OPTICAL IMAGING IN BREAST CANCER:
FLUORESCENCE & ČERENKOV

Brian W. Pogue PhD

Outline

1. Dual-probe fluorescence imaging for lymph node cancer detection
2. Čerenkov Imaging in Radiation Therapy
3. Hybrid Molecular imaging

Example 1: Detecting lymph node involvement with Exogenous molecular imaging
LYMPH NODE DETECTION

Lymphoscintigraphy  Methylene Blue procedure

1) Procedures today remove nodes for the purpose of assay
2) Delay between surgery and lymph node analysis
3) High morbidity (axillary nodes)

Dual Dye injection: Targeted & Reference

EPIDERMAL GROWTH FACTOR RECEPTOR
TARGETED FLUORESCENT IMAGING

Methylene blue  EGFR binding peptide + IRDye800

Fluorescence Signal

Fluorescence Signal
FLUORESCENCE IMAGING OF AXILLARY LYMPH NODES

Injecting Rat Forepaw

High Variability!!

DUAL REPORTER COMPARTMENT MODEL

Targeted Tracer

Untargeted Tracer

\( \frac{dC_t}{dt} = F_lC_t(t) - F_lC_f(t) e^{-\frac{t}{k_3}} \)

\( \text{BP} = k_3 / k_4 \)

Tichauer et al., Phys Med Biol 2012

SIZE \rightarrow AFFINITY – TRANSPORT EFFECTS

Shorter clearance time

Lower affinity

Longer clearance time

Higher affinity

Affibody (7 kDa)

Shorter clearance time

Lower affinity

Longer clearance time

Higher affinity
LYMPH NODE METASTASIS CANCER MODEL

Control

Tumor Bearing

KINETICS OF EGFR-TARGETED TRACER CAN PREDICT TUMOR BURDEN

Raw Intensity shows no difference

Binding ratio has large difference!!

RECEPTOR CONCENTRATION VALIDATED WITH Q-PCR

Quantitative PCR of entire node

Ex Vivo DNA Assay
THE FINANCIAL BARRIERS TO MOLECULAR IMAGING:

Lack of existing paradigm for molecular guided surgery = NO BILLING CODE

Modest financial payback for diagnostics (vs. therapeutics)

REDUCING COSTS:
GMP PEPTIDE SYNTHESIS & PHASE 0 TRIAL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cost</th>
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<td>GMP Recombinant Synthesis Run</td>
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<tr>
<td>Toxicity Testing Rodents</td>
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<td>Phase 1 Trial</td>
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<tr>
<td>Total</td>
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Recombinant production route cannot be financed by the NCI, but peptide synthesis can!!

Industry/Academic Partnership for Targeted Fluorescent Receptor probe

Affibody IRDye800 - Affibody ABY-029 - Dartmouth

2015

2016

2017
Cerenkov Imaging in Radiation Therapy

The Čerenkov effect

\[
D = \frac{1}{\rho} \int \Phi \left( -\frac{d\gamma}{dx} \right) dE
\]

Čerenkov production

\[
N = \frac{1}{\rho} \int \Phi \left( \frac{dN}{dx} \right) dE
\]

Čerenkov emission, energy & dose

High production of Čerenkov in EBRT relative to PET or brachytherapy

Production is largely flat with energy > 1 MeV
Multiple Angle Beam Imaging

Images at different angles

Reconstructed 3D volume with FBP

Glaser et al, Optics Lett. 2013

Beam Tomography with Čerenkov

FBP recon


3D ČERENKOGRAPHY OF LINAC BEAMS

Square beam

Complex shaped beam

Glaser et al, Optics Lett. 2013
Imaging Complex Treatment plans in real time

AAPM TG Report # 119

Čerenkov Video
Time-integrated

Čerenkov Video
Time-integrated

David Gladstone, Thursday presentation AAPM
Optical dosimetry system v3.0  Low Cost option  
($250 in parts)

Web cam $50
Nightvision monocular $150
filter $50

MONTE CARLO MODELING – GEANT4 & TISSUE OPTICS PLUG-IN

Čerenkov in Humans
Čerenkov dose imaging
tracking skin dose with room lights on!

Jarvis et al, IJROBP (2014)

IMPROVEMENTS IN SNR TO ALLOW ČERENKOV IMAGING

Sunlight
Room light
dimmed lights
Čerenkov

Gated Acquisition - 10^5x gain
(3 μsec pulses @ 200 Hz)


First imaging of Čerenkov emission from human tissue

Entrance Čerenkov
Exit Čerenkov

- Whole breast radiotherapy with dynamic field.
- Real time monitoring possible.

Jarvis et al, IJROBP (2014)
Dynamic beam field monitoring

Čerenkov emission identifies beam field dynamics due to MLC motion in real time (fps ≈ 2.5).

Jarvis et al, IJROBP (2014)

Options for Gated Cameras

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<tr>
<th>Camera Model</th>
<th>Sensor Type</th>
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<th>Resolution (pixels)</th>
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<th>Gate Time</th>
<th>QE of Detector at 700 nm</th>
<th>QE of Intensifier at 700 nm</th>
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Jacqueline Androzzi, AAPM talk (Thursday AM)

Video rate imaging (30 frames per second) with EM-ICCD
12 patient pilot trial completed

Hitchcock et al, (submitted, 2014)

Respiration tracking:
- edge extraction
- temporal correlation

Rongxiao Zhang, AAPM talk (Thursday AM)

Total Skin irradiation

Jacqueline Andreozzi, AAPM talk (Thursday AM)
Molecular Imaging In Vivo?

Use blue Čerenkov to excite NIR emitting molecular reporters in tissue

Oxygen sensitive phosphor

Sergei Vinogradov, UPenn

Zhang et al, J. Biomed Optics. 2013

Oxygen imaging with luminescence lifetime tomography

Could be done with dose ≈ CT scan

Holt et al, Phys Med Biol (in press)
SUMMARY:

1. Real-time water tank imaging
2. Real-time in vivo imaging
3. Molecular Sensing with Čerenkov luminescence

Čerenkography & Čerenkoscopy Team

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Adam Glaser
Rongxiao Zhang
David Gladstone, DSc
Lesley Jarvis, MD PhD
Shudong Jiang, PhD
Audrey Prouty

Development Fund
www.dartmouth.edu/optmed/

QUESTIONS?
The relative error along the central axis between the Cherenkov light emission and dose for 0.5, 1.0, 2.0, 4.0, and 10.0 cm diameter beams for the 6X, 6FFF, 18X, and 18FFF beams.

The relative error along the central axis between the Cherenkov light emission and dose for 0.5, 1.0, 2.0, 4.0, and 10.0 cm diameter beams for the 6X, 6FFF, 18X, and 18FFF beams.

(a) The central axis curve for the AP-PA treatment is plotted. (b) The corresponding lateral curves at $d_{max}$, 50 cm, and at the isocenter (100 mm) are shown.
Quality assurance plays a fundamental role in radiation treatment of cancer. While modern techniques offer the ability to deliver precise doses of radiation to tumour tissue, this advantage is lost if the equipment is not reliable and accurate. Regular and precise calibration of radiotherapy apparatus is thus an essential procedure in hospitals.

New accelerator enhances radiotherapy accuracy, Nov. 19, 2008