Towards personalized medicine – integration of imaging into therapy

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Imaging and therapy

100 years later…
Image Guided Radiation Therapy
100 years later…
Image Guided Surgery

100 years later…
What did medical physics contribute?

- **Imaging advances**
  - New imaging modalities: MRI, PET, combined modalities
  - Improved imaging technologies: contrast, resolution, noise, speed, accuracy

- **Treatment advances**
  - New RT technologies: Co-60, linacs, IMRT
  - Surgery: Minimally invasive procedures

- We can be very PROUD of these achievements!

100 years later…
Where is medical physics in Tx chain?

Shore et al 2012, Br J Urol Int, 6: 22
"4 P’s of medicine": Individuals respond differently to environmental conditions, according to their genetic endowment and their own behavior. In the future, research will allow us to predict how, when, and in whom a disease will develop. We can envision a time when we will be able to precisely target treatment on a personalized basis to those who need it, avoiding treatment to those who do not. Ultimately, this individualized approach will allow us to preempt disease before it occurs, utilizing the participation of individuals, communities, and healthcare providers in a proactive fashion, as early as possible, and throughout the natural cycle of a disease process.

Elias A. Zerhouni, M.D.
Director, National Institutes of Health (NIH), 2008

**Imaging in treatment process**

PRE Tx | TREATMENT | POST Tx | TREATMENT

DIAGNOSIS | STAGING |

TREATMENT SELECTION | TREATMENT SELECTION |

TREATMENT ASSESSMENT
TREATMENT SELECTION

PRE Tx | TREATMENT | POST Tx | TREATMENT

DIAGNOSIS | STAGING | TREATMENT SELECTION | TREATMENT SELECTION | TREATMENT ASSESSMENT

FMISO PET in HN

FMISO PET + (hypoxia) + TPZ boost
FMISO PET - (no hypoxia)
FMISO PET focal uptake mildly larger than bgrd
FMISO PET + (hypoxia) + chemo boost


FES PET in Breast

LABC or Metastatic Br CA
Primary Tamoxifen Rx

Recurrent or Metastatic Br CA
Aromatase Inhibitor Rx

Linden et al 2006, J Clin Oncol, 19: 2797
FES PET SUV=1.5
(P < 0.01 for both)
Linden et al 2006, J Clin Oncol, 24: 2793
DCE/DSC MRI in GBM

Yao et al. 2011, Sem Rad Oncol, 21:147

Radiation Therapy

Small fractional TV w High-CBV

P=0.002

Great fractional TV w High-CBV

FTV = 0.07

Can we image everything - lung?

Sequist et al. 2011, Min Oncol, 22:261

MICAD: Molecular Imaging and Contrast Agent Database

1260 agents listed (July 2012)
But can we really use them all?

1. Credentialing
2. Modality creation
3. Supporting tools
4. Development
5. Clinical trials

Role for medical physics?

Highly interdisciplinary
- Cell/molecular biology
- Chemistry/radiochemistry
- Radiology
- Medical physics
- Pharmacology
- Medicine
- Engineering
- Mathematics
- Material science
- Computer science

NO, this makes imaging essential, and complementary

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

...branched evolutionary tumor growth, with 63 to 69% of all somatic mutations not detectable across every tumor region...
**Treatment response assessment**

- **WHO (1979, 1981)**\(^1,2\)
  - anatomic

- **RECIST (2000, 2009)**\(^3,4\)
  - Response Evaluation Criteria In Solid Tumors
  - anatomic, CT/MR based
  - unidimensional
  - 4 response categories (CR, PR, SD, PD)

<table>
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\(^1\)WHO 1979, \(^2\)Miller et al. 1981, \(^3\)Therasse et al. 2000, \(^4\)Eisenhauer et al. 2009

**Power of molecular imaging**

- FDG PET response correctly predicts response to Gleevec in majority of patients
- FDG PET response correctly predicts SD and PD, while CT does not
- FDG PET response *proceeds* the CT response (shrinkage) by several weeks
- FDG PET response is strongly associated with a longer progression free survival (82% vs. 12% after 1 year) and closely correlated with subjective symptom control

Van der Aalst 2008, The Oncologist 13(suppl 2), 8
Acute myeloid leukemia

Specificity = 43%
NPV = 64%

Day 14 BMBx
Day 28 BMBx


How early can imaging predict future?

Pre-therapy
Post-therapy (2 wks)
CLINICAL OUTCOME (6 mo)

Complete remission
Resistant disease

Vanderhoek et al 2011, Leuk Res 35: 310

Early treatment response assessment

Complete Remission (6 mo)
Resistant Disease (6 mo)
Post-therapy
Day 6
Day 5
Day 4
Day 2

Better than Higgs!!!
Heterogeneity of the response

Imaging vs biopsies

Role for medical physics?

ADVANCED IMAGE ANALYSIS

FLT PET CT Mask FLT PET Bone Marrow

NPV = 64%

Percentage of Bone Marrow

SUV

Complete Remission
Resistant Disease

8/2/2012
FDG PET in NSCLC

HR = 2.27
(1.70-3.02 95% CI)
N=1474

Berghmans et al 2008, J Thorac Oncol, 3: 6

PET-based response assessment

- EORTC, NCI Recommendations (1999, 2005) 1,2
  - SUV-based approach
    - SUV\textsubscript{mean} and SUV\textsubscript{max}
    - Response categories with thresholds (CR, PR, SD, PD)

- PET Response Criteria in Solid Tumors (PERCIST) (2009) 3
  - SUV-based approach
    - SUV\textsubscript{peak}
    - Response categories with thresholds (CR, PR, SD, PD)

1Young et al 1999. 2Shankar et al 2006. 3Wahl et al 2009

Images are more than just one number!

- Size measures
  - Volume
    - 1D size (axial)
- Standardized Uptake Value (SUV) measures:
  - SUV\textsubscript{mean}
  - SUV\textsubscript{peak}
  - SUV\textsubscript{max}
  - SUV\textsubscript{peak}
- Uptake Non-uniformity measure:
  - SUV\textsubscript{sd}
- ...
Different measures tell different stories

GOOD RESPONSE  POOR RESPONSE  NEW LESIONS

Role for medical physics?

SCANNER HARMONIZATION
- UW GE DVST S2N2 vs Dis/cc measured for different reconstruction settings
- NCI Gemini TF S2N2 vs Dis/cc measured for one reconstruction setting
- Phantom measurements to characterize the scanners
- Comparative patient data from UW and NCI studied
- Patient S2N2 data presented using phantom data for reference

TREATMENT SELECTION - AGAIN
Origins of treatment resistance

...several lines of evidence support the hypothesis that resistant tumors are a mixture of sensitive and resistant cells...

Summary

- Medical physics has been extremely successful, but it has "captured" only a small part of the interface between imaging and therapy – **ENORMOUS POTENTIAL!!!**
- Future of medicine – personalized therapy – is complex, but extremely exciting, don’t wait - **EXPAND HORIZONS!!!**
- **MANY ESSENTIAL ROLES** we should play beyond radiotherapy and diagnostic imaging:
  - Clinical trial design
  - Molecular imaging chain
  - Advanced image analysis
  - Quantitative imaging
  - Modeling
  - …

CJ’s FUTURE

Pondering her future… … Easy decision…

Courtesy of Stephanie Harmon and her niece CJ, March 2012

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Medical physics and ART

Courtesy of Koala Yp and her mom, January 2012