The role of radiomics in oncology treatment

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The oncology pain point

The primary endpoints to evaluate cancer treatment (RECIST & survival) are:

• Not linked to the cancer phenotype
• Not sensitive to subtle, yet important, changes

Consequently we are virtually blind when taking decision on:

• How to treat patients
• How to proceed in treatment development programs
Resulting issues in the field

- **Large cost of failed clinical trial**
- **Promising drugs halted**
- **Shorter time under patent**

- **Suboptimal treatments**
- **Large societal costs**
- **Unnecessary burden to patients**

- **Treatment development**
- **Patient care**
Current solutions: biomarkers

- Screen patients on biology linked to the therapeutic pathway of the drug (tissue or blood)

Same tumor, same slice:

- PDL1 – negative
- PDL1 – positive

• PD-L1 alone is not an optimal biomarker
• Additional biomarkers are needed....
Radiomics in oncology

Quantitative imaging features are a non-invasive way of having a 3D (local & global) quantification of the tumor near instantaneously.

Individually or as a combination these features are tangible and sensitive endpoints to be used in clinical practice and oncologic drug development.
Begins with imaging

- Non-invasive, 3D and easy to repeat → important as tumors are spatially and temporally heterogeneous!

**New Hardware (e.g. MR-PET)**
- Expensive, needs staff training, maintenance

**New Imaging Biomarkers (e.g. HX4)**
- Expensive, not easy to obtain, single use

**New Software**
- Affordable, automated, multiple uses
The radiomics hypothesis

Humans are apes
There is only so much information we can hold at the same time

Quantitative Image Analysis
Will disrupt current interpretative, subjective imaging

Lambin et al. EJC, 2012; Lambin et al. Nat Rev Clin Oncol 2017
How good is your judgement?
Handcrafted features

1. Tumor image intensity
2. Shape
3. Texture
4. Multi-scale filtering
5. Advanced features (Fractal, features, Radial gradient...)

Lambin et al. EJC, 2012; Lambin et al. Nat Rev Clin Oncol 2017
Example: Handcrafted features

Lambin et al. EJC, 2012; Lambin et al. Nat Rev Clin Oncol 2017
Deep features

Feature visualization of convolutional net trained on ImageNet from [Zeiler & Fergus 2013]
Example: deep features
Usability of Radiomics

• Screen responder phenotype
• Measure exact response
• Predict outcome
Enrolling the right patients faster via routine images

Finding tumors with the right characteristics requires the right tools. Without them, it would be like looking for a needle in a haystack.

* Simple illustration of how the patient screening can be accelerated
Efficient treatment development

Evaluate drug efficacy in a setting optimized to demonstrate compound safety (i.e., demonstrate sensitivity to change in small sample size).

- Phase I: Evaluate drug efficacy in a setting optimized to demonstrate sensitivity to change in small sample size.
- Phase II: Evaluate drug efficacy in a setting optimized to demonstrate activity (i.e., demonstrate enhanced sensitivity to change as compared to standard primary endpoint, explore the possibility of responder stratification).

- Phase III: Evaluate the exact responder phenotype, allowing for CDx development and enabling dynamic monitoring of therapeutic efficacy and efficiency (i.e., improved results in less time).

* Example case of 11 samples which showed no measurable effect with iRECIST but showed an effect when measuring the heterogeneity of the tumor’s intensity and the spikiness of its shape. (Measure at V1 = baseline, V2 = post-treatment)

Radiomics proceed to next phase with confidence
Combination therapy

The main individual effect of the novel drug is on feature 10.

Radiomics allows to evaluate the added effect of individual compounds in combination therapy.
Predict response

2014
Training/Testing
Netherlands (stage I-IIIb)

2017
MVP / Regulatory
CE marked Class I

2018
External Validation
Netherlands (stage I-IIIb),
Denmark (stage I-IIIb), & Italy (stage IV)

2019
Prospective validation / Regulatory
Netherlands (stage I-IIIb) / FDA 510k Class II
Biology… From an image?

Lambin et al. Nat Rev Clin Oncol 2017
A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study.
Radiomics to demonstrate biology

Radiomics model HPV predictions vs molecular assay p16

Consistent and significant split between survival curves for HPV+ and HPV- determined by p16 (Red) and Radiomics (Blue)

Leijenaar et al., BJR 2018; EGFR-RAS: Rios Velasquez et al. Cancer Res 2017
### Table 2

#### Summary of systematic review with RQI-scoring.

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Modality</th>
<th>Disease</th>
<th>Biological correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo et al. [12]</td>
<td>MR</td>
<td>BC</td>
<td>A genomic dataset of 144 genomic features for 70 genes, including 70 gene expression features (normalized read counts of RNA-seq data); 70 copy number (Array Comparative Genomic Hybridization) features, and 4 methylation features (Infinium Human Methylation450 BeadChip)</td>
</tr>
<tr>
<td>Grossman et al. [11]</td>
<td>CT</td>
<td>LC</td>
<td>Gene expression of 21,766 unique genes (custom Human Expression Atlas) and 209,734 distinct transcripts using the Human Cancer Genome Project (HCGP) microarray chip, Immunohistochemical staining for CD3, a T-cell co-receptor and CD8, a T-cell co-receptor</td>
</tr>
<tr>
<td>Aerts et al. [14]</td>
<td>NSCLC</td>
<td>BC</td>
<td>Gene expression: APEX-chip with the custom chip HsRII.2x20,000 for BRE, 2x20,000 for INN</td>
</tr>
<tr>
<td>Varambally et al. [15]</td>
<td>NSGDC</td>
<td>BC</td>
<td>Amplification of 9p21 involving cyclin E gene (CCNE1)</td>
</tr>
<tr>
<td>Velazquez et al. [16]</td>
<td>CT</td>
<td>LAC</td>
<td>EGR1 and KRAS mutation status</td>
</tr>
<tr>
<td>Li et al. [17]</td>
<td>CT</td>
<td>BC</td>
<td>Core biopsy assessment of expression of ER, PR, HER2, MammnFusion (79 genes), Unistate DX (21 genes), and PBSTo (50-gene) assays</td>
</tr>
<tr>
<td>Yu et al. [18]</td>
<td>MR</td>
<td>IGG</td>
<td>Parallel slide PCR assessment of inactivating Dyl deitygenase 1 (DD1) status</td>
</tr>
<tr>
<td>Grossman et al. [19]</td>
<td>MR</td>
<td>GBM</td>
<td>Gene expression: eRNA; 583 genes sets containing 13 genes and at least 500 genes</td>
</tr>
<tr>
<td>Ito et al. [20]</td>
<td>CT</td>
<td>GBM</td>
<td>Gene expression: EGFR mutation and copy number status</td>
</tr>
<tr>
<td>Yu et al. [21]</td>
<td>CT</td>
<td>IGG</td>
<td>Parallel slide PCR assessment of inactivating Dyl deitygenase 1 (DD1) status</td>
</tr>
<tr>
<td>Yap et al. [22]</td>
<td>FDG-PET</td>
<td>NSCLC</td>
<td>Tissue samples of primary tumors through biopsy or surgical resection. Somatic mutations were tested using a PCR-based method (eDNA, KRAS exons) or PROBE (mass spectrometry genotyping technique analyzing &gt; 470 unique mutations in 41 exons)</td>
</tr>
<tr>
<td>Geser et al. [23]</td>
<td>CT</td>
<td>LC</td>
<td>Tumor histopathologic subtype. Mutation testing was done for both EGFR and KRAS using multiplex PCR</td>
</tr>
<tr>
<td>Yoon et al. [24]</td>
<td>FDG-PET</td>
<td>CT</td>
<td>Tumor histopathologic subtype. Molecular analysis: genomic DNA or RNA extracted from lung tumors using standard protocols (PNA/Ramp Mini Kit and Gamp DNAprep Kit; Ginger, Hidden, Germany: ALC, RQI, and RQI fusion assay using eRNA for gene expression assays)</td>
</tr>
<tr>
<td>Esmailnejad et al. [25]</td>
<td>CT</td>
<td>NSCLC</td>
<td>Two genomic biomarkers (E2CC and E3CC), were evaluated using the selected tumor specimen and a standard BHC-based analytic method</td>
</tr>
<tr>
<td>Banh et al. [26]</td>
<td>CT</td>
<td>CRC</td>
<td>GEMMA gene expression</td>
</tr>
<tr>
<td>Aerts et al. [27]</td>
<td>CRB</td>
<td>NSCLC</td>
<td>Genomic DNA from snap frozen tumor reection specimens analyzed for most common EGR-1-persisting mutations (exons 5 and 21) with PCR-based methods. EGFR wild-type (WT) tumors were also tested for KRAS mutations</td>
</tr>
<tr>
<td>Cheek et al. [28]</td>
<td>CT</td>
<td>eRCC</td>
<td>eRCC mutation status</td>
</tr>
<tr>
<td>Hanania et al. [29]</td>
<td>CT</td>
<td>PMNN</td>
<td>Quantitative analysis of resected specimens of the pancreatic cystic and pancreatic parenchyma to differentiate high grade from low grade lesions</td>
</tr>
<tr>
<td>Soo et al. [30]</td>
<td>CT</td>
<td>LC</td>
<td>Surgical resection specimens, transbronchial lung biopsy, CT-guided percutaneous biopsy or clinical examination and therapy to differentiate between benign and malignant pulmonary nodules/tumors</td>
</tr>
<tr>
<td>Ba et al. [31]</td>
<td>CT</td>
<td>LAC</td>
<td>Histopathologic tumor grade assessment based on specimen from complete resection</td>
</tr>
<tr>
<td>Pena et al. [32]</td>
<td>CT</td>
<td>eRCC</td>
<td>Histopathologic analysis malignancy</td>
</tr>
<tr>
<td>Gimmert et al. [33]</td>
<td>MR</td>
<td>PC</td>
<td>Histopathologic Gleason tumor grading</td>
</tr>
<tr>
<td>Biedlbaum et al. [34]</td>
<td>MR</td>
<td>BC</td>
<td>Tumor histopathologic grade</td>
</tr>
<tr>
<td>Berumen et al. [35]</td>
<td>CT</td>
<td>PMNN</td>
<td>Tumor histopathologic grade. RNA-mRNA from archived plasma using NGSsequencing RNAcount digital technology</td>
</tr>
<tr>
<td>Zhang et al. [36]</td>
<td>MR</td>
<td>Ultrason</td>
<td>Tumor histopathologic grade</td>
</tr>
<tr>
<td>Guo et al. [37]</td>
<td>CT</td>
<td>BC</td>
<td>Tumor histopathologic grade (Norrin), Tumor staining with hematoxylin-emin and examined in formalin-fixed, paraffin-embbeded material. Expression of ER, PR, HER2, and E7 was assessed by IHC analysis</td>
</tr>
<tr>
<td>Song et al. [38]</td>
<td>CT</td>
<td>LAC</td>
<td>Tumor histopathologic subtype</td>
</tr>
<tr>
<td>Peil et al. [39]</td>
<td>CT</td>
<td>NSCC</td>
<td>Tumor histopathologic subtype</td>
</tr>
<tr>
<td>Parme et al. [40]</td>
<td>CT</td>
<td>NSCC</td>
<td>Tumor histopathologic subtype. HPV status</td>
</tr>
<tr>
<td>Jin et al. [41]</td>
<td>CT</td>
<td>PM</td>
<td>Immunohistochemical staining of snap-frozen tumor sections in liquid nitrogen</td>
</tr>
<tr>
<td>Zhang et al. [42]</td>
<td>CT</td>
<td>Ultrason</td>
<td>Core biopsy or fine-needle aspiration cytology for histopathologic assessment</td>
</tr>
<tr>
<td>Coqroren et al. [44]</td>
<td>MR</td>
<td>NSCC</td>
<td>Immunohistochemical analysis of corollary sections. Hematoxylin-eosin staining performed to characterize tumor cell density. Tumor hypofusion was determined using the HypoXpert dye (pseudotumore detection)</td>
</tr>
<tr>
<td>Chou et al. [45]</td>
<td>CT</td>
<td>LA C</td>
<td>Tumor histopathologic subtype</td>
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<tr>
<td>Wu et al. [46]</td>
<td>CT</td>
<td>LC</td>
<td>Tumor histopathologic subtype</td>
</tr>
<tr>
<td>Li et al. [47]</td>
<td>CT</td>
<td>MB</td>
<td>Immunohistochemical molecular classification/subtyping (ER, PR, E7, HER2) based on tumor biopsy</td>
</tr>
<tr>
<td>Greep et al. [48]</td>
<td>MR</td>
<td>PC</td>
<td>PSA level analysis</td>
</tr>
<tr>
<td>Wang et al. [49]</td>
<td>MR</td>
<td>BC</td>
<td>Expression of ER, PR, HER2, and KIT by immunohistochemical analysis of tumor specimens</td>
</tr>
<tr>
<td>Yen et al. [50]</td>
<td>FDG-PET</td>
<td>cRCC</td>
<td>Tumor samples processed for snap freezing to liquid nitrogen; formalin fixed and paraffin-embbeded. Defers Tissue Studio software used to measure microvascular density (MVD) in CD3 stained slides</td>
</tr>
</tbody>
</table>

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**References:**
- Lambin et al. Nat Comms 2014
- Grossman et al. elife 2017
- Sanduleanu et al. Rad Oncol 2018
Biology

• A Western blot is also an image
Variability control!

- How can you combine images from different images, different acquisition?
Variability control!

- Post-processing harmonisation of features (also used with gene arrays)

Reuze et al. IJROBP. 2018.
Variability control!

COMBAT
Post-reconstruction harmonization
A gaussian filter initially described for use in genomic data

Conclusion

- Radiomics has characteristics
  - Full 3D
  - Temporal repeats
  - Phenotype is indicative for genotype
  - Quantifiable
  - Automated
  - Sensitive

- To play a central role in oncology treatment

- When used in the right way