Positron Emission Tomography for Oncologic Imaging and Treatment

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Outline

• Physics of PET and PET-CT
• Oncology Imaging with FDG PET
• PET and Radiation Treatment Planning
• Non-FDG PET Oncology Imaging
  – Bioanatomic Imaging and Treatment
• Summary

Work supported in part by research grants from North Carolina Baptist Hospital, Varian Medical Systems, and GE Healthcare

Physics of PET and PET-CT

• Coincidence detection of two 0.511 MeV photons
• Annihilation radiation from positron-electron pair
• Photon directions at 180° at annihilation point - different from decay point → range of positron
• Positron emitters with biological compatibility
• Low Z (typically), proton rich, short half-lives
• “Local” production with a cyclotron

PET Radionuclides

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorine 18 (18F)</td>
<td>110 min</td>
</tr>
<tr>
<td>Carbon 11 (11C)</td>
<td>20 min</td>
</tr>
<tr>
<td>Nitrogen 13 (13N)</td>
<td>10 min</td>
</tr>
<tr>
<td>Oxygen 15 (15O)</td>
<td>122 sec</td>
</tr>
<tr>
<td>Rubidium 82 (82Ru) (cardiac)</td>
<td>75 sec</td>
</tr>
</tbody>
</table>
Coincidences: Detected Events

- True
- Scattered
- Random

PET Device Parameters

- Resolving time – detector material
- Spatial resolution – nominally, detector size
  - 4 to 6 mm (voxel size)
- Temporal resolution – acquisition time, gating (?)
- Number of detectors – SNR, spatial resolution
- Aperture size – 70 cm max – large bore?
- 2D or 3D acquisition modes – both are volumes
- Several others, inter-related

Attenuation Correction

- Correction for attenuation along ray path
- Methods – volume image of patient
  - Nuclide scan or CT-based

Oncology Imaging with FDG PET

- Diagnosis – less common
- Staging - yes
- Target Definition - developing
  - Radiation treatment
  - Other “targeted” therapy
- Re-staging – yes
- Treatment Evaluation – developing

Adapted from Rohren, Turkington, Coleman: Radiology 2004; 231:305-332

From Rohren, Turkington, Coleman: Radiology 2004; 231:305-332
Why PET Oncology Imaging?

- Distribution of activity is imaged
  - Physiology, function, biology
- Complementary to (~anatomic) CT and MR
- Increased sensitivity compared to CT alone
- Indications approved for reimbursement
  - Most approved indications are for oncology
- Devices available (market saturated?)
- Image handling toolsets maturing, available (?)

Why PET?

A Picture of the Patient

CT-PET Hybrid Imaging for Tumor Diagnosis and Treatment Planning

(Courtesy General Electric Healthcare)

PET-avid tumor registered with CT obtained at the same time

Example: Non-Small Cell Lung Cancer

Diagnosis | Staging | Re-Staging

Example: Colon Cancer

Initial Staging | Initial Staging | Re-Staging

From Rohren, Turkington, Coleman: Radiology 2004; 231:305-332
**Clinical Imaging (FDG) with PET**

- $^{18}$F-Fluorodeoxyglucose (FDG) only
- Imaging of tumor glucose metabolism: glycolysis
- Non-specific imaging agent – metabolically active sites
- Staging, re-staging of lung, breast, colon, cervical, head/neck, melanoma, lymphoma. Some diagnosis.
- Difficulties with small tumors (< 3 – 10 mm diameter)
- Use increasing – 200 PET-CT scanners in 2 years* (7)
- PET-CT hybrid scanners: registration solved


**PET and Radiation Treatment Planning**

- **Main contribution – Staging, aka. Target Localization**
  - Very important: stage determines treatment approach
  - Binary results: presence/absence of disease, metastasis
- **Dramatic differences – binary (?)**
  - Treatment mode: reamo, chemo, beamo (EG Shaw)
    - none, one, all three? 10-30% NSCLC patients stage changes
  - Radiation treatment fields: ie, inclusion of nodes
    - Estimation – better coverage of target with PET in 30 – 60% of patients receiving definitive radiation treatment*2

Colon Cancer: Possible Treatment Fields

- Initial Staging
  - Simple Field
  - No Treatment
  - Simple Field

- Initial Staging
  - Simple Field
  - No Treatment

- Re-Staging
  - Field Includes Nodal Region

Adapted from Rohren, Turkington, Coleman: Radiology 2004; 231:305-332.

FDG PET and Staging, Localization

- Change in stage before and after PET-CT

<table>
<thead>
<tr>
<th>PET-CT stage</th>
<th>Before PET-CT stage</th>
<th>Change in stage</th>
<th>PET-CT stage</th>
<th>Change in stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>II</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>III</td>
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<td>IV</td>
<td>2</td>
<td>3</td>
<td>IV</td>
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</tr>
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PET and Radiation Treatment Planning

- Secondary contribution – Target Definition
  - Image-based target extent, shape – quantitative
  - Important topic
  - Subject of investigation: concepts, methods, tools

- Secondary contribution – Treatment Monitoring
  - Image-based response and evaluation of treatment
  - Important topic
  - Subject of investigation: concepts, methods, tools

"Secondary" to become "Primary"?
Target Definition

• Qualitative: Expert clinical review
  – Visual, inclusion of clinical history and data
  – Above background

• Quantitative: Voxel intensity values
  – 40-50% of peak intensity (above background?)
  – Standardized Uptake Value (SUV) of ROI
    • i.e., SUV > 2.5 indicates positive for cancer
  – Region determined by PET, extent by CT

FDG PET and Radiation Treatment

Change in PTV and prescribed dose

<table>
<thead>
<tr>
<th>GTV-CT</th>
<th>GTV-PET-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of PET-CT may reduce GTV/CTV</td>
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GTV: CT v PET-CT

Use of PET-CT may reduce GTV/CTV

GTV-CT  GTV-PET-CT


Process: PET in Radiation Treatment

• Cancer diagnosis → biopsy, imaging
• Treatment position, immobilization
• PET imaging in treatment position
• Expert image review
• Image transfer – DICOM, other?
• Image registration (if needed)
• Target localization and definition – method TBA?
• Treatment planning
Radiation Treatment Planning with PET

- Setup reproducibility the primary concern
- Poor setup reproducibility may require deformable image registration

These can be separate units or a combined PET-CT

Patient Positioning And Immobilization

- Flat Tabletop
- Immobilization Device

3-Mode Fiducial Markers

- For face mask patients, markers are attached to the mask
- For body mould patients, markers are attached to the skin
PET-CT Image Registration

Hybrid PET-CT Scanner

- Combined helical, multislice CT scanner mated to a PET scanner
- Possibly three scans acquired during procedure
  - Attenuation correction CT
  - PET: 2D or 3D acquisition
  - Treatment planning CT, with contrast if necessary

Return To Target Definition

- Quantitative: Voxel intensity values
  - 40-50% of peak intensity (above background?)
  - Standardized Uptake Value (SUV) of ROI
    - ie, SUV > 2.5 indicates positive for cancer
    - Region determined by PET, extent by CT
    - Calibrated method for scanner?

Radiation Treatment Planning with PET Target Definition

- Depending on image window and level setting, target volume can change by 50%
- SUV not a part of DICOM data
- SUV utility unclear
**Standardized Uptake Value (SUV)**

- Semi-quantitative measure of glucose metabolism
- Essentially: Average voxel value within an ROI
  - normalized by activity and body weight
- Relative to an individual patient
  - Malignancy vs benign
  - Tumor grade
  - Treatment response
  - Prognosis (?) – biological models

In part from Rohren, Tarkinsson, Coleman: Radiology 2004; 231:305-332

**SUV Limitations**

- Semi-quantitative measure of glucose metabolism
- Definition of the ROI (CT? self-referencing), and its location over time (ie, scan to scan)
- Tumor heterogeneity: necrosis, variable grade
- Tumor volume changes with time
- Small tumors difficult to image (size → resolution)
- Glucose load?
  Consensus? Quantification of FDG uptake?


**SUV Phantom Investigation**

- Threshold SUV-function can be determined via measurement to enable definition of an FDG PET GTV
- Depends on mean target SUV
- May be better than constant-valued SUV (ie, “2.5” or 50% FWHM)
- Difficult for low SUVs (SUV < 2.0)
- Tested in patient population

From Black, Grill, Kestin, et al., JROBP 60(4):1272-1282, 2004

**Approaches to PET-Target Definition**

- 40-50% of peak intensity (above background?)
- Standardized Uptake Value (SUV) of ROI
  - ie, SUV > 2.5 indicates positive for cancer
- Region determined by PET, extent by CT
- Calibrated method for scanner?

In common – digital image with voxel intensities
The Digital Contour
A Threshold Process

FDG PET and CT Image Registration
Original CT defined PTV
Paraesophageal node seen on PET, but not CT

Courtesy of A Kirov, MSKCC
### Target Volume Differences

- New target area not previously covered
- Change in target volume
- Union of CT + PET

### GTV-CT and GTV-PET

Other Issue: Inter-observer Variation

### Other Issue: PET Artifact Near a Cavity

### PET in Brachytherapy

- Applicators, critical structures and tumor contoured
- Software places sources at predefined positions with respect to applicator tips
- Source strengths and treatment times optimized
- Alternatively, deliver conventional dose distributions

**Tilted Coronal View**

- Target
- Tandem
- 65 Gy/hr
- 18 Gy/hr
Non-FDG PET Oncology Imaging
Biological and Molecular Imaging

- Hypoxia: F-misonidazole (U Wash)
- Hypoxia: Cu-ATSM (Wash U)
- Proliferation: C-Thymidine (U Wash)
- Blood flow: Water
- Others: permeability, DNA synthesis, tumor receptors, chemotherapy drugs
  Radiopharmaceutical development important

Does It Matter?
Indicators of Cancer Diagnosis, Treatment, and Evaluation can be Molecularly Imaged

- Hypoxia and indicators/results of hypoxia
- Cell proliferation and cell cycle sensitivity
- Apoptosis
- Growth factors, stroma and vascular environments
- Radiosensitivity and radioresistance
  Molecular Signature

IMT (Thymidine)-SPECT/MRI: GBM
Proliferation
(from Grosu, Weber et al, Technical University of Munich)

Methionine PET: Anaplastic Astro
From Weber, Grosu* et al, Technical University of Munich

* Grosu et al, ASTRO 2002. MET PET delivered additional information in 79% patients with resected gliomas
Bioanatomic Imaging and Treatment
BAIT – Wake Forest University

• Can tumor biology be imaged?
  – MR, MRs, PET, SPECT, fMR
• Can image-based tumor biology direct “biologically correct” cancer therapy
• RTP has been/is anatomically based
• What will molecular images contribute?

Paradigm Shift for Radiation Oncology

a shift to
• Biological and Molecular Target Volumes
• Bio-physical Modeling
• Custom Dose Coverage of Target Volumes
  made possible by
• Quantitative Use of Bio-molecular Images
• Hi-Tech Radiation Treatment, called:
  Intensity Modulated Radiation Treatment

Bioanatomic Brain Tumor Protocol
Goal: Measure Spatial Distribution of Hypoxia

IRB approved protocol
• 5 patients, 1" CNS (GBM)
• CT + MR + PET
• PET Perfusion: O-15 H₂O
• PET Hypoxia: F-18 F-Misonidazole

PET Scan Sequence
• Attenuation, ring source
• Timing: 50 mCi O-15 H₂O
• Perf: 2 x 50 mCi O-15 H₂O
• Hypox 1: 10 mCi F-18 miso
• Hypox 2: 10 mCi F-18 miso

Patient 3: Bioanatomic Imaging
F18 Misonidazole PET and MRI Spectroscopy

Applications
• 3D RTP (IMRT)
  • “Biologically targeted” therapy
  • Response assessment

MR Spectroscopy
Conformal Radiation Treatment

- Conventional treatment (rectangular dose distribution)
- Conformal (dose matches target shape)
- Bioanatomic IMRT (dose matches target shape and biology)

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The Ideal Dose Distribution?
A “New” Model

- The target model is wrong!

- Higher Dose
- Lower Dose
- Non-homogeneous dose distribution

Is the target model wrong?

PET Imaging and Biological Models

- Mathematical Representations of Effect
- Model Generation
  - Theoretical models: bio-physio-molecular principles
  - Micro models: fit of bio-molecular observations
  - Macro models: fit of clinical observations
- Model Application
  - Predictive models: guidance of therapeutic decisions
  - Predictive models: estimation of prognosis
- Image-Based: what does voxel intensity mean?

Biological Modeling: Dose Function Histogram
SPECT Lung Perfusion, Normal Tissue Injury
(Munley/Marks, Duke/WFU)

- Normal lung sparing

- Post-treatment
The Digital Imaging Process

- Acquisition Mode/Device
  - MR (MR, mMR, fMR), PET (FDG, hypoxia, perfusion, proliferation); SPECT, Optical (in vivo microscopy, tomography)

- Post Acquisition Processing
  - Reconstruction, Transfer

- Manipulation/Application
  - Classification, Localization, Registration, Segmentation, Measurement [spatial, intensity], Physical and Biological Models

- Secondary Image Generation
  - DRRs, Composite Images

- Display
  - Observation, Evaluation

Digital Imaging and RTP

Image Content and Pixel Meaning

Images provide 3D and 4D information. The challenge is to extract the morphologic, pathologic, biologic, physiologic, or metabolic “meaning” of the image numbers.

Imaging Science Tasks

- Classification/Estimation

- Hypothesis of data, (tumor, kidney)

- Physical and Biological Models

- Imaging Science Tasks

- Classification/Estimation

- Image: SNR, contrast, ...

Four outcomes

- True positive (TP), Sensitivity (TPF)

- False positive (FP), Specificity (1 - FPF)

- True negative (TN)

- False negative (FN)

11C-Methionine PET
Regional Salivary Gland Function

Right side: mean dose 30Gy       Left side: mean dose 57 Gy


a) Volume of distribution of 11C-methionine
b) K, the net metabolic clearance of 11C-methionine

Limitations and Opportunities
PET Oncology Imaging And Treatment

- Image resolution, SNR, specificity, sensitivity
- Scan speed, effects of motion, gating
- FDG and radiopharmaceutical development
- Image registration/image processing tools
- Kinetic modeling
- SUVs, equivalent reference values
- Patient positioning
- RTP target delineation
- RTP dose compartments and resolution

Why Image Patients?
A Picture of the Patient

- The patient is his own best representation
- An image set is only an approximation
- Do we know what the numbers mean?
  “A picture tells…”

Summary

- Physics of PET and PET-CT
- Oncology Imaging with FDG PET
- PET and Radiation Treatment Planning
  - Target definition
- Non-FDG PET Oncology Imaging
- Limitations and opportunities with PET
- Paradigm shift for Radiation Oncology
  - Molecular and Bioanatomical targets/volumes, digital images
    - Biologically optimized “dose” distributions, biological models
- Growth of PET, PET-CT in the RadOnc clinic

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