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Positron Emission Tomography (PET scans) – what a chiropractor needs to know and when a Chiropractor should order one

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Section I – PET for bone and joint conditions

What is Positron Emission Tomography?

Positron Emission Tomography (PET) is an imaging modality that is greatly expanding in usage, mainly because of its ability to show physiology rather than just anatomy unlike many other imaging modalities.Thus, because this is a growing field, I felt that I needed to research and discuss with you what PET is and when to use it. Plus, is there an application for PET in the chiropractic field?

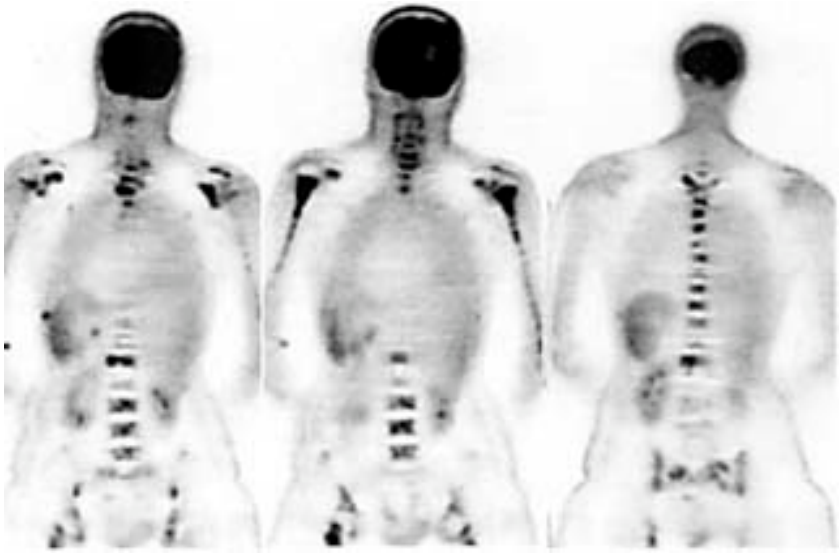

Figure 1. PET of bone courtesy of Jenna Murphy

First, PET is a form of nuclear medicine (Figure 1). The nuclear medicine that you are probably most familiar with is bone scans, used to detect fractures, infections, arthritis, tumors, and osteonecrosis (the bread and butter of chiropractic). The value of both these modalities is they demonstrate metabolic activity and thus present the physiology of the structure instead of just the static anatomy obtained through the classic plain film, computed tomography (CT), and magnetic resonance imaging (MRI). Bone scan and PET produce gamma rays so yes; there is patient dose from ionizing radiation to consider when ordering either modality.

Figure 2. PET scanner

PET uses positron-emitting radionuclides to produce annihilation radiation (Figure 2). This annihilation produces gamma rays that then are received by a detector system. Different radiopharmaceuticals are available for PET imaging and thus depending on the radiopharmaceutical, monitoring of the in vivo activity of glucose, amino acid, phospholipids, receptors, etc. can be imaged. The most common radiotracer used in PET is F-18 fluoro-2-deoxy-D-glucose, known as FDG, which is an analogue of glucose. The patient is given FDG and FDG will emit radiation as it decays. Cells with higher glucose metabolism will accumulate

more FDG and thus more radiation will be emitted from these cells. The gamma detector will receive the emitted radiation and thus an image can be produced showing which body regions are metabolizing the most glucose. Two F18-FDG PET image acquisition frameworks commonly used are static and dynamic acquisitions, with static being more common due to its convenience. In static acquisition, the patient is scanned 60 minutes after the tracer is administered, while in dynamic, continuous imaging occurs over the 60 minutes. What does excessive glucose utilization mean clinically? The main use of PET is in detecting malignant cells. Malignant cells have a greatly increased glucose metabolism compared with the surrounding tissues. This makes since because cancer is nothing more than mutated cells that divide out of control. If the cells are dividing at a rapid rate, they will need energy to reproduce, just like you need sugar to grow. The faster a tumor grows the more glucose it will utilize and thus the more radiation that will be released from that site with the use of PET imaging. While we will spend a large portion of this course on PET as a cancer modality, I wanted to first explore opportunities for chiropractors to utilize PET imaging.

Key points:

- PET uses positron-emitting radionuclides and produces gamma rays
    - Type of nuclear imaging
- PET is most widely used in cancer detection
- PET is a functional imaging modality

Chronic osteomyelitis

Osteomyelitis is a bone infection. *Staphlococcus aureus* is commonly the culprit in both acute and chronic osteomyelitis, accounting for ninety percent of all bone and joint infections. Since bone is completely enclosed by skin and is protected from any direct route of transmission, how does a person contract osteomyelitis? There are four routes of transmission. Hematogenous spread is the most common route of transmission meaning that organisms in the blood seed the bone with infection. The other methods of transmission include spread from other organs, direct implantation such as an impalement, or postoperative infection. Diagnosing chronic osteomyelitis is important to prevent complications like Marjolin's ulcers and SAPHO syndrome (synovitis, pustulosis, hyerostosis, and osteitis syndrome). Imaging is appropriate to diagnose chronic osteomyelitis. When radiography, leukocyte scintigraphy, bone scintigraphy, gallium scintigraphy, CT, MRI and PET were compared for the diagnosis of chronic osteomyelitis, PET was the most sensitive and specific. Sensitivity is to detect patients who have a condition. One-hundred percent sensitivity means that everyone with a condition was detected, but does not take into account false positives (people testing positive that do not have the condition). Specificity is determining how many of the patients who tested positive actually had the condition. One-hundred percent specificity means that everyone who tested positive had the condition, but does not take into account false negatives (people having the condition but tested negative). Thus, the best test would have one-hundred percent sensitivity and specificity, meaning that all people who had the condition tested positive and all people who did not have the condition tested negative. Of course, there is no test that is one-hundred percent specific and sensitive but some tests can come close. PET has ninety-six percent sensitivity and ninety-one percent specificity in detecting chronic osteomyelitis. Thus, a negative 18F-FDG PET scan effectively rules out chronic osteomyelitis. If a false positive ensues, the culprit is most likely malignant bone tumor since both conditions have a high accumulation of 18F-FDP and may share macrophage-related mechanisms of tracer uptake. The conclusion is that if you have a patient that you suspect has

chronic osteomyelitis, send that patient for a PET scan. You can even do one better and send for a merged technology. The physiology identified with PET can be merged with the anatomy identified by CT or MRI. For a PET-CT evaluation, the osteomyelitis microbiologically verifies the primitive foci, and the images have histomorphometric correspondence. In F-FDG PET-MRI evaluation, the doctor gets even more valuable information for surgical planning compared with PET-CT and has the added benefit of reduced radiation dose and more soft tissue information.

Key points:

- PET is the best imaging modality for detecting chronic osteomyelitis

- PET with CT or MRI can even provide more information than PET alone due to the added anatomical detail provided by CT or MRI.

Relapsing Polychondritis

Dr. DeGeeter presented a case report in The New England Journal of Medicine of a patient suffering from a fever of unknown origin with persistent cough. Knowing that FDG-PET was useful in identifying areas of active inflammation, the doctor ordered the scan. The accumulation of FDG in inflammation is based on the fact that activated granulocytes use glucose as an energy source after activation during the metabolic burst. The scan showed marked tracer uptake in all rib cartilages, larynx, trachea, and major bronchi. PET helped determine a biopsy site and the patient was diagnosed with relapsing polychondritis. After treatment with methylprednisolone and dapsone, the disease went into remission and the follow-up PET scan showed that the condition had resolved. Since this case report, stand-alone PET has been largely replaced by the merged technology with anatomical diagnostic imaging, like computed tomography (CT). PET/CT allows for the anatomical detail of CT while also getting the physiological changes of PET.

I'll provide a little synopsis of relapsing polychondritis because it is an uncommon connective tissue disorder, but it does commonly coexist with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). SLE and RA patients frequently use chiropractic services so you may see this in practice. As the name implies, this is an episodic inflammation of cartilage. It commonly affects the ribs and articular cartilage, as seen in this case study, and also affects the nose, ear, trachea, larynx, and sclera. The sites are tender and edematous and the respiratory involvement may present as cough or hoarseness. The respiratory component is the greatest concern, because it can lead to the requirement of a tracheostomy. The diagnosis is typically made by signs and symptoms with catch phrases like auricular chondritis and saddle nose deformity. Radiologically, the condition can present with sacroiliitis or present like RA, with hand involvement leading to arthritis mutilans. As with all autoimmune diseases, the cause is unknown and unlike the other autoimmune diseases, there is no association with HLA-B27 antigens.

The conclusion is that PET is helpful in diagnosing relapsing polychondritis and was beneficial for following the course of the disease. If you suspect this condition, PET is appropriate.

Key points:

- Relapsing polychondritis can be diagnosed and followed with FDG-PET/CT.

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Section II – PET for Parkinson's Disease (Figure 3)

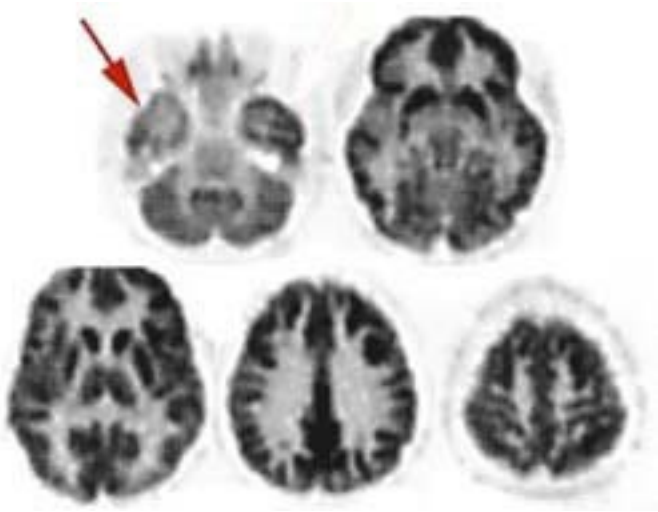

Figure 3. Brain PET courtesy of Jenna Murphy

People occasionally ask me the difference between osteopaths and chiropractors, since osteopaths often use adjustment procedures. My oversimplified answer is, do you believe that life is in the blood or in the brain? Chiropractors spend much of their schooling in neurology and focus heavily on the impact of the adjustment on the nervous system. Therefore, I thought it might interest chiropractors that PET is used in some neurological diseases.

Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder with classic signs of distal resting (pill-rolling) tremor, rigidity, bradykinesia (slow movement), asymmetric onset, and up to 80% of patients eventually develop dementia. Other commonly seen signs include decreased olfaction, micrographia (handwriting that is hard to read and smaller than usual), and late-onset postural instability. Because of the motor component, stretching, strengthening and balance training may be offered by chiropractors to improve gait speed, balance, and improved activities of daily living. Parkinson's patients often suffer from constipation; therefore, discussions about high-fiber diets may be beneficial.

Because Parkinson's patients make less dopamine, a chemical affecting the brain's ability to control body movements, many patients will be placed on dopamine agonists. This medication can delay the onset of the motor complications. The dopamine agonists are not as good as levodopa at controlling motor symptoms however. Therefore, many patients may be given Levodopa. The problem with Levodopa is that long term use causes dyskinesia among other things. Parkinson's disease is subdivided into early-stage and late-stage based on the motor complications of Levodopa. Early stage means that the patient has been on the drug for less than five years or has no motor complications from the drug. Late stage is characterized by motor complications from Levodopa. Such complications include: dyskinesia (involuntary movement of a body part or respiratory muscle group), "on-off" effect (fluctuating effectiveness of medication), or "wearing off" (drug no longer controls the Parkinson's symptoms at the same dose). Amino acids interfere with the Levodopa absorption; therefore, patients may need a chiropractor to form a healthy low protein diet. In addition, the condition and the medications

often induce depression, dementia, and psychosis. Because chiropractors often see their patients more frequently than allopaths, being conscious of these mental conditions may be essential.

For long-term management of your Parkinson's patient, you may wish to obtain The Unified Parkinson's Disease Rating Scale (UPDRS).
Go to: http://onlinelibrary.wiley.com/doi/10.1002/mds.22340/full
and on the right under under Article Tools, click on get PDF.

Surgery is now an option. Patients receive deep brain stimulation of the subthalamic nucleus. The surgery does help the motor functions, but still, there is no cure for this condition. Five percent of patients over eight-five years of age will develop Parkinson's with a total U.S. prevalence of 0.3 percent of the population.

Key points:

- Parkinson's is a neurodegenerative disorder causing the patient to not produce enough dopamine
- Patients cannot be cured but signs and symptoms are often managed with dopamine agonists or Levodopa
    - Both drugs have their limitations and complications
- Surgery has been shown to be effective for improving motor function

One difficulty is determining true idiopathic Parkinson's disease from other Parkinson's like diseases. There are other diseases that are not helped by Parkinson's medications so proper diagnosis is important. Unfortunately, the only definitive diagnosis of idiopathic Parkinson's disease is the histologic demonstration of the intraneuronal Lewy body inclusions in the substantia nigra compacta, which is unlikely to occur in a living patient. Thus, the difficulty becomes to diagnose the patient without taking brain samples. This is where functional imaging plays a role. Transcranial sonography has been used but the findings do not correlate well with the disability rating and remains static over time despite progression of symptoms. Since this is a disease of controlling symptoms, sonography is limited in practical usefulness. MRI is not sensitive enough to show the atrophy of the lentiform nucleus, seen in many atypical Parkinson presentations. MRI is sensitive however to the changes in striatal structures. Thus, MRI has some value but does have limitations as well. PET on the other hand CAN show issues with the lentiform nucleus as evidenced by the reduced lentiform nucleus glucose metabolism with FDG-PET. PET can show the function of the dopamine terminals in Parkinson's patients in three ways. PET can assess the availability of presynaptic dopamine transporters. Remember that FDG-PET monitors glucose but other radiopharmaceuticals can be used to tag different molecules with PET imaging. Sup 18F-dopa-PET shows a marker of terminal dopa decarboxylase activity and dopamine turnover. Sup 11C-PET can demonstrate the availability of vesicle monoamine transporters in dopamine terminals. Early hemiparkinsonian patients show bilaterally reduced putamen dopaminergic terminal function. Clinical features arise when approximately fifty percent of this terminal function is lost. Thus, PET shows correlation between function and clinical features, unlike sonography. For example, levels of putamen sup 18F-dopa uptake is inversely related to bradykinesia and rigidity, but not tremor. What that means is that the tremor is not directly related to nigrostriatal degeneration.

When rigidity and bradykinesia begin, globus pallidus interna sup 18F-dopa uptake is increased by fifty percent but falls over the course of the disease. With these subnormal levels, disability becomes severe and Levodopa motor complications begin.

Key points:
- PET has uses that sonography and MRI cannot accomplish
- PET findings correlate well with clinical presentation

The previous discussion about PET for Parkinson's was showing that PET is useful for correlating the physiology of the disease with the signs and symptoms seen. PET is also beneficial for the initial diagnosis of Parkinson's as well. In patients suspected of having dopamine-deficient Parkinson's disease, fifteen percent showed normal dopamine terminal function on PET. Only three percent of these patients were still believed to have Parkinson's two years later based on signs and symptoms progression. What this means is that without PET, Parkinson's disease was over diagnosed and PET helped to clearly define true Parkinson's patients.

PET is also useful to determine what patients will develop Parkinson's disease. The inherited form of Parkinson's disease shows mutations in the LRRK2 gene. Sup 11C-metylphenidate PET can assess the striatal dopamine storage capacity, vesicular monoamine transporter binding, and DAT binding in family members. There was a strong correlation between PET findings and LRRK2 gene mutations; therefore, PET can help determine the carriers of the Parkinson's gene mutation.

Next, let's discuss treatment of Parkinson's disease and PET findings. As previously mentioned, many Parkinson's patients suffer from depression. To treat depression, many patients are given serotonin reuptake inhibitors. PET showed that serotonergic loss did not contribute to depression and thus there is no rationale behind giving this medication to treat depression in these patients. Some Parkinson's patients on dopaminergic medications develop problems with gambling or hypersexuality. PET has shown that these gamblers show greater disease in ventral striatum D2 binding, thus physiologically explaining why this gambling side-effect has occurred.

Key points:
- PET reduces the risk of over diagnosing Parkinson's disease
- PET can predict carriers of Parkinson's gene mutations
- PET can explain which medications are appropriate and why they cause certain side-effects

SPECT is another functional imaging modality that has similar function with regards to Parkinson's that PET has but is beyond the scope of this course.

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Section III – PET with oncology

When most people think of PET scans, the association is usually with oncology and by far, that it is the most common usage of the technology. Oncology was actually the precipitating event causing me to write this course. My mother died from metastatic breast cancer and her rib metastasis was detected with PET. That is what inspired me to learn more about PET.

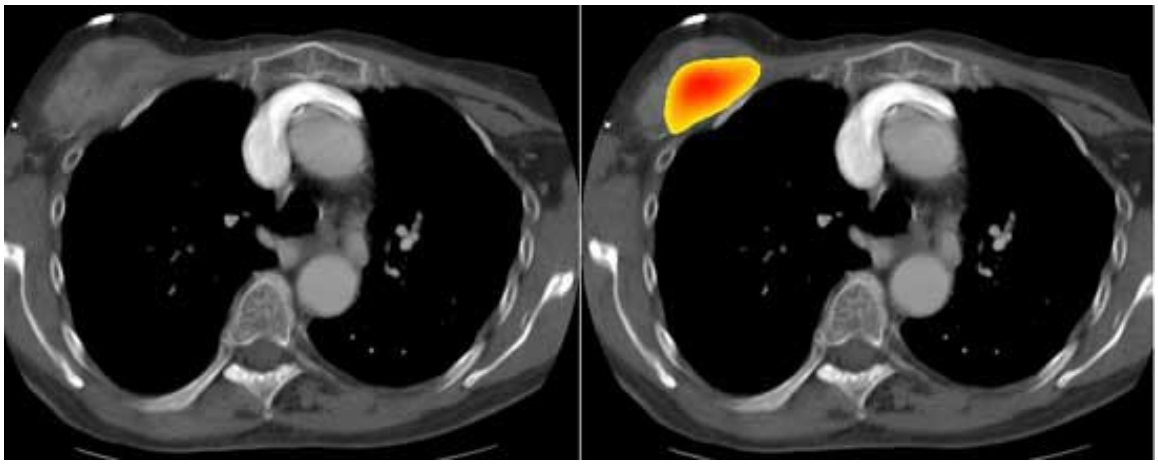

Figure 4. Note the PET-CT fusion in this case of breast cancer courtesy of Jenna Murphy
PET in breast imaging (Figure 4)

Women with high risk factors for breast cancer start breast screening exams earlier than other women. No woman is at higher risk for breast cancer than those with the BRCA gene. Thus, these women receive mammography, ultrasound, and MRI earlier and more frequently than most women in hopes of catching disease early. Unfortunately, BRCA carriers are known to have denser breasts than their peers and no microcalcifications. Mammography and ultrasound are both subject to breast density and become less diagnostic with denser breast tissue. MRI does not have this limitation but MRI only has a sensitivity of detecting cancers in seventy-one percent of patients. Many of the cancers demonstrated benign features on MRI. In order not to miss these cancers, radiologists often over-diagnose breast cancer on MRI by calling any abnormality cancer. The result is many scared women and unnecessary biopsies. One study showed a three times higher biopsy rate with MRI of benign lesions than when mammography was utilized. What can be done with imaging to overcome these limitations?

I imagine you think I will say, "In steps PET to save the day". In some respects, that is true but PET has some set-backs as well. First, PET is not widely available and breast cancer is everywhere in the United States. Second, PET is a source of ionizing radiation, unlike ultrasound and MRI. I just think of all the radiation my mother has had. If the breast cancer didn't kill her, the radiation induced osteosarcoma may have emerged at some point. She

had CT scans, bone scans, PET scans, not to mention all the radiation for treatment of both breasts and now ribs. I am concerned with another ionizing radiation test. On top of these risks, PET with CT has been found to be very useful. It provides the functional components of PET with the high-resolution anatomy of CT. Sounds great until you realize that these scans range from 12-16mSV in radiation. Lastly, PET has a lower sensitivity but higher specificity than MRI. That means that PET misses more lesions but if a lesion is detected, it can definitely determine that it is cancer and not benign. The number of benign biopsies would be less but more cancers would be missed.

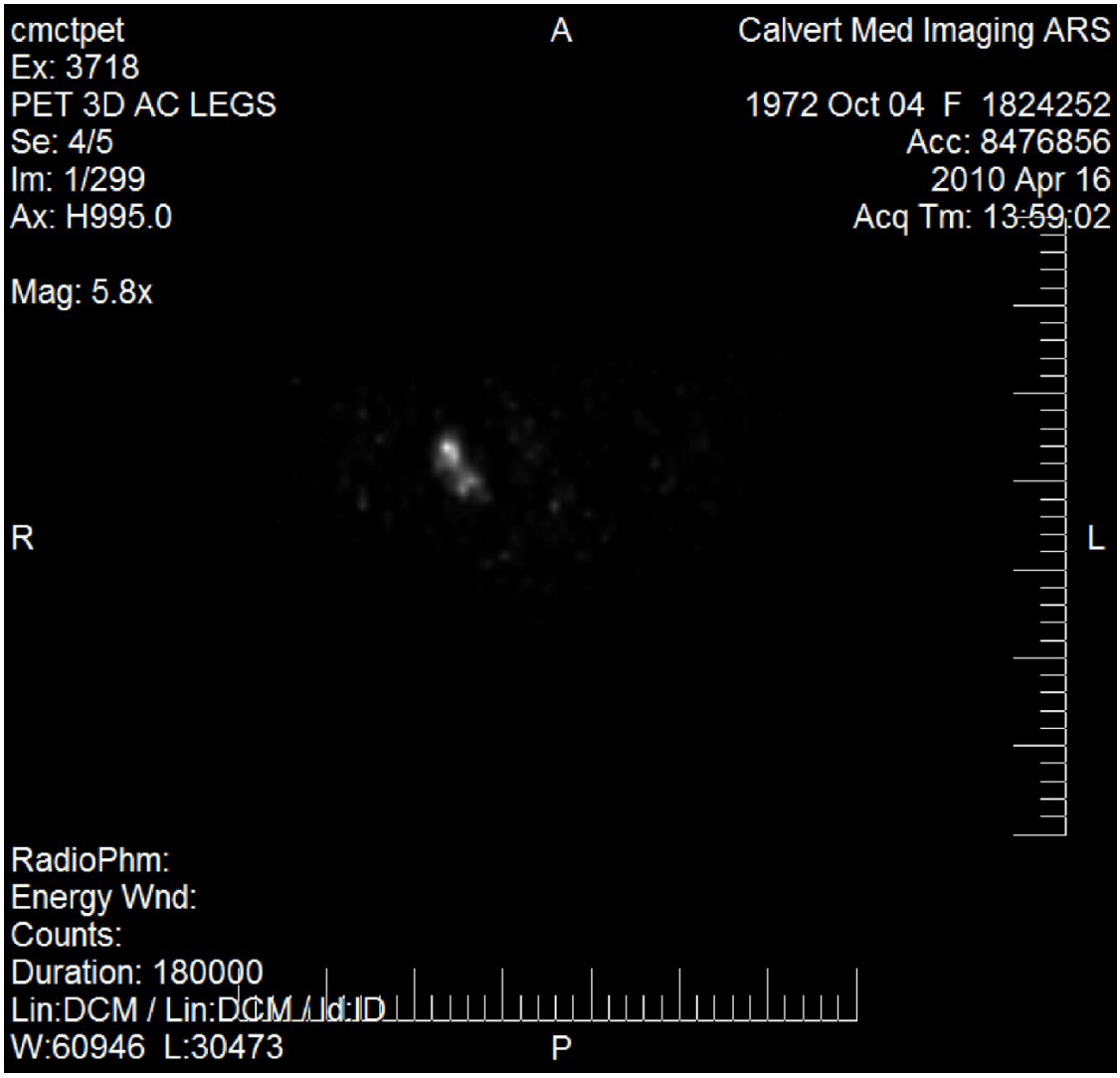

Figure 5. Metastasis to the leg

Now that I've discussed the bad, what is good in PET. Metastasis to the skeleton was detected more often with PET than with CT or bone scan (Figure 5). Sup 18F-FDG-PET/CT has a positive predictive value of eighty-nine percent for metastasis and is used for staging in advanced cancers. PET clearly identifies active disease while CT and bone scans cannot. PET is useful to determine early response to treatment. PET-CT has been good to show ovarian cancer in BRCA carriers because both breast and ovarian cancers are likely in BRCA carriers. PET-CT had a positive predictive value of one-hundred percent and a negative predictive value of eighty-one

percent in determining ovarian malignancies which was better than transvaginal ultrasound, which had seventy-eight negative predictive value and eighty-percent positive predictive value. PET-CT has been shown to detect abdominal metastasis from ovarian cancer better than pelvic CT and resulted in a changed management of sixty percent of patients in one study (Figure 6).

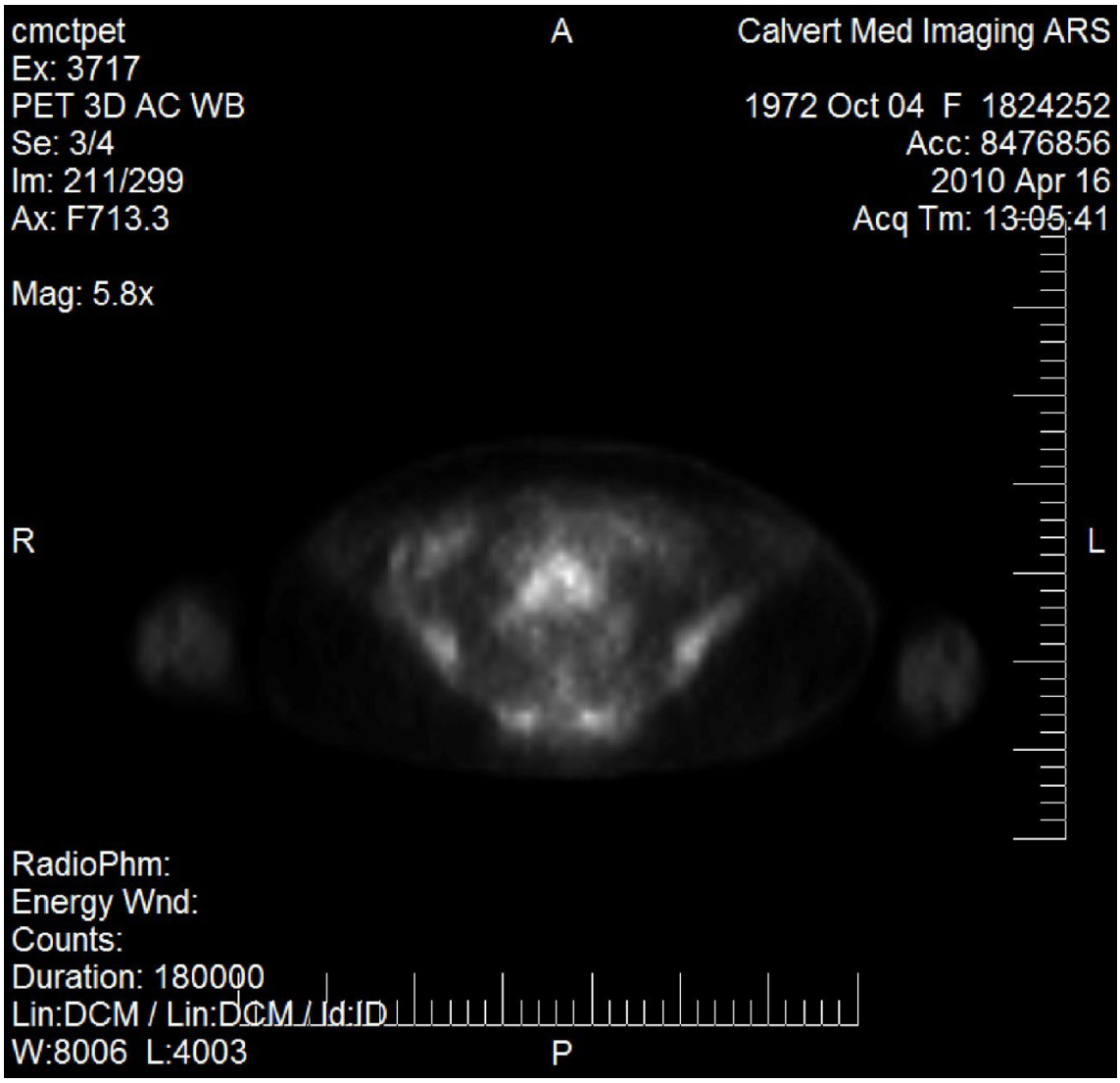

Figure 6. PET scan of the pelvis.

How does PET image the breast? There are two types of breast imaging with PET. Scanners called breast-PET and positron emission mammography (PEM) exist. Breast PET works by rotating or encircling the breast with detectors which prevents superimposition of structures. PEM works by using a curved detector that images the breast under compression, so there is some superimposition of structures. Not all breast cancers are equally detectable. Infiltrating ductal carcinoma accumulates more of the radiopharmaceutical than infiltrating lobular tumors making infiltrating ductal carcinoma easier to detect.

Key points:

- PET and especially PET-CT is widely used for the diagnosis of breast and ovarian cancer
    - This is a source of ionizing radiation
- Breast-PET and PEM are breast specific scans using PET
    - PET is not widely available

PET with lung cancer

While breast is the most common cancer in women, no cancer kills more men and women than lung cancer. PET-CT is commonly used for the initial staging of lung cancer because CT alone often cannot determine if a lung nodule is benign or malignant. PET alone has poor spatial resolution thus the merging of the two techniques is advantageous for diagnosing lung cancer. Clinical management was changed in forty-one percent of patients in one study when using PET-CT than either PET or CT alone. The PET-CT combination allowed for detection of metastatic sites, differentiated lung inflammation and atelectasis from malignancy and demonstrated precise lymph node positions. The hybrid technology, PET-CT, is routinely used for the evaluation of lung nodules and for staging of lung cancer. The addition of PET reduced the rate of futile thoracotomies, invasive surgery or inappropriate surgeries. While research is still limited, MacManus concluded that PET may be not only cost effective but cost saving, when preventing unnecessary surgical procedures.

Key point:

- PET-CT was the most accurate diagnostic imaging technique for classifying lung cancers

PET and lymphoma

The literature shows mixed results when using FDG-PET or PET-CT in cases of lymphoma. PET can diagnose, stage, and monitor treatment for lymphoma patients, both non-Hodgkins and Hodgkins. PET-CT does whole body imaging and does help with determining biopsy locations. Halanaik states that "approximately two-thirds of patients with Hodgkins disease and fifty percent of patients with non-Hodgkins lymphoma show persistent mass lesion on morphological imaging modalities after treatment, however FDG-PET-CT shows absence of metabolic activity in these lesions and lower incidence of relapse in these groups of patients." What this author is saying is that even after treatment, a mass will show and without PET, there is no anatomical way of determining if the mass is an active lesion. PET shows metabolic activity and thus will determine if treatment was successful in obliterating the cancer, even though the mass may still remain.

The negatives for PET and PET-CT in cases of lymphoma include the false positives that occur due to inflammation or infection. Remember, that FDG-PET only shows glucose activity but does not identify the cause of the metabolic activity. Post surgery, radiation, or chemotherapy can cause inflammatory changes that cannot be differentiated from active cancer.

Certain types of lymphoma have a high false negative result which means that the patient still has cancer and yet, the test came back negative for cancer. Low grade lymphoma, follicular lymphoma and CNS lymphoma all commonly have false negative PET scans. Another issue with PET-CT is the amount of radiation. Patients suffering from lymphoma are younger than other cancer patients and are more susceptible to negative radiation effects. Juweid

demonstrated that PET only provided early disease detection in two percent of treated patients.

Eighty percent of lymphoma recurrence is detected by physical examination with the use of NO imaging. Therefore, is it reasonable to use repetitive ionizing radiation to monitor for lymphoma recurrence when little benefit has been determined? Juweid concludes that it is unscrupulous to use anything but a yearly chest radiograph to look for recurrence of Hodgkin's lymphoma. Plain film radiographs produce considerably less radiation damage than PET-CT and thus repetitive PET-CT may be inappropriate for these young patients.

Key points:

- Lymphoma has been diagnosed, staged, and successfully followed with PET-CT
- PET-CT can cause false positive and false negative results in lymphoma diagnosis
- Because lymphoma patients are commonly young, PET-CT may produce radiation doses that exceed the cost/benefit standards for use of this modality.

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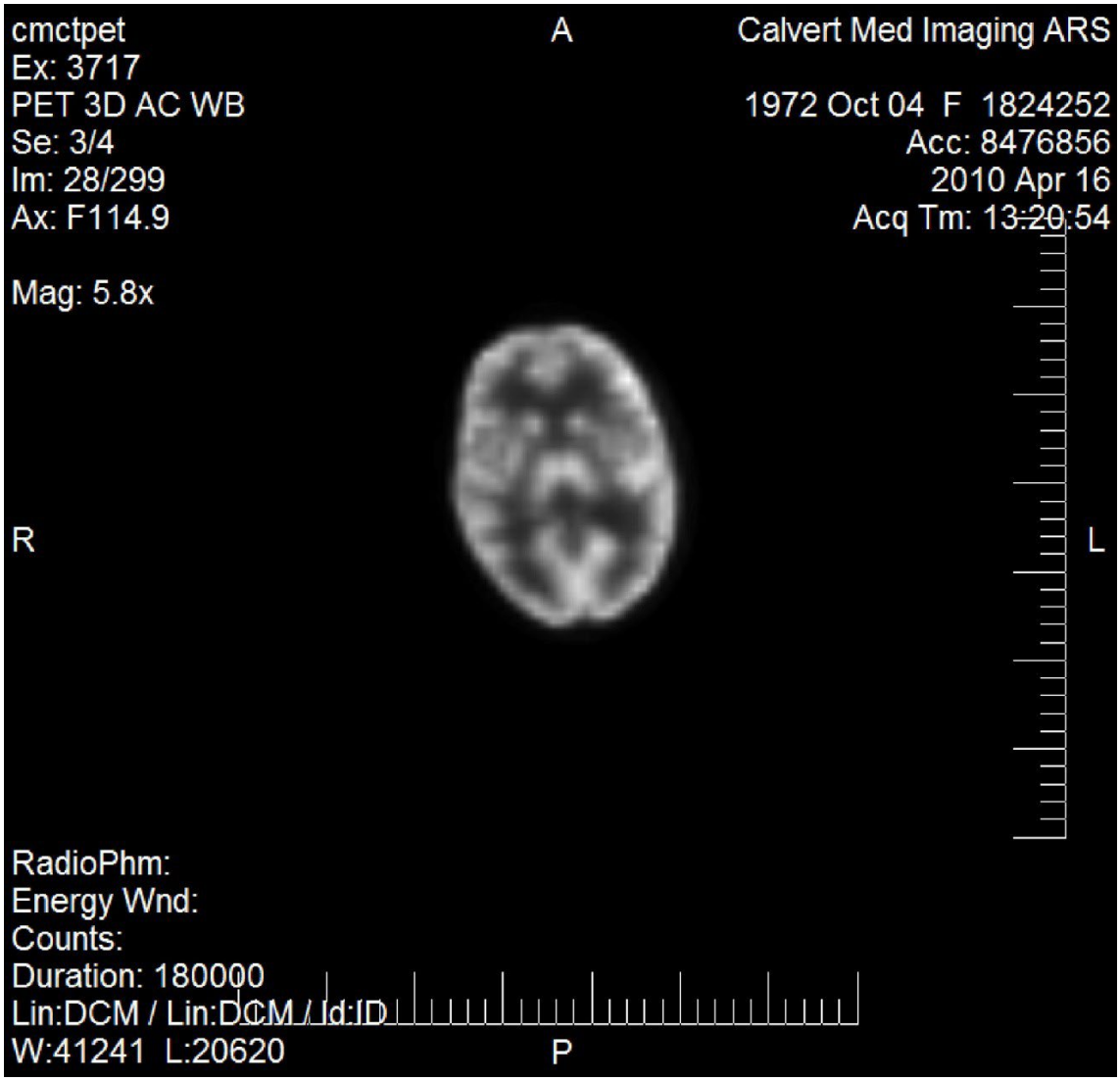

Figure 7a. PET scan of the brain

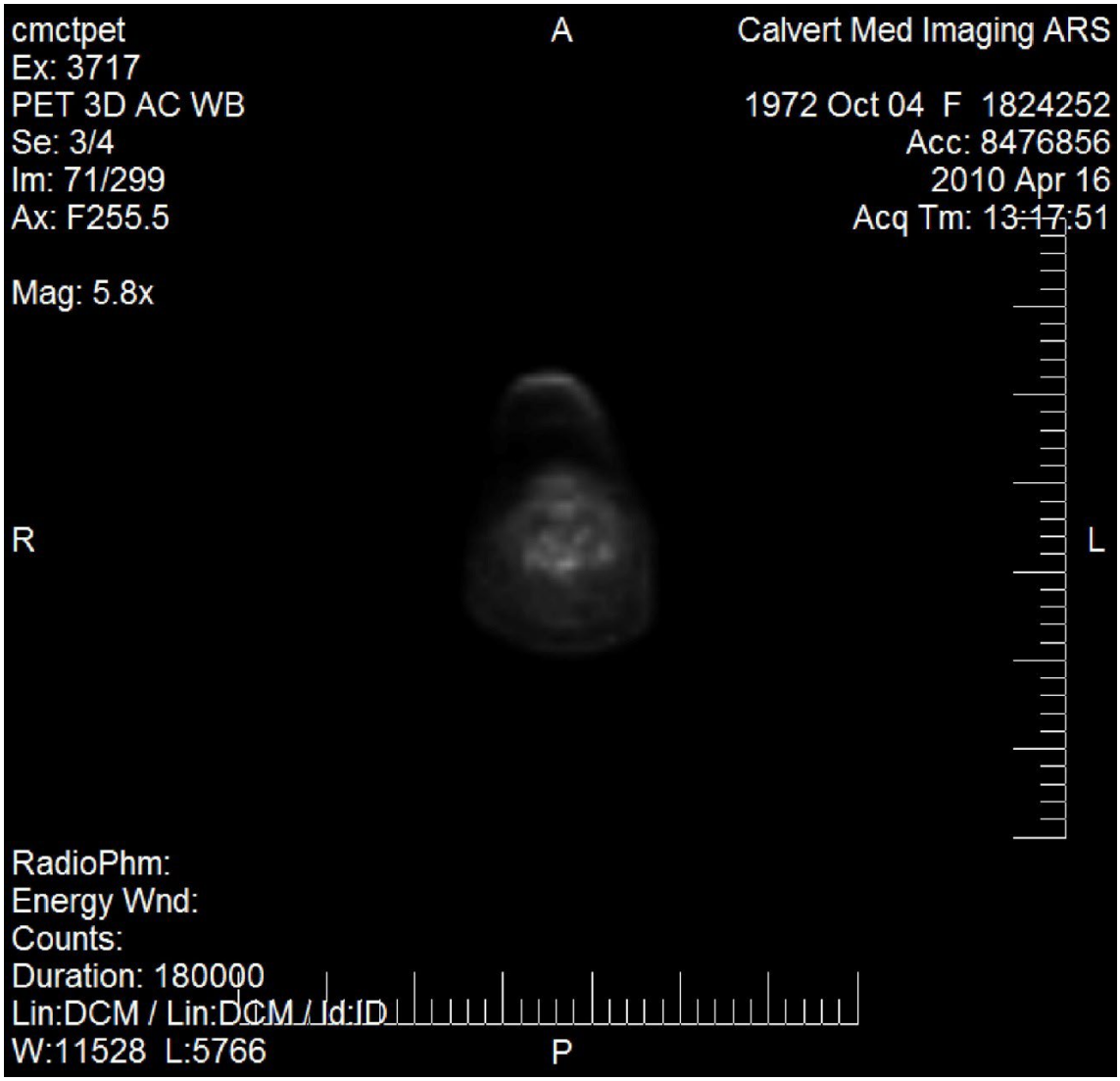

Figure 7b. PET scan of the neck

PET-CT with head and neck cancers (Figure 7a,b)
PET imaging has been around for quite awhile for the diagnosis of intracranial masses. I remember my cousin's metastatic melanoma to the brain was first diagnosed with PET imaging and he has been dead for seven years now. What is new in PET imaging is the use of PET-CT or PET-MRI for head and neck cancers. I will start with PET-CT.

One use for PET-CT is in imaging squamous cell carcinoma of the head and neck. As previously stated, PET can show the metabolic activity of the cancer while CT is best at showing the anatomy and delineation of the mass. The use of PET becomes important with squamous cell cancers of the head and neck because treatment has moved away from surgery toward radiotherapy alone or with chemotherapy. Two-thirds of patients present with advanced disease and thus for organ preservation, surgery is not recommended. Thus, it becomes essential to know the metabolic activity of the mass instead of just its anatomical location. Tumor cell hypoxia and accelerated tumor cell proliferation work against radiotherapy by actually stimulating tumor cell proliferation; therefore, it is essential to know whether there is tumor cell hypoxia and accelerated tumor cell proliferation. This can be deduced by PET-CT but not CT

alone. PET-CT can also determine the effects of radiotherapy early on to determine if this is an appropriate treatment measure for an individual patient.

There are other uses for PET with squamous cell cancer of the head and neck. In some cases, biopsy may not be appropriate for these cancers. PET can also be used in place of a biopsy. PET can visualize the primary tumor plus any metastatic lymph nodes before and during treatment. PET can be used to determine prognosis. For example, tumor cell hypoxia suggests a poor prognosis. I have spent most of the time talking about FDG-PET imaging which is monitoring glucose but other radiopharmaceuticals can be used with PET imaging. This is one case. Nitroimidazole-based radiopharmaceuticals are used with PET to determine this hypoxia. Some squamous cell cancers are radioresistant and so if PET determines the radioresistance, radiotherapy dose can be increased or radiotherapy can be combined with chemotherapy. Therefore, PET can determine patient management. FDG-PET does have a place in head and neck cancers, specifically for post-treatment assessment. FDG-PET was effective in detecting residual or recurrent tumors with ninety-five percent specificity and fifty-nine percent sensitivity. This information has been used to determine whether patients need to be sent for surgery.

As mentioned with lymphoma, PET does show high false positives for lymph node metastasis from squamous cell carcinoma due to the inflammatory process in the lymph nodes. Inflammation and tumor can be differentiated by a different PET radiopharmaceutical known as fluorethyltyrosine (FET-PET), but this usage is rare.

By adding CT to PET, image noise is reduced. Whole body CT scans with a multidetector system lasts only a few seconds because of the CT-based attenuation correction. By merging PET and CT, the whole body PET study acquisition time can be nearly halved. Sounds great but the downside is that there may be significant misregistration between the two modalities. PET is analyzed over several breathing cycles and CT is in one cycle; therefore, merging the media may cause the position of the lungs, for instance, not to line up between the two modalities. Matching the difference in photon energies is also a challenge because PET uses 511 keV photons and CT averages 70 keV. The addition of CT contrast can be problematic as well because to produce an accurate attenuation map between PET and CT, the three tissue types need to be visualized. CT images are divided into air, water, and bone and contrast disrupts this differentiation. Thus, if contrast is needed, the examiner may wish to do a non-contrast CT/PET and follow up with a contrast CT alone. Of course, this does add more radiation dose to the patient. The advantage to PET/CT is that it is an integrated machine and thus patients would not be scheduled for two separate examinations. This provides ease for the patient and allows for joint reporting of PET and CT.

Key points:

- FDG-PET is useful for detecting recurrent or residual head and neck tumors after treatment
- Nitroimidazole-based radiopharmaceuticals are used with PET to determine tumor cell hypoxia which is associated with a poor prognosis
- While there are many advantages to merging PET-CT, there are some complications of this merger.
    - IV/oral contrast use
    - Speed of the exam
    - Photon energy differences

PET-MRI with head and neck cancers

MRI is the gold standard for diagnosis of gliomas. Although contrast MRI does show tumor activity, it is only indirectly determined based on the breakdown of the blood-brain barrier. MRI does not specifically measure tumor size or activity but is mainly a measure of vascular leakage. Enhancement does not necessarily mean tumor progression and a lack of contrast uptake does not necessarily mean tumor regression. PET-MRI is used to target the biological activity of tumor cells. Because FDG-PET demonstrates glucose utilization, healthy brain tissue can be differentiated from low grade gliomas, high grade gliomas and radionecrosis. FDG-PET is not useful for detecting residual gliomas after therapy but methionine-PET is effective.

Nothing is perfect so what is the downside to PET-MRI. Obviously, the test would be more expensive than MRI alone and PET is a source of ionizing radiation that is not found with MRI alone. The PET-MRI hybrid is only in prototype phase and thus will not be readily available. The first PET-MRI hybrid was not even invented until the late 1990s so this is a very new technology. PET-MRI has a longer acquisition time than PET alone; therefore, strategies may be needed to diminish head movement during this extended examination. PET-MRI shows some more streak artifacts in coronal and sagittal sections than PET-CT but the artifacts can be eliminated with proper filtration. Unfortunately, filtering reduces spatial resolution. The trade-off is that PET-CT has much more exposure to ionizing radiation than PET-MRI so it is a cost-benefit analysis for the ordering physician. PET-MRI also has some interpretation advantages over PET-CT, namely higher soft-tissue contrast, and advanced MRI technique availability such as perfusion imaging, diffusion imaging, and MRI spectroscopy.

Key points:

- PET-MRI shows the biological activity of tumor cells
- PET-MRI is comparable to PET-CT in image quality and quantitative data
- PET-MRI is better than PET-CT in patient dose, soft-tissue contrast, and advanced MRI technique availability
- PET-MRI is inferior to PET-CT in streak artifacts and reduced spatial resolution with filtration

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Section V – PET with dementia

PET with Alzheimer's disease

Dementia is a common problem in the elderly of the United States and the cases of dementia continue to increase. Dementia affects ten percent of people over sixty-five years of age and half of individuals over ninety years of age. There are several forms of dementia such as vascular dementia, dementia with Lewy bodies, and frontotemporal dementia, but by far the most abundant cases of dementia belong to Alzheimer's disease. Alzheimer's disease accounts for half of all dementias. Alzheimer's disease is even more prevalent than this statistic suggests because Alzheimer's disease in conjunction with any other dementia is labeled mixed dementia. To diagnose dementia, a person must have cognitive impairment in at least two domains, which include memory, language, calculations, orientation and judgment. This impairment must result in social or occupational disability. One may still have cognitive impairment and not meet the diagnostic criteria for dementia. This type of cognitive impairment that does not limit activities of daily living affects nineteen percent of people under seventy-five years of age and twenty-nine percent of people over eighty-five years of age. Eighty percent of those with mild cognitive impairment will develop Alzheimer's within six years. Alzheimer's disease begins decades before symptoms emerge. Then comes the prodromal stage with amnesia symptoms and then the disease progresses to the terminal stage with extensive loss of basic cognitive functions. The sequence of pathology can be documented with various biomarkers. First, amyloid metabolism is disrupted. Then, the markers for tau phosphorylation show aggregation. Lastly, inflammation, neurodegeneration and synaptic dysfunction commence.

The most common test to assess dementia is the Mini-Mental State Examination (MMSE). The test checks cognitive function through questions on memory, orientation, naming, reading, copying, writing, and completing three step commands. The test is helpful because it takes less than ten minutes to complete and comes with a scoring system of zero to thirty points. Those patients scoring less than twenty-four points are determined to have significant cognitive impairment. Here is my complaint about the MMSE. I know that this is anecdotal but interests in conditions come from real life situations. I witnessed my grandmother being given the MMSE. They asked her questions like, "who is the president" and "what day of the week is it?" This lady had been living in a nursing home without newspapers or television and every day was the same. Why would she know what day of the week it was? I know when I was a child home on summer recess; I often had no idea what day it was because there was no schedule and I wasn't demented. If your life occurs entirely in your own building, why would you know who the president was because it has no bearing on your life? While the MMSE has stood the test of time as being an important assessment tool, I was interested in the day when we could visualize dementia and get away from the indirect testing. Now is the time! In 2011, the National Institute on Aging-Alzheimer's Association workgroup updated the 1984 diagnostic criteria to not only include the neuropsychological testing but added advanced imaging like PET and cerebrospinal fluid measures.

Even old-school FDG PET is useful. There is reduced resting regional glucose metabolism in the posterior cingulate gyrus, hippocampus, parietal and temporal lobes with lesser involvement in the prefrontal cortex. Primary motor visual areas are spared. Using rats, Lai showed that the decreased hippocampus activity on FDG PET could be improved with acupuncture at HT7. The idea is that acupuncture increases cerebral blood flow to the hippocampus and this may help

people with memory impairment. This pattern of reduced regional glucose metabolism is found in Alzheimer's disease but it is also found in Parkinson's disease. Thus, glucose metabolism will not differentiate Alzheimer's disease from Parkinson's disease. For Parkinson's disease, use F-9-Fluoropropyl-(+)-dihydrotetrabenazine [18F-FP-(+)-DTBZ] PET because it shows dopaminergic neuron loss associated with Parkinson's disease. For Alzheimer's disease, the goal is to visualize the amyloid-beta (Abeta) plaques that are hallmark for Alzheimer's disease and precedes the dementia. Imaging of these plaques would mean early diagnosis. 2-(1-[6-[2-[F-18] fluoroethyl) (metyl) amino]-2-naphthyl] ethylidene) malononitrile (FDDNP) can be injected for use with PET scanning. FDDNP binds to these plaques and neurofibrillary tangles which are also seen in Alzheimer's disease. The amount of binding is directly proportional to the amount of cognitive impairment. Because of this, patients with mild cognitive impairment can be differentiated from true Alzheimer's disease. How amazing is that! We no longer have to wait until autopsy to diagnose Alzheimer's disease. Because of early diagnostic ability, treatments designed to prevent plaques and tangles are now being developed. In one study, the only side effects from the PET scan were bruising due to venipuncture and two patients complained of transient headache. FDDNP is not affected by patients taking cognitive enhancing medications. FDDNP-PET can be used to monitor the progression of Alzheimer's disease as well. Patient's followed over two years showed FDDNP binding increases that directly related to the clinical evidence of disease progression. FDDNP-PET will provide objective findings for subjective clinical features. One patient in Small's study died and therefore autopsy findings were compared to FDDNP-PET imaging findings and there was a direct correlation to the FDDNP binding and the tangles and plaques found at autopsy. When new drugs are developed to stop plaque and tangle formation or dismantle existing plaques and tangles, FDDNP-PET will likely be used to demonstrate effectiveness of the drug.

FDDNP is not the only radiotracer used for the diagnosis of Alzheimer's disease with the use of PET. The gold standard Abeta PET tracer is (11)C-labeled Pittsburgh compound B because it has high selectivity for all forms of Abeta, such as soluble oligomers, insoluble fibrils, and plaques over other pathologic proteins. The downside to this gold standard is it only has a 20-minute half-life so it is only valuable for clinical sites that have cyclotrons immediately available. Thus, tracers with longer half-life times like (18)F-BAY94-9172 with a 110-minute half-life have more practical usage. (18)F-BAY94-9172 is an Abeta ligand and the binding of this tracer to the Abeta plaques matched the post-mortem distribution. Now, this is a newer tracer but preliminary studies have shown one-hundred percent sensitivity and ninety percent specificity for detection of Alzheimer's disease. The down side to this tracer is that it only labels the plaques and does not adequately label tangles, Pick bodies, Lewy bodies or glial cytoplasmic inclusions (other components of dementias). Animal studies have shown this radiotracer to be safe from toxicity and there have been no adverse events in the human study groups. With this tracer, accumulation occurred in the frontal and posterior cingulated cortex with lesser amounts in the lateral temporal or parietal cortex. There was sparing of the occipital, primary sensorimotor and medial temporal cortex and no binding to the cerebellar cortex in patients with Alzheimer's disease. The PET scans took only thirty minutes which should be tolerable for most elderly patients. Shorter scan times are possible but need to be validated before general use.

Key points:

- Amyloid-beta plaques and neurofibrillary tangles are hallmarks of Alzheimer's disease
- FDDNP-PET can be used to identify these plaques and tangles
- FDDNP-PET is used to diagnose Alzheimer's disease, follow the progression of the

disease and may be used to determine treatment effectiveness
- (18)F-BAY94-9172 is a new radiotracer used with PET that has shown high sensitivity and specificity for diagnosing Alzheimer's disease and differentiating Alzheimer's disease from other forms of dementia

PET with other dementias

While FDDNP-PET has been studied for Alzheimer's disease diagnosis, other forms of dementia diagnosis may also benefit from this technology. For example, frontotemporal dementia has shown binding of FDDNP in the frontal and temporal regions but not the parietal and thus differentiates frontotemporal dementia from Alzheimer's disease. (18)F-BAY94-9172 can also differentiate frontotemporal dementia from Alzheimer's disease.

Key points:
- PET may be useful in differentiating other dementias besides just Alzheimer's disease

Conclusion

PET is a relatively new technology and the merging of PET with CT and MRI is even newer. PET radiotracers continually evolve to open up new diagnostic opportunities. This course has discussed PET with bone and joint, Parkinson's disease, dementia, and oncology. The complete use of PET is still yet to be determined due to the infancy of the technology. I wanted to close with an interesting little case report that didn't really fit in any other section of the course.

A patient presented with adenopathy in the axilla and the patient was sent for FDG-PET to rule out cancer. PET showed an increase in uptake in the axilla suggesting tumor. When the patient went to biopsy, the axillary node showed lymphoid tissue, granulomatous inflammation and an abundant black pigment. The conclusion was that the black pigment activated macrophages producing a positive PET scan. What was the black pigment? It was tattoo ink that had been transported to the lymph nodes. So if you want a scare story for not tattooing, here is one freaky example of negative consequences to body tattoos. Strange, but true!

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