{nd} biopsy and define strategy after progression
**RECIST limits (4)**

- **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

- 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 analytics possible: interoperability?
  - Gathering data from different databases may over-represent a population (patient nomadism)

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

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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?

- 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
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)

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**T Tirkes RSNA 2014**

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**PERCIST**

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

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