INTRODUCTION TO CLINICAL PET

OBJECTIVES

UPON COMPLETION OF THIS PROGRAM, PARTICIPANTS WILL BE ABLE TO COMPLETE THE TASKS LISTED HERE:

- Explain how the biomarker F-18 FDG provides useful metabolic information used in the early detection of cancer.
- Describe the unique clinical information that PET imaging using F-18 FDG provides in the T-N-M staging process of cancer.
- Define the primary differences between anatomic imaging with CT or MR and functional imaging with PET imaging.

INTRODUCTION

PET is the most advanced medical imaging technique available today. PET is based on imaging metabolic processes in the body. Since metabolic changes generally precede changes in anatomy, PET can often detect cancer sooner, or identify the full extent of disease more accurately, than CT, MRI or other anatomic imaging modalities.

PET is based on $^{18}$F-Fluoro-deoxyglucose (FDG) – a positron emitting radiopharmaceutical.

CLINICAL FOCUS

- Oncology 60-90%
- Cardiology 10 – 40%
- Neurology 0 – 10%
- At a typical clinical PET center, over 90% of clinical PET studies performed today are oncology procedures.
PET imaging takes advantage of the many unique characteristics of cancer cells. Cancer cells grow rapidly and exhibit elevated rates of consumption of energy sources such as glucose, carbohydrates, and the DNA building blocks of amino acids and proteins. Shown here are some metabolic differences between normal tissue and cancer tissue.

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**CANCER TISSUE**

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**Cancer Tissue**

- There are many metabolic differences between normal tissue and cancer

  **Cancer tissue:**
  - Increased glycolysis (rate of glucose, or sugar, consumption)
  - Increased protein synthesis
  - More anoxic and hypoxic cells (abnormal reduction of O\textsuperscript{2} content)
  - Increased or decreased number of receptors
  - Increased DNA synthesis
  - Increased blood flow
  - Increased amino acid transport

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**F-18 FDG PET PHYSIOLOGY**

The most common radiopharmaceutical used in PET imaging is F-18 FDG (2-Fluoro-deoxyglucose.) FDG is a normal glucose molecule where one hydroxy group (OH-) has been replaced by a fluoride ion (F-).

While this small modification to the glucose molecule has no effect on the rate at which glucose is transported across the cell membrane, once inside the cell the FDG becomes trapped. After entering a cell, normal glucose is converted to glucose-6-phosphate by hexokinase.

That phosphate molecule is then metabolized into carbon dioxide and water via the Krebs cycle. In this way, glucose contributes energy to the cell for growth.
Similarly, FDG is metabolized by hexokinase to FDG-6-phosphate, but at that point the molecule becomes *trapped in the cell* and no further metabolic breakdown takes place.

In fast growing cancer cells, glucose is pulled across the cell membrane and into the cell at an elevated rate compared to normal, healthy cells, as is the FDG.

The faster FDG enters a cell, the faster the FDG-6-phosphate accumulates in the cell. When FDG is labeled with positron emitting $^{18}$F, we see an accumulation of $^{18}$F activity in cells with high consumption rates of glucose.

In other words, cancer cells collect large amounts of positron emitting $^{18}$F-FDG-6-phosphate and can be identified as hot spots on a PET scan.

**POSITRON ANNIHILATION**

When a positron decay event occurs, a positively charged particle with the mass of an electron is emitted from the nucleus of an atom. That particle is called a positron.

The positron is emitted with an energy that is unique to the nuclide that has decayed (e.g. fluorine-18). After being emitted the particle will slowly lose energy as it travels some distance (the particle range) that is proportional to the energy emitted.

When the positron comes nearly to a stop it will combine with an electron in an annihilation event. During annihilation, the positron and electron convert their mass entirely into energy. This energy is dispersed in the form of two 511 keV photons that generally travel apart at 180º.

These two gamma rays (photons) can be detected by a PET scanner and used to identify the location of the positron decay in a patient.
Therefore, if there is an accumulation of positron-emitting $^{18}$F-FDG anywhere in the patient, the PET scanner will identify the location of the source of positrons, or the location of the accumulated FDG. This indicates the presence of cancer cells, and occasionally infection or inflammation.

Shown here is a description of the positron annihilation.

**Positron Annihilation**

- Positron travels 1-3 mm (depending on energy) and annihilates with electron.
- The mass in the two particles is converted into energy.
- The energy is ALWAYS conserved in the form of two 511 KeV photons.
- Momentum is conserved by photons traveling at 180° to each other.

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**TNM STAGING**

Nearly all cancers exhibit sharply increased metabolism and almost all cancers are staged according to the TNM system. Staging is the determination of the extent of disease and is used to determine the prognosis or the survival chance of the patient, as well as the appropriate treatment.

Each cancer type has unique definitions for each element of staging. Generally, oncologists will not treat a patient until he/she has been appropriately TNM-staged.

TNM staging defines the:

- Extent of primary tumor (T),
- Nodal involvement (N), and
- Presence of metastatic disease (M).
The T-stage definition may range from T0 to T4. This number describes the location, size and aspect of the primary tumor.

The N-stage may range from N0 to N4. A higher number indicates a larger number of nodes are involved, and the location of nodal involvement.

Finally, the M-stage may range from M0 to M1. M0 indicates the absence of metastatic disease while M1 indicates the presence of metastatic disease.

TNM Staging details are shown here.
"T" STAGING WITH PET

The T-stage is used to make the differential diagnosis, to determine whether there is a malignant tumor present or not. Traditional oncologic diagnostic techniques are often riddled with significant side effects and risk factors. Hence, a less invasive procedure is of value.

Other imaging techniques based on anatomical appearances, such as CT, require the presence of a tumor of significant size before detection is possible. Another issue, if the patient has undergone previous surgery to remove disease in the area of concern then the remaining scar tissue may make the CT very difficult to interpret.

PET imaging is very valuable since it is non-invasive, and more importantly, it frequently detects disease earlier than anatomic imaging methods because changes in metabolism generally precede changes in anatomy.

Also, PET imaging is extremely sensitive and can identify the presence of disease long before it has grown to a detectable size for CT or MRI.
“T” Staging with PET

DIFFERENTIAL DIAGNOSIS ($T_x$)
- Determines if a primary tumor is benign or malignant
- Traditional differential diagnostic techniques are not always risk free (i.e. bronchoscopy, colonoscopy …)
- Anatomical imaging (CT, MRI, US) has limitations due to required tumor size or complications of scar tissue
- Metabolic activity imaging with FDG can show malignancy based on glucose consumption rates
- Be aware: If malignancy is shown, the oncologist will want the answers to the other stages ASAP, preferably in the same imaging run

RECURRENT COLORECTAL CANCER

Colorectal cancer is a great example of the importance of PET imaging. The only cure for colorectal cancer is surgery, so nearly all colorectal patients have surgery early in their course of disease.

Since one-third of all colorectal cancer patients experience recurrent disease within two years, it is common for radiologists to have difficulty interpreting follow-up restaging CT scans due to the presence of scar tissue.

Alternatively, PET imaging easily detects highly metabolic tumor cells, particularly when surrounded by scar tissue which has almost no FDG uptake at all.

The literature shows PET imaging to have a much higher accuracy in the detection of colorectal recurrence. PET diagnostic accuracy for colorectal cancer is >90% while CT accuracy ranges from 50-60%.

**Recurrent Colorectal Cancer**

- 1/3 of all Colorectal Cancers recur within 2 years.
- Detection of local colorectal recurrence

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>92%</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>CT</td>
<td>25-73%</td>
<td>71%</td>
<td>96%</td>
</tr>
<tr>
<td>Barium Enema</td>
<td>80%</td>
<td>45%</td>
<td>85%</td>
</tr>
<tr>
<td>CEA Level</td>
<td>---</td>
<td>59%</td>
<td>84%</td>
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- Despite a negative CT, 25-50% of patients will have non-resectable lesions at time of laparotomy.
- PET has been shown to detect unsuspected lesions in 28% of studies.
“N” Staging with PET

NODAL INVOLVEMENT ($N_x$)
- Indicates the number and location of invaded lymph nodes.
- High end dedicated PET systems will show the 5 mm nodes before any volume change occurs and the CT is still normal.
- Importance of the “N” aspect
  Example: colon cancer

<table>
<thead>
<tr>
<th>5 year survival rate</th>
<th>$T_{1-2} N_0 M_0$</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_2 N_1 M_0$</td>
<td></td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>(with a 21% recurrence rate)</td>
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Colorectal Cancer
CT: Suggests lymph node involvement near the rectal primary
PET: Confirmed CT AND identified unsuspected solitary met in the liver

Large solitary met

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LUNG CANCER

Lung cancer is an important disease when it comes to accurate staging and is an excellent example of the effectiveness of PET imaging.

Nearly 180,000 people present each year with an abnormal chest X-ray. 30% of these people are diagnosed with benign lesions based on the result of their X-rays and are sent home.

Approximately 20-30% of the remaining ~130,000 also present with benign lesions; however, CT alone is not able to differentiate them from malignancy. In the absence of PET imaging, many of these patients would go on to expensive, invasive, unnecessary surgeries.

Studies show that for 1 cm nodules in the lung, CT misses almost 92% of malignant lesions. CT alone had a 60% accuracy rate in lesions over 2 cm in size. When PET imaging was also used on these patients, 32% of the patients were either up-staged or down-staged based on more the accurate PET results.

In a direct head-to-head comparison of PET and CT in the staging of the mediastinum, PET was shown to be 82% accurate versus 52% for CT. In this study, PET changed patient management in 29% of patients.

Lung Cancer Example

- Second leading cause of death behind heart disease
  - 130,000 new cases each year
- 20-30% lesions are benign, but CT cannot differentiate these from the malignancies.
  - Resected Lymph Nodes
    50% are benign, surgery was unnecessary
  - Size of metastatic disease
    | Size   | %         |
    |--------|-----------|
    | 1 cm   | 8%        |
    | 1-2 cm | 30%       |
    | >2 cm  | 60%       |
- PET frequently changes the TNM stage
  - PET increased correctly the TNM in 14%
  - PET decreased correctly the TNM in 18%

Source: Rigo e.a. EANM communication 1997
Lung Cancer N Staging

• Staging the mediastinum, nodal disease
  • Determine surgical candidacy
  • Eliminate unnecessary thoracotomy

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<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>PET</td>
<td>82%</td>
<td>88%</td>
<td>93%</td>
</tr>
<tr>
<td>CT</td>
<td>52%</td>
<td>63%</td>
<td>80%</td>
</tr>
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</table>

• Staging whole body*
  – PET found more malignant lesions and changed patient management in 29% of cases

* “Cancer Management: A Multidisciplinary Approach”; 1996 PRR Huntington NY

"M" STAGING WITH PET

The M-stage indicates the presence or absence of metastatic disease. This is very important to the oncologist because a localized disease may be treatable with surgery and/or radiation therapy. A general chemotherapeutic approach is required if the disease has spread elsewhere in the body.

Many cancer types have typical patterns for the spread of metastatic disease. For example, colorectal cancer typically spreads as a single met in the liver and perhaps a single met in the lung. Other cancer types are much less predictable.
To complicate matters, standard CT protocols often stop at the adrenal gland at the base of the liver and do not scan below that point. If the patient has disease in the abdomen or lower abdomen it is guaranteed to be missed. Melanoma, in particular, requires a full head-to-toe PET study, since it is more likely to spread anywhere in the body.

PET is frequently credited with finding unsuspected disease.

### “M” Staging with PET

**SPREAD OF METASTATIC DISEASE (M<sub>x</sub>)**
- Indicates the number of distant metastases
- Distant metastatic patterns are typical for each cancer type
- Spiral CT screens wide areas for distant mets, but may not see them (iso-dense tissue) or cannot differentiate the benign from malignant masses. Generally doesn’t scan below the adrenal gland.
- Because of the importance of the M-stage, PET oncology exams are always at least partial body scans ranging from at least the neck to the kidneys (lungCa), and generally to mid thigh.
  - Melanoma generally includes a full body scan.

**Lung Cancer**
- Bone Scan: Negative
- PET: Shows primary AND identifies distant met in the right femur
The value of PET imaging is clearly in the power of metabolic imaging versus anatomic imaging. The ability to identify disease prior to visible anatomic changes allows for earlier detection of disease. It also alleviates the uncertainty that anatomical imaging techniques face in the presence of scar tissue.

In addition, for therapeutic monitoring, anatomic techniques can only give information once a structural change in the tumor has occurred.

PET imaging can provide a much earlier indication of the state of the cancer cells and can clearly delineate a reduction in the metabolic rate of a dying tumor.

### PET vs. MRI/CT/US

<table>
<thead>
<tr>
<th>Anatomic</th>
<th>Metabolic</th>
</tr>
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<tbody>
<tr>
<td>Localization of mass</td>
<td>Identification of change in cell biochemistry</td>
</tr>
<tr>
<td>Difficult to differentiate scar tissue from recurrence</td>
<td>Straight forward delineation of disease from scar</td>
</tr>
<tr>
<td>Difficult whole body assessment</td>
<td>30-minute whole body study</td>
</tr>
<tr>
<td>Slow to assess response to therapy, must wait for anatomic change</td>
<td>Fast assessment of therapy effectiveness due to change in metabolism</td>
</tr>
<tr>
<td>Requires concentrations of contrast agents that alter metabolic processes</td>
<td>Trace quantities of FDG do not change metabolism</td>
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WHY USE PET IMAGING IN ONCOLOGY?

PET makes a unique contribution to the TNM staging of cancer that is unrivaled by traditional imaging techniques.

Reimbursed PET Procedures

**Oncology**
- Lung Cancer
- Colorectal Cancer
- Lymphoma
- Melanoma
- Esophageal
- Head & Neck
- Breast (Staging & Therapy Monitoring)

**Cardiology**
- Myocardial Viability
- Myocardial Perfusion

**Neurology**
- Epilepsy
- Alzheimer’s Disease

PET Scan Patient Preparation

- Fast 4-6 hours prior to test
  - Fasting glucose level < 110-130 mg/dL
- 5-15mCi 18F-FDG administered IV infusion
  - Contralateral injection to suspected tumor site
  - Dosage depends on camera type
- Rest in dimly lit room for 30-90 minutes
- Scanning time is 45-60 minutes
  - Depends on camera type and disease type
QUIZ

QUESTION #1
PET imaging is the latest technique available to image:

- Anatomy
- Metabolism

QUESTION #2
The PET radiopharmaceutical, FDG, is used to measure which factor related to cancer cells?

- Increase in protein synthesis
- Increased blood flow
- Increase in glucose consumption

QUESTION #3
Which factor below is NOT true during positron decay?

- Two 511 keV photons are produced
- Photons travel at 180° from each other
- A single electron is emitted from the nucleus of that atom

QUESTION #4
TNM staging is important for oncologists to:

- Schedule frequency of follow-up visits
- Define appropriate treatment
- Order appropriate lab tests

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QUESTION #5

One reason PET is more effective than CT in staging colorectal cancer is:

- PET can easily differentiate cancer from scar tissue
- PET is faster than CT
- PET provides a lower radiation dose to the patient than CT

QUESTION #6

The Rigo, et al, study referenced in this course showed that CT missed what percentage of metastatic disease in lung cancer patients?

- < 10%
- 50%
- > 90%

QUESTION #7

It is important to understand whether there is distant metastatic disease present in order to change from localized therapy approaches (surgery or radiation therapy) to general chemotherapy.

- True
- False

QUESTION #8

Which of the following does NOT describe PET imaging?

- Identifies change in cell biochemistry
- Difficult whole body assessment
- Fast assessment of therapy effectiveness
QUESTION #9

"N" staging indicates:

- Location, size, and aspect of primary tumor
- Number and locations of invaded lymph nodes
- The presence of distant metastases

QUESTION #10

"T" staging indicates:

- Location, size, and aspect of tumor
- Number and locations of invaded lymph nodes
- Presence of distant metastases