PET is Underutilized in Oncology

Brent D. Murphy, MS, DABR
• President, Radiological Technologies University
  • Nationally Accredited, FAFSA, GI/VA Loan, F-1 Student Visa
  • Offers Degrees in Medical Dosimetry, Medical Physics, MHA, NanoMedicine
• President, ARC
  • Dosimetry and Physics Certification Board Review Courses
• President, Dade Moeller Health Group
  • Physics/Dosimetry Contracts: New Model Maximizing the Dosimetrist
  • Remote Planning Services
  • Other Service Lines: Linac Commissioning, Diagnostic, Nuclear Medicine

Disclosures (Professional)
• Medical Physicist by Trade
• Medical Dosimetrist by Heart
• Not Politically Tactful, Maybe Diplomatic
  • Physicians
  • Medical Physicists
• Collaborative
• Biased Visionary
  • Imaging, Imaging, Imaging…Contouring
  • Plan Metrics
  • Radiobiological Based Treatment Planning
• Billing…
• Medical Dosimetry Practitioner

Disclosures (Personal)
PET is Underutilized

- **By # Procedures Performed**
  - Available Scanner Limited
  - Availability of Isotope(s)
  - Re-Imbursement
- **By Use of Understanding**
  - Oncologists, Radiologists, Technologist
  - Integrated Care Team
- **By Misuse of Understanding**
  - Missed Reads
  - TNM Staging
  - Contouring
  - Use for Evaluating Outcome
- **By Future Potential Uses (Research)**
2,000 PET-CT Units
>1.5M Studies
• Isotope Manufacture
• New Isotopes
• Procedure and Review
  • Prognostic Predictor
  • Scan Frequency
    • Pre-Tx
    • Midcourse Chemotherapy
    • Post Chemotherapy
    • Midcourse RT
    • Post RT
• Integration into Treatment Validation

Pet is Underutilized
Lack of Support for Future Developments
Pet is Underutilized
What is the Solution?

• More Scanners → $$$
• More Cyclotrons → $$$
• More Research → $$$
• New Isotopes → $$$
• Protocol Development → $$
• Insurance Reimbursement → $$
• Training and Education

Least Expensive Fix at this Point
Pet is Underutilized

Outline of this Talk

• Review of PET Principles and What We Know…and May Not Know
• Review of Use for Different Body Sites (Lung / H/N)
• Future Developments
• Role of Medical Dosimetrist with the Advancement of PET
PET Process (A to Z)

- Select Isotopes
- Isotope Production
- Isotope Quality Assurance / Quality Control
- Isotope Shipment, Receipt, and Validation
- Patient Prep, Patient Injection, Patient Rest
- PET Scanning
- PET Scan Read and Evaluation
• Foundation of PET: Select Isotopes B+ Decay and Coincidence Counting

unstable nucleus emits positron

positron annihilates with electron
two 511 photons are emitted simultaneously in opposite directions

TRUE coincidence

PET
Positron Emission Tomography
<table>
<thead>
<tr>
<th>Isotopes Used</th>
<th>T1/2</th>
</tr>
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<tbody>
<tr>
<td>F-18:</td>
<td>110 minutes</td>
</tr>
<tr>
<td>C-11:</td>
<td>20 minutes</td>
</tr>
<tr>
<td>N-13:</td>
<td>10 minutes</td>
</tr>
<tr>
<td>O-15:</td>
<td>2 minutes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short T ½ limits the isotopes that are currently employed</td>
</tr>
<tr>
<td>Range of Distribution from Cyclotron is dictated by the half life</td>
</tr>
<tr>
<td>F-18 FDG is the predominant isotope used</td>
</tr>
<tr>
<td>Radius of Distribution for most suppliers is 2-4 hours</td>
</tr>
</tbody>
</table>
PET Tracer: FDG

18F-fluorodeoxyglucose (FDG) is taken up by cells proportionate to their metabolic rates.
### Patient Prep

- Patient preparation:
  - Fast for 6 hours
  - High Protein, Low Carb Diet
  - Avoid Strenuous Exercise
- Blood sample for glucose (no hyperglycemia)
- Wear Warm Clothing

### Injection & Wait

- Injection: 10mCi – 15mCi FDG
- Wait for 30min, 60min, 120min
- Relaxation Room
- No Speaking
- Little Motion
- Urinate Prior to Study
PET Scanning Principles
• PET/CT Protocol
• Standard Body PET/CT
• Uptake Time – 60 minutes
• Patient Positioning – Head First, Supine with arms above the head (for optimal thoracic imaging).
• Scan Length – Base of Skull to the mid-thigh (from just Inferior to the eyes to between the Pelvis and the Knees)

**Scan Duration – 15 - 30 minutes (generally 8 - 10 bed positions)**
• 1.5 minutes per bed position for patients with BMI < 25
• 2 minutes per bed position for patients with BMI between 25 and 30
• 3 minutes per bed position for patients with BMI ≥ 30

• Scan Direction – From Head toward Feet

**PET Scanning Protocol (Body)**
• 1. Normal Uptake
• 2. Sensitivity / Specificity
  • 2a. Shortcoming: False –
  • 2b. Shortcoming: False +
• 3. Shortcoming: Registration
• 4. Detection / Staging
• 5. SUV & Contouring
• 6. Evaluate Tx Response
• 7. Prognosis Predictor

Educating, Re-educating, Advancing
1. Normal Uptake
   Normal PET - CT Body Scan
1. Normal Uptake
Abnormal PET - CT Body Scan

Ref 4
• PET-CT Sensitivity and Specificity is greater than that for CT or MRI for many body sites. PET is considered to be superior for nodal involvement and distant metastases.
• True positive: Sick people correctly diagnosed as sick

• False positive: Healthy people incorrectly identified as sick

• True negative: Healthy people correctly identified as healthy

• False negative: Sick people incorrectly identified as healthy
sensitivity = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}} = \frac{\text{number of true positives}}{\text{total number of sick individuals in population}}

= \text{probability of a positive test, given that the patient is ill}

specificity = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}} = \frac{\text{number of true negatives}}{\text{total number of well individuals in population}}

= \text{probability of a negative test given that the patient is well}
<table>
<thead>
<tr>
<th>Staging</th>
<th>Sensitivity (%) FDG-PET</th>
<th>Sensitivity (%) CT</th>
<th>Specificity (%) FDG-PET</th>
<th>Specificity (%) CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>83</td>
<td>64</td>
<td>91</td>
<td>74</td>
</tr>
<tr>
<td>Head / Neck Cancer</td>
<td>87</td>
<td>62</td>
<td>89</td>
<td>73</td>
</tr>
<tr>
<td>Esophageal Cancer</td>
<td>73</td>
<td>50</td>
<td>90</td>
<td>69</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>90</td>
<td>81</td>
<td>93</td>
<td>69</td>
</tr>
<tr>
<td>Gyn: Ovarian, Cervical, Uterine</td>
<td>54</td>
<td>48</td>
<td>96</td>
<td>76</td>
</tr>
</tbody>
</table>

PET-CT Sensitivity / Specificity
2a. False Negatives

Sick people incorrectly identified as healthy

- Histology
  - Low-grade glioma
  - Low-grade lymphoma
  - Bronchoalveolar lung cancer
  - Hepatoma
  - Renal cell carcinoma
  - Prostate cancer

- Size < 10mm
- Post prandial scans
- Hyperglycemia
  - > 150 mg/dL
56 year man with HCV, end stage liver disease, and presumed hepatoma
57 year old man with stage IV left tonsillar scca treated with chemoradiation 21 months ago. Patient was lost to follow-up until he was referred for PET/CT. Coronal images show low FDG uptake in the brain, and high uptake in the heart and skeletal muscles.
69 year old man with 2.3 cm RUL NSC lung cancer. FBS = 309 mg/dL. No insulin was given. Coronal images show a good quality scan with high FDG tumor uptake (max SUV 5.4)
63 year old man with 5 cm RUL adenocarcinoma. FBS = 299 mg/dL; 90 minutes after 15u of reg insulin IV FBS = 179 mg/dL at which time FDG was injected. Coronal images show a “muscle scan” with faint tumor uptake (max SUV = 2.0)
2b. False Positives
Healthy people incorrectly identified as sick

- Normal physiology
- Granulomas and other infections
- Adenomas
Physiologic Uptake

FDG subcutaneous infiltration

Ref 4
Physiologic Uptake
Tonsillar Hyperplasia
Physiologic Uptake

Ref 4:
Nodular Hyperplasia

74 y/o man with metastatic disease to neck from unknown primary, now NED after chemoXRT

Ref 4
Physiologic Uptake: Brown Fat
• What is Brown Fat Artifact?
  • Increased Uptake in Areas of Supraclavicular, Mediastinal, Paraspinal Area
  • If Cold or Tense, glycolysis in Brown Fat is increased

• Methods to Reduce Brown Fat Artifact
  • Reassurance
  • Heat
  • Sedatives
  • Beta Blockers
Adenoma

63 y/o man 4 months post chemoXRT for R tonsil cancer
T2N1M0

Ref 4
Infection

68 year old man with solitary lung nodule. Biopsy: aspergillosis (fungal infection)
• False negative FDG PET *can be reduced by* careful patient selection for appropriateness and proper preparation

• False positive FDG PET *can be reduced by* correlation with CT and knowledge of potential pitfalls
3. Registration & Artifact

- Motion Artifact
- Attenuation Artifact
- Metal Artifact
- Contrast Artifact
• T-Staging: Would not typically be used solely for T-staging (typically based on size of tumor) due to resolution issues.
• M-Staging: Metastatic Disease.

4. Detection / Staging
Physiology of FDG tumor uptake

FDG signal in tumor is dependent on 1) delivery (blood flow), 2) transport into the cells, and 3) phosphorylation.

FDG tumor uptake ~ number of viable cancer cells
• Distinguish between tumor uptake and normal tissue uptake
Lung
Colo-Rectal
Detection: Lung Tumor showing active and necrotic areas
• Does it Really Make a Difference?

5. SUV & Target Contouring (w/o PET vs with PET)
• SUV Defined: Tissue Concentration / (Activity Injected / Body Weight)
• Semi-Quantitative Value that is Simple
• SUV of 2.5 or higher is considered to indicative of malignant disease
• Conversely
  • Non-malignant tissues can read around 2.5
  • Small Tumor may have SUV < 2.5
• Region of Interest Defined
• Activity Injected
• Plasma Glucose Levels
• Competition with Endogenous Glucose
• Rate of Phosphorylation
• Body Size and Body Composition
• Tumor Type
• Scanner SNR Properties
• Image Reconstruction Algorithm
• Time Between Image Injection and Acquisition

Standard Uptake Value Dependencies
# Standard Uptake Values

<table>
<thead>
<tr>
<th>Tumor Type / Tissue Type</th>
<th>Range of Average SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Liver</td>
<td>1.7 – 2.7</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>3.2 – 6.5</td>
</tr>
<tr>
<td>Head and Neck SCC</td>
<td>3.2 – 9.4</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>3.5 – 12.8</td>
</tr>
<tr>
<td>Non Hodgkin’s Lymphoma</td>
<td>8.0 – 12.5</td>
</tr>
</tbody>
</table>
• FDG-PET has been shown to have greater sensitivity and specificity compared to CT and MRI.

• Aid in reducing the risk of Geographic Miss of Primary Tumor and Lymphatics

• Minimize Volume of Normal Tissue included in the PTV
• Patient Management
• Size and Shape of GTV and Subsequent PTV
• Observer Variability
• Radiation Technique and Dose Escalation
Impact of PET-CT on Targets

Patient Management

- Upstaged (20%-30%)
  - Curative to Palliative
  - Change in TNM Staging (as high as 36% change)
    - Lung
    - Head / Neck
    - Esophagus

- Debbie Downer
- Theoretically, the use of PET in Target Delineation should improve Outcomes
- Not demonstrated Yet
- However, PET Based Staging seems to be Predictive

Ref 5
<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th># of Scans</th>
<th>% Change in Intended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>5,309</td>
<td>35.1</td>
</tr>
<tr>
<td>Ovary</td>
<td>4,509</td>
<td>41.4</td>
</tr>
<tr>
<td>Bladder</td>
<td>3,578</td>
<td>37.9</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3,314</td>
<td>39.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>3,025</td>
<td>36.9</td>
</tr>
<tr>
<td>Small Cell Lung</td>
<td>2,983</td>
<td>41.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>2,877</td>
<td>35.8</td>
</tr>
<tr>
<td>Uterus</td>
<td>2,869</td>
<td>36.5</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1,784</td>
<td>48.7</td>
</tr>
<tr>
<td>Connective Tissue</td>
<td>1,350</td>
<td>36.4</td>
</tr>
<tr>
<td>Nonmelanoma skin</td>
<td>1,057</td>
<td>31.4</td>
</tr>
<tr>
<td>Liver and intrap hepatic bile ducts</td>
<td>1,038</td>
<td>42.9</td>
</tr>
<tr>
<td>Cervix</td>
<td>984</td>
<td>32.7</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>806</td>
<td>39.7</td>
</tr>
<tr>
<td>Other female genital</td>
<td>709</td>
<td>37.1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>629</td>
<td>35.6</td>
</tr>
<tr>
<td>All other</td>
<td>4,042</td>
<td>36.6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>40,863</td>
<td>38.0%</td>
</tr>
</tbody>
</table>
• PET can only be used to refine differences greater than or equal to the spatial resolution of the PET Scanner employed
• By Theory: 4mm at Best
• Clinically: 5mm-7mm

• **Lung**
  • PET significantly alters target volume in 60% of patients
  • Most result in increase of volume

• **Head/Neck**
  • PET-CT based GTV was smaller in 75% as compared to CT
  • Pathological Confirmation: PET volume most accurate as compared to CT and MRI (Laryngeal Cancers)

• **Esophagus**
  • PET-CT Based Length best matched EUS
  • Volumes not reduced on (-) PET
  • Volumes Expanded on a (+) PET

**Impact of PET-CT on Targets Size and Shape of GTV and Subsequent PTV**
• Observer Variability
• Sites with Highest Variability
  • Lung:
  • Head / Neck
  • Esophagus
• Great Impact on Target Delineation

• Lung: Variables
  • Selection of Window
  • Atelectasis
  • Pneumonitis
  • Tumor Motion
  • Imaging Expertise

• Lung Metrics
  • Concordance Index: Defined
  • Max/Min Ratio: As high as 7.6

Impact of PET-CT on Targets
Observer Variability
Impact of PET-CT on Targets

Observer Variability: Change W/L
Impact of PET-CT on Targets
Radiation Technique and Dose Escalation

• Retrospective Studies: 3D, NSCLC
  • Evaluation of Coverage of CT Based Target vs PET-CT Based Target
  • 26% of cases, Min Dose to PTV was less than 25%
• Retrospective Studies: IMRT, H&N SCC
  • Evaluation of Coverage of CT Based Target vs PET-CT Based Target
  • 25% of cases, Min Dose to GTV was less than 95%
• What is the optimal PET volume for Radiation Therapy? The Tumor’s Edge
• Who needs to contour this volume?
• *Threshold Techniques Using SUV (2.5)*
• Voxel Values in PET images are related to Activity (Bq/cm³)
• Range of Values can be great based on Tumor inhomogeneity
• Range from 2,000 to 20,000

**Defining the Target**
**Qualitative Segmentation: Visual**
• Window/Leveling will alter apparent size and shape
• In PET, this effect is pronounced due to large range of intensity values

• Appropriate W/L Depends on:
  • Vendor normalization method
  • Size of Patient
  • Radiotracer Uptake by Surrounding and Non Malignant Tissues

Defining the Target
Qualitative Segmentation: Visual
Defining the Target
Quantitative Segmentation

• Thresholding: Selecting a Value
  • Low Threshold Value: Larger Volume
  • High Threshold Value: Smaller Volume
  • Thresholds: 40% of Max
  • Lung Thresholds: 15% of Max (accounts for Motion)

• Thresholds will Dependent on:
  • Background
  • Tumor Type and Location
  • Tumor Size
  • PET Resolution
Quantitative Segmentation
Threshold: 40% and 30% of Max
SUV & GTV Delineation

Clearly Defined Lung Tumors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SUV Max</th>
<th>GTV (Visual) (cc)</th>
<th>GTV 2.5 (cc)</th>
<th>GTV 40% (cc)</th>
<th>GTV Auto (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>14.7</td>
<td>66.5</td>
<td>64.8</td>
<td>26.1</td>
<td>28.5</td>
</tr>
</tbody>
</table>

Ref 8
<table>
<thead>
<tr>
<th>Author (Ref)</th>
<th>Method of Target Delineation</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paulino</td>
<td>50% Isointensity Level</td>
<td>25% of Patients under-treated with IMRT when PET-GTV not used</td>
</tr>
<tr>
<td>Heron</td>
<td>Visualization</td>
<td>40% Patients had additional disease not visualized on CT</td>
</tr>
<tr>
<td>Wang</td>
<td>SUV 2.5</td>
<td>In 50% of cases, PET-CT based GTV different from CT-based GTV</td>
</tr>
<tr>
<td>Ashamalla</td>
<td>Halo</td>
<td>68% had significant GTV modification based on use of PET/CT</td>
</tr>
<tr>
<td>Geets</td>
<td>Segmentation Algorithm</td>
<td>PET-GTV significantly smaller than CT or MRI based GTV. Decreased dose to ipsilateral parotid glands.</td>
</tr>
</tbody>
</table>
### Frequency
- Midcourse TX Chemotherapy
- Midcourse TX Radiation Therapy
- Post Treatment Evaluation
- Follow Up Frequencies

### Evaluate
- Primary Disease Site / Size
- Lymphatic Sites / Size
- SUV Values
- Distant Metastases

6. Evaluate Tx Response
Pre and Post Tx: 2 Cycles Chemotherapy
PET Negative, CT Positive
Monitoring Response

63 year old man stage 3A lung cancer, has received 4 cycles of chemotherapy
Evaluate Tx Response: Esophagus
Evaluate Tx Response: Lymphoma: Post Chemotherapy

Ref 7
GTV Reduction after 1 and 3 Rounds of Chemotherapy
PET-CT GTV Reduction after 3 Rounds Chemotherapy
• Can Pre-Course PET be used to Predict Outcome?
• Can Mid-Course PET be used to Predict Outcome?
• Can Post-Tx PET be used to Predict Outcome?
• What are the key factors?
  • Max SUV
  • Avg SUV
  • New Metrics

7. Prognosis Predictor
• Normal Anatomy
• Treatment Related Side Effects
• **Artifacts:**
  • *Attenuation Correction Artifacts*
  • *Patient Motion Between Scans*
• Patient Position: Use Appropriate Immobilization
• Target Delineation

**Head & Neck**

Problems with PET-CT Target Delineation
• Uptake in:
  • Skeletal Muscle with Exercise
  • Breathing Muscles with Hyperventilation
  • Cervical Muscles with Tension
  • Laryngeal Muscles with Vocalization
  • Salivary Glands

Head & Neck
Problem: Normal Anatomy
• Inflammatory conditions can be manifested with increased FDG uptake

• Post Treatment: *Wait 3 months* to assess cervical nodal disease

• *Radiation Pneumonitis*: mimics an infection or malignant neoplasm

**Head & Neck**  
**Problem: Treatment Related Side Effects**
Contouring Techniques
- Visualization is Most Common
- Threshold Based: SUV of 2.5 – 3.0
- Threshold Based: SUV 50% of Max

Why so important?
- Some literature notes that a 5% change in threshold contour level can translate into a 200% change in volume.
• SUV Threshold Techniques

• **Difficulty**
  • *Motion Blurs Out Concentration (SUV Value)*
  • *Inhomogeneity of Uptake within tumor mass*
  • *Low SUV due to Partial Volume Effect with Small Nodes*

• Halo Technique: SUV: 2.0 +/- 0.4

• Spatial Resolution of PET: 6mm
  • Cell Density
  • Range of Positron in Different Tissue

**Lung (NSLC)**

**Problem: Tumor Edge Definition**
• Significant Image Blur: Scans take Several Minutes
  • Respiratory Motion
  • Cardiac Motion
• Solutions:
  • Gated Image Acquisition
  • Image Reconstruction Techniques
• Improved Protein Synthesis Techniques → “virtually any physiologic molecule can be labelled with a positron emitter and images using PET technology”

• Development
  • Viability Agents
  • Labeled Amino Acids
  • Labelled Fatty Acids
  • Labeled monoclonal antibodies

Future Advancement of PET Radiotracers for Targeting
Future Advancement of PET
Hardware / Software Technology

• Scanner Technology
• PET Mammography
• PET Probes
• Reconstruction Algorithms
• Body Specific Imaging
• Respiratory Gating
• Use of Microspheres and Future Nanoparticles
• Dual Labelled Isotopes
  • Tagged with a Therapy Isotope
  • Tagged with an Imaging Isotope
• Y-90 Microspheres for Metastatic Liver Cancer
• Tag the Y-90 Microsphere with \( ^{86}B^+ \) Emitter
Role of the Medical Dosimetrist in the Advancement of PET

• **Technical Expert with PET for the Department**
  • Engaged in PET-CT Simulation Process
  • Engaged with the Protocol Development
  • Imaging Anatomy Expert
    • Fusion
    • Contouring
    • Targeting
  • Engaged in the Treatment Evaluation Process using PET
  • Metrics, Metrics, Metrics

• **Medical Dosimetry Practitioner**
• **Internal Study (Retrospective or Prospective)**
• 2 Physicians (Key!); Remember this is Educational
• 20 Lung Patients
• Plans Generated
  • CT Based Target
  • PET-CT Based Target
• **Contour Metrics Evaluated**
• **Plan Metrics Evaluated**
• **Lessons Learned**

**Championed Project**

**Ref: UO Health Science Center Study**
References

1. PET-NET and others
2. Isotope Production Ref Presentation
4. Segal, MD, Stanford Presentation
5. Paulino, PET-CT in RT Planning, 2008
10. Ortega, UOHSC, “Utilization of FDG PET-CT in Target Volume Delineation”
• PET is imperfect
• PET is yet to be explored
• PET Training / Education is Needed for Staff
• PET has played a major role in RT
• PET can play an important role over the next decade in RT
  • Prognostic Predictor
  • Staging
  • Target Delineation
  • Treatment Evaluation
• Future Developments Should be Supported