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

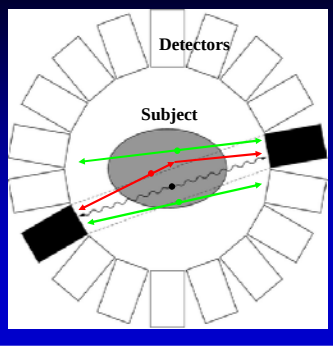
- Coincidence detection of two 0.511 MeV photons
- Annihilation radiation from positron-electron pair
- Photon directions at 180° at annihilation point - different from decay point → range of positron
- Positron emitters with biological compatibility
- Low Z (typically), proton rich, short half-lives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

PET Radionuclides

Radionuclide	Half-Life
Fluorine 18 (^{18}F)	110 min
Carbon 11 (^{11}C)	20 min
Nitrogen 13 (^{13}N)	10 min
Oxygen 15 (^{15}O)	122 sec
Rubidium 82 (^{82}Ru) (cardiac)	75 sec

Coincidences: Detected Events

- True
- Scattered
- Random



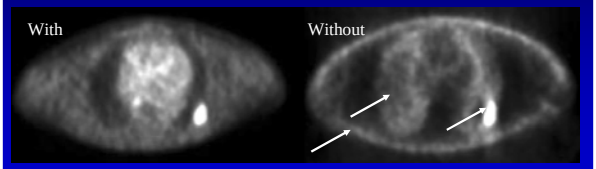
Adapted from Rohren, Turkington, Coleman, Radiology 2004; 231:305-332

PET Device Parameters

- Resolving time – detector material
- Spatial resolution – nominally, detector size
  - 4 to 6 mm (voxel side)
- 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



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

Oncology Imaging with FDG PET

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

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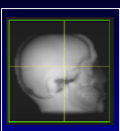
Why PET Oncology Imaging?

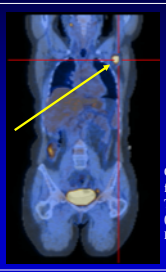
- Distribution of activity is imaged
  - Physiology, function, biology
- Complementary to (~anatomic) CT and MR
- Increased sensitivity compared to CT alone
- Indications approved for reimbursement
  - Most approved indications are for oncology
- Devices available (market saturated?)
- Image handling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

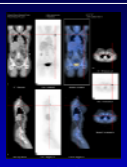
Why PET? A Picture of the Patient



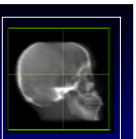
MR "Radiograph"

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





CT-PET Hybrid Imaging for Tumor Diagnosis and Treatment Planning: (Courtesy General Electric Healthcare)



MR "Radiograph" with bone added - the MR is changed into a CT-like radiograph

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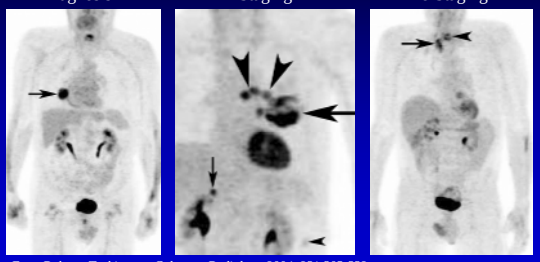
Example: Non-Small Cell Lung Cancer

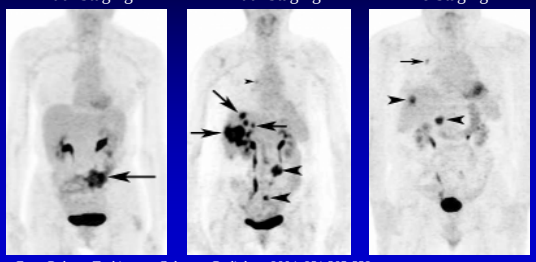
Diagnosis | Staging | Re-Staging



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

Example: Colon Cancer

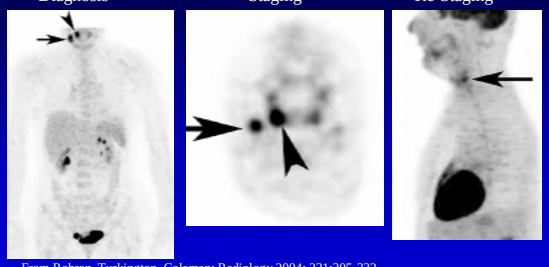
Initial Staging | Initial Staging | Re-Staging



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

Example: Head & Neck Cancer

Diagnosis | Staging | Re-Staging



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Approved Indications: Oncology FDG PET

Cancer	Diagnosis	Staging	Re-Staging	Monitoring (Clin Trial)
Lung	X	X	X	X
Solitary Node	X (Char)			
Colorectal	X	X	X	X
Lymphoma	X	X	X	
Esophageal	X	X	X	X
Head/Neck	X	X	X	X
Breast + mets, recur	X	X	X	X
Thyroid	X	X	X	X
Cervical, + mets?	X	X	X	X
Brain				X
Ovarian				X

Caveat: A summary: Restrictions and latest information on:
http://cms.hhs.gov/manuals/103_cov_determ/ncd103c1_Part4.pdf

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* (?)
- PET-CT hybrid scanners: registration solved

*From Bradley, Thorstad, Mutic, et al., IJROBP 59(1):78-86, 2004.

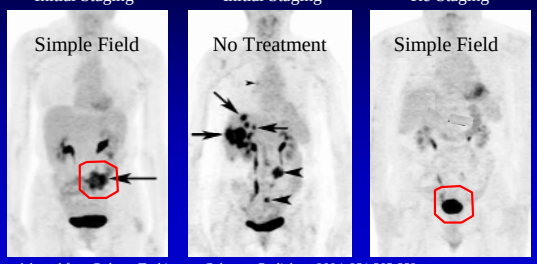
PET and Radiation Treatment Planning

- 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*

*From Bradley, Thorstad, Mutic, et al., IJROBP 59(1):78-86, 2004.

Colon Cancer: Possible Treatment Fields

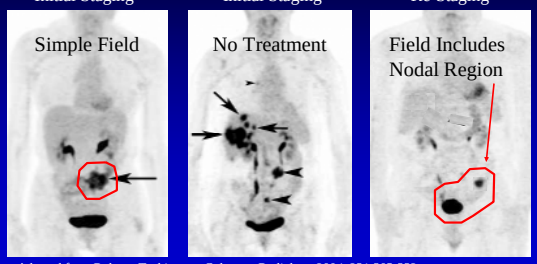
Initial Staging | Initial Staging | Re-Staging



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

Colon Cancer: Possible Treatment Fields

Initial Staging | Initial Staging | Re-Staging



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FDG PET and Staging, Localization

Change in stage before and after PET-CT

Table 4. American Joint Committee on Cancer stage before and after PET-CT.

		No. patients by post–PET-CT stage							
Pre–PET-CT stage	No. patients	I	II	III	IVA	IVB	IVC	Upstage ratio	Downstage ratio
I	1	1	—	—	—	—	—	0/1	0/1
II	2	—	1	—	—	—	1	1/2	0/2
III	10	—	1	8	1	—	—	1/10	1/10
IVA	21	—	—	—	20	—	1	1/21	0/21
IVB	2	—	—	—	—	1	1	1/2	0/2
IVC	0	—	—	—	—	—	—	0/0	0/0
Total	36	1	2	8	21	1	3	4/36	1/36

Abbreviation: PET, positron emission tomography.

From Koshy, Paulino, Howell et al., Head & Neck, 27:6 494-502, 2005.

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
    - ie, 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 5. Summary of changes in management with PET-CT.

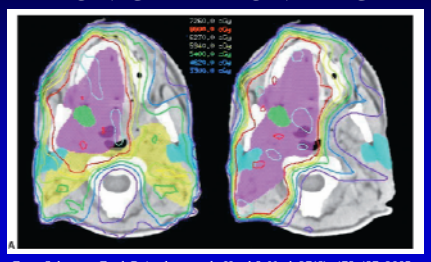
Patient no. and disease site	Pre-PET-CT TNM (AJCC stage)	Post-PET-CT TNM (AJCC stage)	Management changes
1 Maxillary sinus	T3N2M0 (III)	T4aN0M0 (IVA)	Increase in PTV to encompass tumor identified on PET
2 Unknown primary (base of tongue)	T0N2bM0 (IVA)	T1N2bM0 (IVA)	Decrease in initial PTV as primary site was found (nasopharynx not included); primary tumor in oropharynx received higher RT dose
3 Unknown primary (vallecula)	T0N1M0 (III)	T1N1M0 (III)	Decrease in initial PTV as primary site was found (nasopharynx not included); primary tumor in oropharynx received higher RT dose
4 Tonsil	T2N2bM0 (IVA)	T3N2cM0 (IVA)	Increase in PTV to include PET identified tumor extension to deep muscles of tongue and contralateral (right) neck disease; increase in RT dose to right neck
5 Larynx	T2N0M0 (II)	T3N2cM1 (IVC)	Diffuse metastatic disease and bilateral neck metastasis seen only on PET; RT intent changed from curative to palliative; RT volume decreased to include only esophageal mass causing dysphagia; and RT dose decreased to palliative 30 Gy
6 Tonsil	T2N1M0 (III)	T3N0M0 (III)	No change in RT dose or volume; based on the finding of N0 status with PET, a decision to not give chemotherapy and treat with RT alone

From Koshy, Paulino, Howell et al., Head & Neck, 27:6 494-502, 2005.

GTV: CT v PET-CT

Use of PET-CT may reduce GTV/CTV

GTV-CT GTV-PET-CT

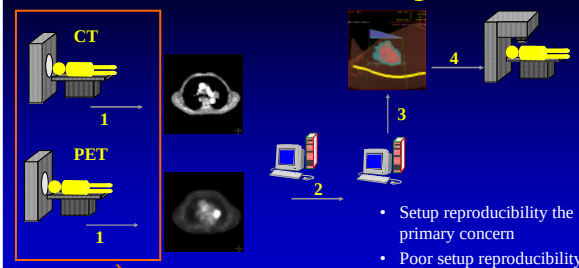


From Schwartz, Ford, Rajendran, et al., Head & Neck 27(6): 478-487, 2005.

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

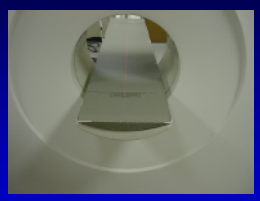
Radiation Treatment Planning with PET



These can be separate units or a combined PET-CT

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

Patient Positioning And Immobilization



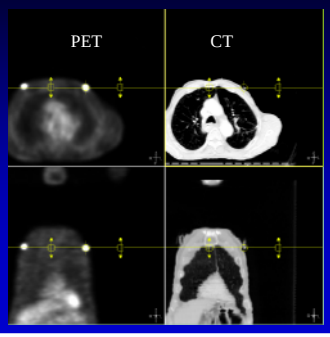
Flat Tabletop

Immobilization Device

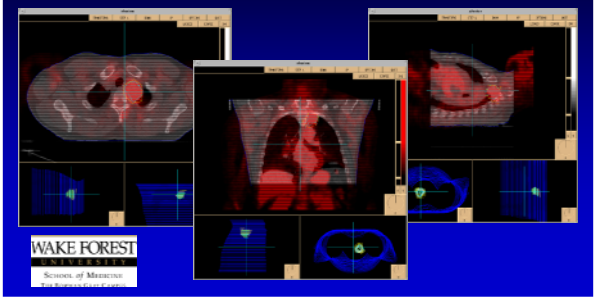
3-Mode Fiducial Markers

- For face mask patients, markers are attached to the mask
- For body mould patients, markers are attached to the skin

3-Mode Fiducial Markers



PET-CT Image Registration



Hybrid PET-CT Scanner

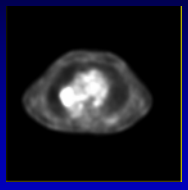
- Combined helical, multislice CT scanner mated to a PET scanner
- Possibly three scans acquired during procedure
  - Attenuation correction CT
  - PET: 2D or 3D acquisition
  - Treatment planning CT, with contrast if necessary

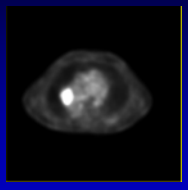
Return To Target Definition

- 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 v benign
  - Tumor grade
  - Treatment response
  - Prognosis (?) – biological models

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

SUV Limitations

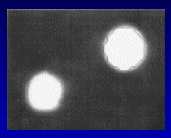
- Semi-quantitative measure of glucose metabolism
- Definition of the ROI (CT? self-referencing), and its location over time (ie, scan to scan)
- Tumor heterogeneity: necrosis, variable grade
- Tumor volume changes with time
- Small tumors difficult to image (size → resolution)
- Glucose load?

  Consensus? Quantification of FDG uptake?

In part from Greven: Sem Rad Onc 14:2, 2004.

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



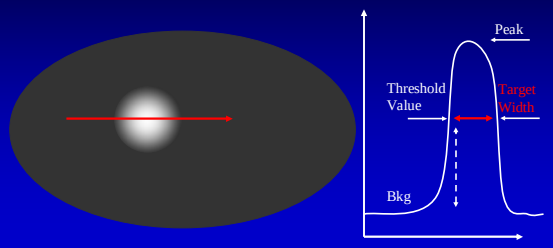
From Black, Grills, Kestin, et al., IJROBP 60(4):1272-1282, 2004

Approaches to PET-Target Definition

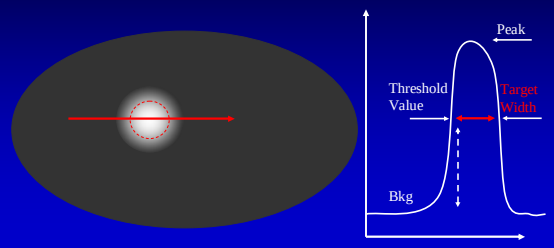
- 40-50% of peak intensity (above background?)
- Standardized Uptake Value (SUV) of ROI
  - ie, SUV > 2.5 indicates positive for cancer
- Region determined by PET, extent by CT
- Calibrated method for scanner?

In common – digital image with voxel intensities

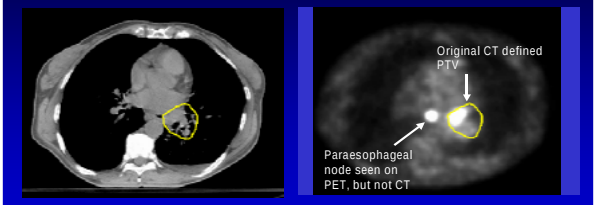
The Digital Contour
A Threshold Process



The Digital Contour
A Threshold Process

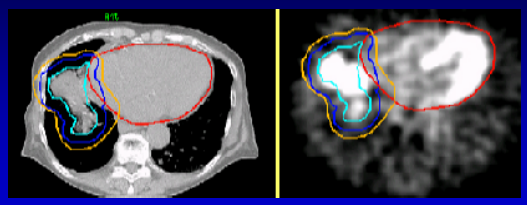


FDG PET and CT Image Registration



Courtesy of A Kirov, MSKCC

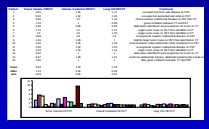
FDG PET and CT Image Registration

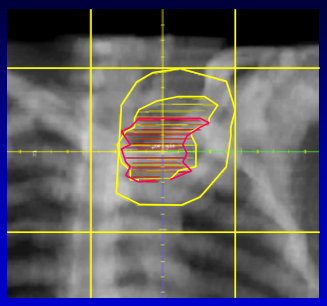


Courtesy of A Kirov, MSKCC

Target Volume Differences

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

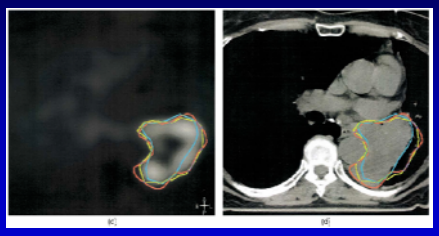




Tomlinson, Russo, Bourland: ASTRO 2000

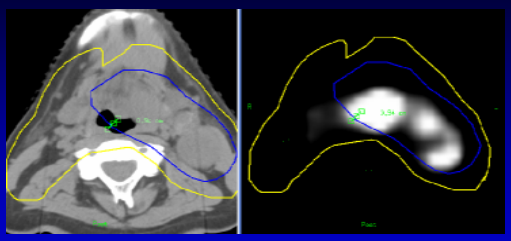
GTV-CT and GTV-PET Other Issue: Inter-observer Variation

PET CT



From Caldwell, Mah, Ung, et al., IJROBP 51(4):923-931, 2001

Other Issue: PET Artifact Near a Cavity

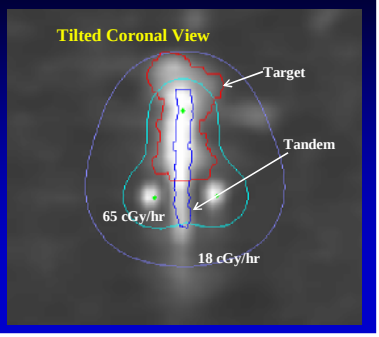


RT planning contours displayed on registered CT (left) and PET (right) images from a PET/CT scan, showing PET signal appearing to originate from a ~1 cm wide air cavity inside the trachea.

Courtesy of A Kirov, MSKCC

PET in Brachytherapy

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



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?

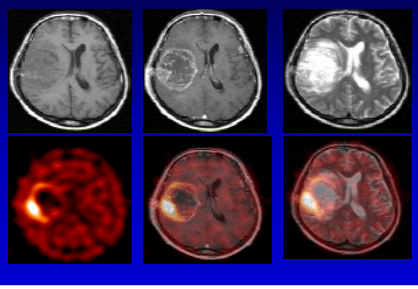
Indicators of Cancer Diagnosis, Treatment, and Evaluation can be Molecularly Imaged

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

Molecular Signature

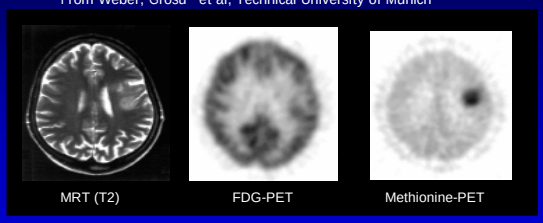
IMT (Thymidine)-SPECT/MRI: GBM Proliferation

(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

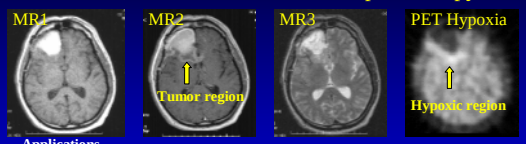
- 5 patients, 1° CNS (GBM)
- CT + MR + PET
- PET Perfusion: O-15 H_2O
- PET Hypoxia: F-18 F-Misonidazole

PET Scan Sequence

- Attenuation, ring source
- Timing; 50 mCi O-15 H_2O
- Perf; 2 x 50 mCi O-15 H_2O
- Hypox 1; 10 mCi F-18 miso
- Hypox 2; 10 mCi F-18 miso

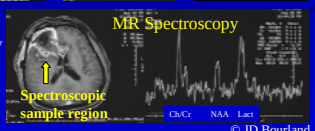
Patient 3: Bioanatomic Imaging

F18 Misonidazole PET and MRI Spectroscopy

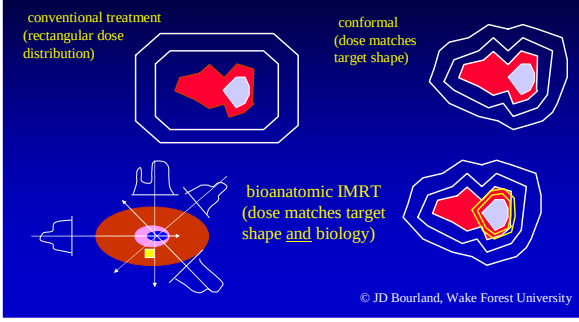


Applications

- 3D RTP (IMRT)
- "Biologically targeted" therapy
- Response assessment



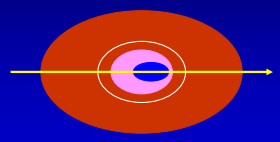
Conformal Radiation Treatment



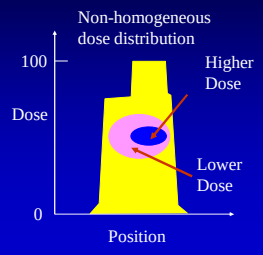
The Ideal Dose Distribution?

A "New" Model

The target model is wrong!



Is the target model wrong?



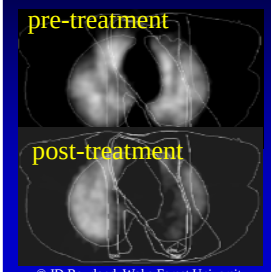
PET Imaging and Biological Models

- 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?

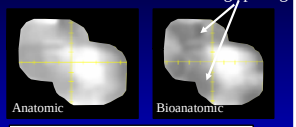
Biological Modeling: Dose Function Histogram

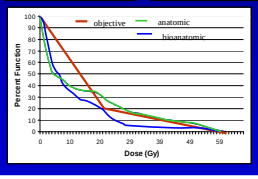
SPECT Lung Perfusion, Normal Tissue Injury

(Munley/Marks, Duke/WFU)

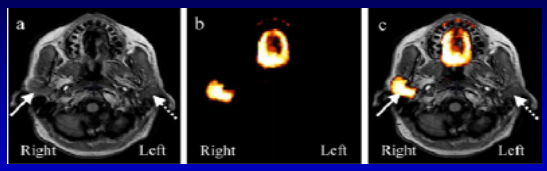


Normal lung sparing





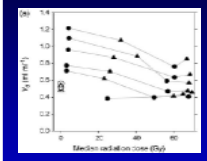
11C-Methionine PET
Regional Salivary Gland Function

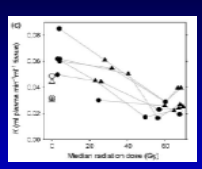


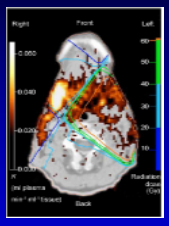
Right side: mean dose 30Gy Left side: mean dose 57 Gy

Buus *et al*, Radiotherapy and Oncology 73:289-296, (2004).

11C-Methionine PET
Regional Salivary Gland Function







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

Buus *et al*, Radiotherapy and Oncology 73:289-296, (2004).

The Digital Imaging Process

- Acquisition Mode/Device
  - MR (MR MRs, pMR, 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.

CT: electron density (attenuation, dose)
MR: proton density, magnetic moment (?)
PET: radionuclide distribution (physiology?)
SPECT: radionuclide distribution (physiology ?)
Other: What does a pixel mean?

Imaging Science Tasks
Classification/Estimation
Hypothesis of data, (tumor, kidney)
Sample object
→ image: SNR, contrast, …

Imaging Science Tasks
Four outcomes
- True positive (TP); Sensitivity (TPF)
- False positive (FP); Specificity (1 - FPF)
- True negative (TN)
- False negative (FN)

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

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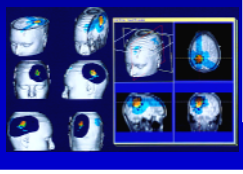
Why Image Patients?
A Picture of the Patient

- The patient is his own best representation
- An image set is only an approximation
- Do we know what the numbers mean?

"A picture tells …"



A collage showing where tumor has regressed, stayed the same, or grown.

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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