Artificial Intelligence at the Cutting Edge of Imaging and Oncology Drug Development
Technology Breakthroughs

1 out of 2 oncology visits – includes a cross sectional imaging study
40% to 45% of all imaging is cancer related
“The role of the radiologist will be obsolete in five years”

April 11, 2017 | Dave Pearson | Healthcare Economics & Policy

The reports of my death have been greatly exaggerated.
~ Mark Twain

The reports of my death have been deflated.
~ Mark Twain
Role of Imaging in Oncology

• Detection
• Characterization
• Staging
• Assessing response to therapy
Detection - Screening

Lung Cancer Screening Saves Lives

• 20% of all lung cancer deaths could be avoided by screening with low dose CT scans
• Lung cancer screening is even more effective than mammography
• LESS than 5% of people who should be screened for lung cancer undergo the test
Cancer Probability: 75%

Benign Probability: 97%

Detection - Screening

# Detection - Screening

## Table: Genetic signatures of CD8 cells

<table>
<thead>
<tr>
<th></th>
<th>MOSCATO gene signature</th>
<th>MOSCATO radiomic signature</th>
<th>TCGA gene signature</th>
<th>TCGA radiomic signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8 cells</td>
<td>***</td>
<td>***</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Cytotoxic lymphocytes</td>
<td>***</td>
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<tr>
<td>T cells</td>
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</tr>
<tr>
<td>B lineage</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Natural killer cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Myeloid dendritic cells</td>
<td></td>
<td></td>
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<tr>
<td>Endothelial cells</td>
<td></td>
<td></td>
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<tr>
<td>Monocytic lineage</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fibroblasts</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

## Diagram: Carcinogenesis and Immunosurveillance

- **Carcinogenesis**
  - Mutations
  - Immune escape

- **Immunosurveillance**
  - Normal
  - Precancer
  - Cancer
  - Regression
  - Elimination
• Unlike most other malignancies, the diagnosis of HCC can be established noninvasively, and treatment may be initiated based on imaging alone, without confirmatory biopsy.

Li-RADS (LR) Classification

<table>
<thead>
<tr>
<th>Arterial phase hypo- or iso-enhancement</th>
<th>Arterial phase hyper-enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm):</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>≥ 20</td>
<td>10-19</td>
</tr>
<tr>
<td>≥ 20</td>
<td>≥ 20</td>
</tr>
</tbody>
</table>

- None: LR-3
- One: LR-4
- ≥ Two: LR-5

ΔV-NC
ΔA-NC
ΔV-A

Characterization – Liver Cancer
Characterization – Liver Cancer

Biopsy proven diagnosis: Hemangioma

Intermediate HCC-Risk

High HCC-Risk

Arterial Phase  Portal Venous Phase  Delta V-A

Sensitivity

Delta V-A features

- KNN (AUC=0.810)
- SVM (AUC=0.778)
- RF (AUC=0.785)

Mokrane Eur Radiol. 2019
Staging – PET CT

PET Scanners per million population
Staging with Artificial Intelligence

ROC AUC value of 0.85

Shaish AJR 2019;212: 238-24
Assessing Response – Prostate Cancer

Attacking AR Axis, Improving Outcomes, and Preparing for the End of OS as a Clinical Trial End Point

By Michael J. Morris, MD
Mount Sinai Kettering Cancer Center
Chair, Alliance Gyn Oncology (GU) Committee

The treatment of metastatic castration-resistant prostate cancer (mCRPC) has undergone some changes in standards of care in the past four years than some solid tumors have seen in 10 or more decades. These changes were largely due to the emergence of second-line therapies that have been shown to improve both progression-free survival and overall survival.

Enzalutamide

Journal of Clinical Oncology

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

Assessing Response – Prostate Cancer

Dennis, Larson et al JCO 2012; 30(5): 519–524
Proposed strategies to accelerate drug development in oncology

Establish meaningful end points
- Invest in the development, validation and use of robust intermediate and surrogate end points to measure tumor burden, patient response and quality of life
- Improve standardized criteria for the interpretation of imaging data
- Use new imaging approaches for in vivo assessment of therapeutic outcomes

Evaluate biomarkers and companion diagnostics
- Develop explicit prospective plans for biomarker analysis within oncology drug trials
- Accelerate the development of companion diagnostics used to predict patient response to a novel therapy

Streamline drug development through modeling
- To determine the minimum active dose and the range of active and tolerable doses
- To facilitate decision-making by Data and Safety Monitoring Boards (DSMBs)
• Overall Survival
• Disease Free Survival
• Objective Response Rate (ORR)
• Complete Response (CR)
• Progression Free Survival (PFS)
• Time to Progression
• Time to Treatment Failure
• Symptom Endpoints
Drug Discovery and Development
“Fit for Purpose” – Imaging Biomarkers

Patients should be categorized as having one of 4 outcomes

- (CR) Complete Response  ➔ Tumors completely disappear
- (PR) Partial Response  ➔ Tumors shrink > 30%
- (SD) Stable Disease  ➔ Tumors stable
- (PD) Progressive Disease  ➔ Tumors grow > 20%
The effect of measuring error on the results of therapeutic trials in advanced cancer

- 16 oncologists each measured 12 simulated tumor masses placed underneath a mattress.
- Two pairs of these tumors were identical in size.
- Only with a difference in size of 50% could the simulated tumors be differentiated.
The effect of measuring error on the results of therapeutic trials in advanced cancer

• There is no “biological relevance” in cut values used for PR or PD
Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry

U.S. Department of Health and Human Services Food and Drug Administration Oncology Center of Excellence Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) December 2018 Clinical/Medica

2. **Objective Response Rate**

ORR is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. Response duration usually is measured from the time of initial response until documented tumor progression. Generally, the FDA has defined ORR as the sum of partial responses plus CRs. When defined in this manner, ORR is a direct measure of a drug antitumor activity, which can be evaluated in a single-arm study. Stable disease should not be a component of ORR. Stable disease can reflect the natural history of disease, whereas tumor reduction is a direct therapeutic effect. Also, stable disease can be more accurately assessed by TTP or PFS analysis (see section III.B.4). If available, standardized criteria should be used to ascertain response. A variety of response criteria have been considered appropriate (e.g., revised RECIST guideline (version 1.1))\(^9\) The response criteria should be predefined in the protocol before the start of the study. The significance of ORR is assessed by its magnitude and duration, and the percentage of CRs. Treatment effect measured by ORR can be a surrogate endpoint to support accelerated approval, a surrogate endpoint to support traditional approval, or it can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, the number of CRs, the durability of response, the disease setting, the location of the tumors, available therapy, and the risk-benefit relationship.
Reproducibility and Reliability of RECIST Baseline Follow-up

For measuring RESPONSE

Which 2 lesions to measure?
Reproducibility and Reliability of RECIST

For measuring PROGRESSION

Example 1
Baseline 3m: Response 14m: RECIST PD 30m: Follow-up

Example 2
Baseline Cycle 4

Are these two PD’s the same?
Reproducibility and Reliability of RECIST

For measuring PROGRESSION

Example 1

<table>
<thead>
<tr>
<th>Baseline</th>
<th>3m: Response</th>
<th>14m: RECIST PD</th>
<th>30m: Follow-up</th>
</tr>
</thead>
</table>

Example 2

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Cycle 4</th>
</tr>
</thead>
</table>

Are these two PD’s the same?
AI for RECIST – Detection and Segmentation
AI for RECIST – Detection and Segmentation

Improved - Reproducibility and Reliability of RECIST
Reliability / Reproducibility ... AND BETTER BIOMARKERS!

Lee HJ, Radiology. Jul 2013
Response

Therapy → Biologic vulnerability → Improved survival

EGFR TKI → EGFR mutation → Improved survival

Radiomics and AI Features to study:
1. RECIST vs. Volumetric response
2. Radiomics
3. AI

Zhao, B, Schwartz LH, CCR Sept 2010
Patient with *EGFR* mutation

**Baseline**

- Diameter = 4.1 cm
- Volume = 163.4 cm³

**21 day follow-up**

- Diameter = 3.9 cm
- Volume = 115.0 cm³

Change in diameter = -3.8%

Change in volume = -29.6%

Patient without *EGFR* mutation

**Baseline**

- Diameter = 2.5 cm
- Volume = 342.0 cm³

**21 day follow-up**

- Diameter = 2.6 cm
- Volume = 460.8 cm³

Change in diameter = 4.0%

Change in volume = 35.0%
Reliability / Reproducibility ... AND BETTER BIOMARKERS!

Delta Gabor Energy (dir135-w3), independent of tumor volume highly correlated with EGFR mutation.
Reliability / Reproducibility ... AND BETTER BIOMARKERS!
Imaging data from two clinical trials, involving four treatment arms and 2,349 patients

- FOLFOX plus panitumumab in first-line, FOLFOX in first-line (PRIME)
- FOLFIRI plus aflibercept in second-line, and FOLFIRI alone in second-line (VELOUR)
AI signature to forecast overall survival in mCRC
... AND BETTER BIOMARKERS! ... How much better?
... AND BETTER BIOMARKERS! ... How much better?

Validation set

**RECIST**

- **p < 0.0001**
- 62
- 166

**AI SIGNATURE**

- **p < 0.0001**
- 203
- 216
Excellent correlation of OS with volumetric growth quartiles

Growth rate values were divided into quartiles. To demonstrate the correlation between growth rates and OS [red = slowest; purple = fastest]
... AND BETTER BIOMARKERS! ... How much better?

Progress towards individualized treatment of colorectal cancer
... AND BETTER BIOMARKERS! ... How much better?

pre-Therapy

post-Therapy
Faculty members:
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Xiaotao Guo
Lin Lu
Pingzhen Guo

Senior Staff Associate:
Hao Yang

Research Radiologists:
Aiping Chen
Feifei
Lin Yi
Linning E
Fatima-Zohra Mokrane

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Susan Bates
Krastan Blagoev
Tito Fojo
Wilfred Stein
Julia Wilkerson

PhD Candidates:
Laurent Dercle
Jingchen Ma

Acknowledgments and THANK YOU!

“Measure what is measurable, and make measurable what is not so”
- Galileo Galilei
Vol-PACT Phase II: Advanced metrics and modeling with Volumetric CT for Precision Analysis of Clinical Trial results

Sharing Data – Artificial Intelligence

Collaboration with imaging data
To optimize drug discovery and patient care