The role of quantitative molecular imaging in therapy development

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Disclosures
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Molecular imaging using PET/CT is a powerful tool for detection, diagnosis, and staging of cancer
Clinical Realm: Diagnostic Accuracy of PET/CT exceeds CT or PET only

<table>
<thead>
<tr>
<th>Tumor entity</th>
<th>References</th>
<th>Purpose of the imaging studies</th>
<th>Number of patients</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>Chen et al. (2008)</td>
<td>Tumor staging</td>
<td>72</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Scholten et al. (2006)</td>
<td>Lesion detection</td>
<td>68</td>
<td>86</td>
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<tr>
<td>NSCLC</td>
<td>Lanthos et al. (2009)</td>
<td>T stage</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>N stage</td>
<td>87</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Shen et al. (2008)</td>
<td>T stage</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>N stage</td>
<td>100</td>
<td>84</td>
<td>ND</td>
</tr>
<tr>
<td>Colonrectal</td>
<td>Kim et al. (2009)</td>
<td>Recurrence</td>
<td>51</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Vodovozov et al. (2009)</td>
<td>Recurrence</td>
<td>94</td>
<td>50</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Monastir et al. (2009)</td>
<td>Staging</td>
<td>73</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Frohge et al. (2009)</td>
<td>Relapse</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Nottveit et al. (2007)</td>
<td>Staging</td>
<td>250</td>
<td>87</td>
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<tr>
<td></td>
<td>Mohr et al. (2007)</td>
<td>Relapse</td>
<td>130</td>
<td>91</td>
</tr>
</tbody>
</table>

*Statistically significant difference when compared with PET/CT. Abbreviations: NSCLC, non-small cell lung cancer; ND, not determined; TMA, tumor microarray.


Expanding the role for molecular imaging to therapy development

We need better therapies

Lung cancer incidence (US)

- More fatalities than any other type of cancer (~28%)
- 116,000 men, 103,200 women diagnosed in 2009
- 88,900 men, 70,490 women died in 2009
- Most common form: NSCLC
- Cigarette smoking still accounts for ~30% of all cancer deaths

CDC & Jemal CA. Cancer J Clin 2009
Lung cancer survival (US)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Breast, female</td>
<td>75</td>
<td>79</td>
<td>89</td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>99</td>
</tr>
<tr>
<td>Lung</td>
<td>13</td>
<td>13</td>
<td>16</td>
</tr>
</tbody>
</table>

Therapies
- Surgery: most potentially curative, but only for very localized disease
- Radiation: combined with chemo can cure in small number of patients. Can provide palliation in most patients
- Chemotherapy: offers modest improvements in median survival for advanced stage disease

An increasing number of high cost, targeted pharmaceuticals are in research and development for oncology

![Diagram of targeted pharmaceuticals]

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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of disease</td>
<td>12.0%</td>
<td>12.3%</td>
<td>12.6%</td>
<td>12.9%</td>
<td>13.2%</td>
<td>13.5%</td>
<td>13.8%</td>
<td>14.1%</td>
<td>14.4%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Percent survival for first-in-human trials</td>
<td>94%</td>
<td>87%</td>
<td>78%</td>
<td>71%</td>
<td>69%</td>
<td>74%</td>
<td>78%</td>
<td>84%</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>% of cancer patients</td>
<td>2.8%</td>
<td>3.4%</td>
<td>4.4%</td>
<td>5.3%</td>
<td>6.7%</td>
<td>8.1%</td>
<td>9.5%</td>
<td>10.3%</td>
<td>11.6%</td>
<td>12.4%</td>
</tr>
</tbody>
</table>

Success rates from first-in-human to registration

![Graph of success rates]


In addition approved drugs are withdrawn (e.g. Bextra, Vioxx, Baycol, Rezulin, Tysabri)
Potential reasons for low success rate

- Easy targets gone
- Wealth of information about targets, little understanding in context of whole organism
- Few animal models translate to humans
- Lengthy clinical trials required to establish efficacy
- Tolerance to risk can be lower with drugs that treat chronic diseases
- Drug development process is inefficient and expensive

Drug development process

Developing a new medicine takes an average of 10–15 years

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Volunteers</th>
<th>Number of Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5250 – 5,000</td>
<td>20 – 100</td>
</tr>
<tr>
<td>2</td>
<td>5,000 – 10,000</td>
<td>100 – 500</td>
</tr>
<tr>
<td>3</td>
<td>~3 – 6 years</td>
<td>1,000 – 5,000</td>
</tr>
<tr>
<td>FDA Review</td>
<td>~3 – 6 years</td>
<td>~300M – 3B</td>
</tr>
<tr>
<td>Scale Up to Mfg.</td>
<td>~3 – 6 years</td>
<td>~1.3B</td>
</tr>
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</table>

Role for Imaging in Drug Development

- Drug development is costly and inefficient
- New tools are needed to identify losers early
  - Rule out unsuccessful methods earlier (before phase III)
  - Improving phase III 'hit rate' from 1 in 5 to 1 in 3 could reduce development costs by ~50% [DiMasi 2002]
- Imaging biomarkers can help
- Quantitative PET imaging has enormous potential to boost efficiency of clinical trials evaluating new therapies [Frank 2003]
Imaging biomarker examples

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Assay</th>
</tr>
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<tbody>
<tr>
<td>Tumor volume</td>
<td>CT, MRI</td>
</tr>
<tr>
<td>β-amyloid</td>
<td>PET</td>
</tr>
<tr>
<td>Tumor proliferation</td>
<td>PET</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>DXA, CT</td>
</tr>
<tr>
<td>Receptor occupancy</td>
<td>PET</td>
</tr>
<tr>
<td>Plaque composition</td>
<td>US, IR, MRI, PET</td>
</tr>
</tbody>
</table>

Courtesy Jeff Evelhoch, Merck

Anatomical imaging biomarker:
Response Evaluation Criteria in Solid Tumors (RECIST)

Response: \(\delta \lambda_{\nu} A < -30\%\) after 4 weeks
Progression: \(\delta \lambda_{\nu} A > +20\%\)

The case for molecular imaging biomarkers
Biomarkers To Quantify Hallmarks of Disease

New uses for existing PET agents
New molecular diagnostic agents
Many different types of PET measurements are needed

Molecular imaging can evaluate primary points of impact in therapy development

Molecular Imaging: Glu Metabolism

FDG is 'trapped' and is a marker for glucose metabolic rates.

*Note: The chemical structures and reactions are depicted in detail in the diagrams, showing the metabolic pathways and the role of [18F]FDG in glucose metabolism.
Cytostatic effects of EGGF Inhibitors

Baseline Day 14

Stage IV disease not suitable for curative surgery or radiotherapy
Uptake of 18F-FDG in primary lesion, lymph nodes, and upper thoracic vertebrae

Hicks, JNM 2009

Quantitative Assessment of Response to Therapy

Breast cancer recurrence

Qualitatively distinct

Quantitatively distinct

Courtesy D Mankoff

Quantitation Improves Characterization of Response

- Make clinical trials of new therapies more effective
- Accelerate adoption of new molecular diagnostics
- Improve individual patient care
- All tied to quantitative accuracy

Nahmias JNM 2007
**Why quantitative imaging matters**

- Measurement error
- Dosimetric trend
- Treatment response trend

quantitative = known measurement error

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**Quantitative Imaging Requirements**

- Prior studies that measure variance
- Defined protocols
- Monitoring of protocols
- Calibration and QA/QC procedures to ensure variance stays within assumed range
- **Optional**: Techniques and procedures that improve the measurement accuracy

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**The Imaging Chain**

- For quantitative imaging, each component of the imaging chain requires
  - Quality Assurance (i.e. protocol)
  - Quality Control (checking what actually happened)
- Outline for all imaging methods:

  imaging physics
  patient status
  scan protocol
  processing & reconstruction
  analysis methods
  final accuracy & precision
  calibration
Sources of Error in SUV Values

SUV = Standardized Uptake Value

\[
SUV = \frac{\text{PET}_{\text{ROI}}}{D'/V'}
\]

PET = measured PET activity concentration

\[
D' = \text{decay-corrected injected dose}
\]

\[
V' = \text{surrogate for volume of distribution}
\]

It is important to minimize SUV errors for serial (e.g., response to Rx) or multi-center studies.

Some potential sources of error are:

- High blood glucose levels
- Variations in dose uptake time
- Uncalibrated clocks (including scanner) and cross calibration of scanner with dose calibrator
- Errors in radioactive dose assay
- Variations in image reconstruction and other processing protocols and parameters
- Variations in images analysis methods: E.g., how ROIs are drawn and whether max or mean SUV values are reported.

Instrumentation Chain for FDG-PET

Error Propagation in PET Imaging
Impact of measurement error on power/sample size

Sample size increases as error increases

Sample Size

True Effect Size (%)

40% error

30%

20%

10%

0%

Doot et al., Acad Rad 2012

Impact of measurement error and sensitivity to true change on sample size

<table>
<thead>
<tr>
<th>Trial Scenario</th>
<th>error</th>
<th># of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single site</td>
<td>10%</td>
<td>12</td>
</tr>
<tr>
<td>(good calibration)</td>
<td>20%</td>
<td>42</td>
</tr>
<tr>
<td>Multi-center</td>
<td>40%</td>
<td>158</td>
</tr>
</tbody>
</table>

Doot et al., Acad Rad 2012

PET/CT scanners are a moving target:
Recent PET Technology Innovations

- Respiratory motion compensation
- Time of flight imaging
- Advanced modeling of PET physics in image reconstruction
- Extended axial field of view
- Cost effective PET/CT scanners
- New detector systems
- PET/MR scanners
- CT dose reduction methods
PET/CT scanners are a moving target

Modified NEMA NU-2 IQ phantom

Different reconstruction methods on the same PET/CT scanner

- Hot sphere diameters of 10, 13, 17, 22, 28, and 37-mm
- Target/background ratio 4:1

Challenges with Implementing Quantitative Imaging - Industry

- There is significant variability between manufacturers in allowable scan protocols and trade-offs in image quality
- There are few, if any, tests of the quantitative accuracy of images transferred between display/analysis systems
- Due to several reasons:
  - Lack of standards by which vendors can assure compliance of acquisition/processing algorithms
  - Lack of convincing (to vendors) evidence of a market for quantitative imaging

Challenges with Implementing Quantitative Imaging - Imaging Sites

- There is a tension with imaging protocols suitable for current clinical practice
- Often there is no standard clinical practice
- E.g. when 'standard of care' is requested, any of the following may occur:
  - Blood glucose levels may be ignored or not reported
  - Tracer uptake time may vary
  - PET images may be acquired in 2D or 3D
  - PET images may be reconstructed with different algorithms
  - PET images may be reconstructed with different smoothing
  - SUVs may be measured differently and/or on different platforms
  - May do an MR or CT scan instead
What do we do?

There are three main routes of action
1. Accreditation authorities
2. Standards definitions and harmonization initiatives
3. Calibration methods and/or phantoms

Quantitative PET/CT Standards and/or Accreditation Bodies in the US

- NEMA/MITA
- AAPM
- ANSI (DICOM)
- Clinical Research Organizations
- ACR
- IAC
- PET Core Labs (CALGB, DFCI, ...)
- ACRIN
- SNM
- FDA
- NRC (DOE), DOT

Quantitative Imaging Initiatives

- ACRIN Centers of Quantitative Imaging Excellence (CQIE)
- Quantitative Imaging Biomarkers Alliance (QIBA)
  - Now includes the Uniform Protocols for Imaging in Clinical Trials (UPICT)
- Quantitative Imaging Network (QIN)
- American Association of Physicists in Medicine Task Group 145 (Quantitative Imaging for PET)
- Reconstruction Harmonization Project (ACRIN / SNM-CTN / QIN / QIBA)
- EANM and EORTC initiatives
Calibration phantoms for Quantitative PET/CT Standards and/or Accreditation

- Uniform Cylinder (used by ACRIN and many others)
- ACR PET phantom
- NEMA NU-2 Image Quality (IQ) phantom
- Modified NEMA Image Quality (IQ) phantom
- SNM CTN phantom
- Cross Calibration Phantom with NIST-traceable 68Ge standard for Dose Calibrator
- Digital reference object

Quantitative imaging can characterize individual response to therapy

**short term drivers**
- Clinical research, Clinical trials, and Drug discovery
- New molecular diagnostic agents
- Assessing individual response to therapy
- SUVs are now routinely reported, and are asked for, by referring physicians

**increasing volume**

CONCLUSION
The role of quantitative PET/CT imaging in therapy development

- There is a need for improved
  - cancer therapies
  - Individualized assessment of therapies
- Quantitative PET imaging can help if we
  - determine the bias and variance
  - constrain (and optionally reduce) the variance
- To enable quantitative PET we need to
  - educate and link together groups in the different areas of responsibility (i.e. big picture)
  - develop standards by which manufacturers and users can assure compliance

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