Introduction
Positron Emission Tomography (PET) is a state of the art diagnostic imaging tool with a wide range of applications in oncology, cardiology and neurology. Distinct from other imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound that use anatomical characteristics as their major diagnostic criteria, PET exploits the metabolic properties of cells to allow imaging at the molecular level. The greatest clinical indication for PET, representing 85-90% of current utilization worldwide, is in oncology. In a wide variety of cancers a PET scan can evaluate the entire body to give a comprehensive staging of the cancer, aid in radiation therapy planning, monitor the success of therapy, and assess for disease recurrence. Furthermore, in certain patients without a known cancer, PET is useful in distinguishing whether a newly discovered mass is benign or malignant.

PET imaging also plays important niche roles in neurology, where it is used to assess dementias, movement disorders, and seizures, and in cardiology, where it is used to assess myocardial viability and perfusion. In addition to these important clinical applications, PET imaging can play a valuable role in a number of research applications.

Physics
PET technology relies on the release of positively charged anti-electrons called positrons from radiopharmaceuticals (tracers), which have been injected into the patient and have localized to a disease process such as cancer. Positron emission takes place when an unstable nucleus with an excess positive charge emits a positron to become stable. A short distance from where the positron is emitted from its source (for example 2-3mm for the fluorine radioisotope $^{18}\text{F}$) it loses energy and interacts with an electron, resulting in annihilation of both the positron and the electron. During annihilation, the masses are converted into two gamma rays, or photons, that travel in a 180 degree path opposite to one another. Two detectors then perceive these photons at virtually the same time, in a process termed coincidence. Thus, when coincidence is detected it is known that the annihilation must have taken place somewhere along the line between the detectors. By recording all the coincidences within a 360 degree field around the patient, a 3 dimensional image can be constructed, reflecting the distribution of the radiopharmaceutical throughout the body.

Radiopharmaceuticals
In nuclear medicine, which includes PET, the tracers used are called radiopharmaceuticals. Radiopharmaceuticals consist of two components, the first of which is the radioisotope which is the radioactive component that undergoes decay, releasing the photons that are detected by the camera. The second component is the pharmaceutical, which is the component possessing the desired physiologic property that results in the radiopharmaceutical localizing to the disease process. The major radioisotopes used in...
PET are radioisotopes of fluorine (\(^{18}\)F), oxygen (\(^{15}\)O), carbon (\(^{11}\)C) and nitrogen (\(^{13}\)N). They are small organic elements that are readily incorporated into organic tracers. Their drawback is their short half-life, with \(^{18}\)F having the longest at 110 minutes, and \(^{15}\)O having the shortest at 2 minutes. With these radioisotopes’ short half-lives, they must either be produced on site (which requires a medical cyclotron) or, in the case of \(^{18}\)F with its 110 minute half life, production can occur at an offsite facility if delivery is possible within about 4 hours. With its recent installation of a cyclotron and radiopharmacy, the PET suite in Halifax can potentially use these radiopharmaceuticals with shorter half-lives.

The most widely used radiopharmaceutical in PET is \(^{18}\)fluoro-2-deoxy-D-glucose (\(^{18}\)F-FDG), a glucose analog labeled with \(^{18}\)F. It is used in the vast majority of clinical oncology and neurology applications, as well as a substantial portion of cardiac PET studies. However, \(^{18}\)F and the other PET radioisotopes can also be incorporated into other organic molecules to be used as tracers to exploit alternate metabolic pathways, both clinically and in research.

**PET-CT**

A PET-CT scanner is a PET scanner integrated with a multi-slice CT scanner. This allows for better localization as it produces both anatomical and molecular images. The CT also employs attenuation correction, which compensates for greater absorption in the center of the body as opposed to the peripheries. The combination of these two technologies has been so successful that it is now the standard.

**PET in Halifax**

The first PET-CT study in Halifax was performed on June 15, 2008 and, until recently, isotope was flown in daily from Montreal. However, with the recent completion of the PET suite in July 2010, the cyclotron and pharmacy is now producing \(^{18}\)F-FDG on site. Demand for PET-CT studies continues to increase. It is currently only funded for oncology studies in Nova Scotia, but the hope is to expand this to the areas of cardiology and neurology.

**PET in Oncology**

In the past few years PET has emerged as a very useful imaging tool in oncology. While PET is a high-end modality that comes with a significant cost, this cost...
can be offset through better staging and diagnosis. As compared to CT, which demonstrates anatomy, PET displays physiology and metabolism. Compared with normal cells, cancer tissue may have increased glycolysis, protein synthesis, DNA synthesis, amino acid transport and blood flow, along with more anoxic or hypoxic cells. A variety of PET radiopharmaceuticals have been developed to image these deviations from normal physiological cell states, allowing PET to detect most forms of cancer. The vast majority of clinical PET oncology imaging is performed using $^{18}$F-FDG, which provides an image of tissue glycolysis. $^{18}$F-FDG behaves in most respects like glucose, entering cells via glucose transporters and being phosphorylated via the enzyme hexokinase. However, unlike glucose, it cannot proceed further along the glycolytic pathway, and remains in the cell. Although $^{18}$F-FDG also enters normal cells, there is substantially greater $^{18}$F-FDG uptake in cancer cells, due to increased glucose transporters. There is also an increase in the enzyme hexokinase, and a decrease in phosphatase, not allowing glucose and $^{18}$F-FDG to exit the cell.

PET provides added value over conventional imaging alone in a number of stages in the management of oncology patients. In cancer diagnosis, PET can be an effective indicator of benign versus malignant lesions. This is particularly relevant in the evaluation of the solitary pulmonary nodule, as discussed later. By imaging the whole body, PET leads to improvements in the staging of cancer, including local tissue involvement and the presence of distal metastases. In conjunction with CT, PET contributes to radiation therapy planning. Finally, the ability of PET to detect cancerous lesions makes it an effective tool for monitoring response to treatment and for subsequent follow-up of cancer patients.

The emergence of PET as an alternate imaging modality has led to an average 30% change in patient management across all cancer imaging, including 37% changes in lung and colorectal cancer, 33% in head and neck cancer, 23% in lymphoma, 23% in esophageal cancer, 29% in melanoma, and 28% in breast cancer. While PET plays a role in many different areas of oncology, this article will review the use of PET in 4 of the most common malignancies.

**Lung Cancer**

Lung cancer is the leading cancer related cause of death in Western society. A possible reason for this disappointing figure is that lung cancer is usually a late diagnosis. To date, CT has been the leading imaging modality used to diagnose and stage lung cancer. The primary curative treatment for lung cancers is surgical resection, but this therapy can lead to futile surgeries in benign or metastatic cancers. By using PET for lung cancer imaging, a more accurate diagnosis and staging may be obtained, reducing these futile surgeries.

CT can be a useful tool in detecting benign versus malignant tumours; however, the diagnosis is made from anatomical characteristics alone. PET has been shown to differentiate benign versus malignant tumors in solitary pulmonary nodules based on FDG uptake. In one meta-analysis, the sensitivity and specificity of FDG-PET in diagnosing focal pulmonary lesions of $\geq$ 1cm was found to be 97% and 78% respectively. Even though PET does demonstrate a relatively high sensitivity and specificity in diagnosing lung cancer, there are certain diseases that can hinder an accurate diagnosis. False-positives can occur in patients with tuberculosis and histoplasmosis and false-negatives in
Figure 4. A young man with Hodgkin’s Lymphoma. Initial CT (not shown) showed extensive mediastinal adenopathy but no disease outside of the mediastinum. Images (left) from a staging PET-CT (top: anterior PET image, bottom: axial fused PET and CT data) showed increased uptake in both supraclavicular (blue arrows) and mediastinal nodes (orange arrows). Images (right) taken from a follow up PET-CT show a complete metabolic response to therapy. Uptake low in the chest on the left is simply physiologic uptake in the heart at both time points, while increased generalized bone marrow uptake is typical post-chemotherapy.

Figure 5. A female with breast cancer underwent PET-CT scanning to assess for distal metastases. The scan showed the primary (orange arrow) and involvement of axillary, supraclavicular, and subpectoral lymph nodes (blue arrows), but no distal metastases.

Figure 6. This patient with prior colorectal cancer was found to have rising tumor marker levels. Conventional imaging was inconclusive, however PET showed a solitary metastasis in the liver (blue arrows), allowing proper therapy to be delivered. Note is made of intense uptake in both kidneys (yellow arrows) which is physiologic.
malignances less than 6mm and bronchioloalveolar carcinomas.\(^4\)

One of the greatest advantages PET has over CT is in the staging of lung cancer. In staging mediastinal cancers, PET has a pooled sensitivity and specificity of 84% and 89% respectively, while CT has a pooled sensitivity of 57% and specificity of 82%.\(^5\) By using PET to stage lung cancers, it has modified the treatment plan in 60% of patients, including high impact changes in 35%.\(^6\) One of the primary roles of lung cancer staging is to determine if the tumor is curative through surgery. Patients considered for surgery include those with stage I-II or stage IIIA.\(^7\) PET has frequently detected distant metastases in 5-10% of these patients with the most common sites being bone, liver and adrenal gland.\(^8\) In preoperative patients, new PET findings usually result in up-staging rather than down-staging, with the overall impact being less aggressive surgery and, more importantly, a reduction in futile thoracotomies from 41% to 21%.\(^9\)

PET is also useful in follow-up imaging after treatment to determine the viability of previously treated tumors. A recurrence of the tumor may be missed with conventional imaging because changes in tumor size and appearance may be due to scar tissue or necrosis. PET can be used to detect changes in tumor metabolism after treatment to determine the presence of residual malignancy in the treated mass. This information can be used for therapy monitoring and assessing for recurrence.

**Lymphoma**

The evaluation of patients with lymphoma includes physical examination, laboratory data, bone marrow biopsy, and imaging. CT has been the accepted imaging modality for Hodgkin’s Lymphoma (HD) and non-Hodgkin’s Lymphoma (NHL) and is the basis of the Cotswold staging classification for HD.\(^10\) CT evaluation for the presence of malignancy in lymphoma is based mainly on size criteria. PET, with its ability to functionally image lymph nodes, has an obvious advantage in the evaluation of malignancy. Further, the sensitivity of CT for extra nodal involvement is not optimal, as CT may miss peripheral sites which may be identified on PET due to the high tumor-to-background activity on PET. CT may also provide images in which it is difficult to distinguish between a malignant and fibrotic tissue following therapy.\(^11\)

Obtaining the correct staging of the disease is crucial for determining the proper patient treatment and prognosis. PET is well suited for whole body imaging and is considerably more useful in staging and assessing follow-ups. The use of PET in initial staging of HD up-staged 28.8% of the patients as compared to other imaging modalities and only 2.7% of the patients were down-staged.\(^12\) The results indicate that PET use in initial staging and diagnosis can impact the expected prognosis of patients with HD. In a meta-analysis of twenty studies that looked at the diagnostic performance of PET in staging lymphoma, PET was found to have a median sensitivity of 90.3% and a median specificity of 91.1%.\(^13\) The pooled false-positive rate was 10.3% and appeared to be higher in those with HD as compared to those with NHL. These results indicate that PET is an effective tool for staging and re-staging patients with lymphoma. In a retrospective study, it was found that of 1537 anatomical sites assessed, 48 of those sites had inconsistent PET and CT findings. Of those 48 sites, PET findings were correct in 83% (31 positive) of the cases, whereas CT had only five correct findings.\(^14\) Furthermore, PET gave the correct staging in 9 of the 53 total patients where CT staging was incorrect.

PET has shown to have better sensitivity and specificity than CT in staging lymphoma. PET scans are occasionally used in the radiation planning process. In a retrospective comparison of PET and CT use to assess the radiation therapy planning process, Lee et al. (2004)\(^15\) found that in 10/17 patients with positive PET and CT findings, the gross tumor volume was found to be smaller on PET in six of the cases. Consequently, the use of PET in radiation planning may reduce the subjectivity of the radiation treatment dose, potentially altering patient management.

PET can also be a useful tool in following post-treatment responses in patients with HD. In 28 patients following treatment for HD, CT had a sensitivity of 25% and a specificity of 42% whereas PET had a sensitivity and specificity of 100% and 83% respectively.\(^16\)

**Breast**

Breast cancer is the most common female cancer in the US and the second most common cause of death in women.\(^17\) Although it is curable if detected early enough, approximately one third of the patients diagnosed with breast cancer will die of the disease.\(^18\) Mammography is the imaging modality routinely used to detect breast cancer and while the sensitivity of mammography is excellent, the specificity is relatively low because of high false-positives.\(^19,20\) While not indicated in routine screening due to its high rate of false-negatives, especially in tumours < 10mm,\(^21\) primary breast cancers visualized on PET may reveal important prognostic factors. A high degree of \(^18\)F-FDG, for example, has
PET's main application in breast cancer is in distal staging and evaluating for recurrence. Clinical response is determined after several cycles of chemotherapy by measuring changes in tumor size as assessed by conventional imaging procedures including CT, MRI, plain film radiography, or ultrasound. A major advantage of PET imaging compared with conventional imaging is that it scans the entire patient for local recurrence, lymph node metastases and distant metastases during a single whole-body examination. PET has a reported sensitivity and specificity of 85.2% and 82.6% respectively in patients with breast cancer after neo-adjuvant chemotherapy.\textsuperscript{24} In 25 women with a suspected relapse of breast cancer, PET showed increased uptake in 43 areas, 22 correctly confirming the area of suspected relapse and 21 indicating other sites of metastases. Compared with conventional imaging, PET revealed additional lesions in two women with primary cancers and three with relapse, changing patient management for five women.\textsuperscript{25}

**Colorectal**

The incidence of colorectal cancer in Western society is approximately 12-13%, making it one of the most common types of cancer. Colorectal carcinoma is the third most common malignancy in men, second in females and fourth leading cause of cancer death.\textsuperscript{26} When diagnosed early, surgical treatment is frequently curative with minimal morbidity and mortality rates.

Colonoscopy and barium enemas are the standard modes of detection of primary colorectal carcinoma. PET has been used as an effective imaging method for recurrent colorectal cancer, but its role in detecting primary lesions has not yet been established. In a prospective study of 45 patients with colonic neoplasms, PET had a sensitivity of 62%. PET only detected 14% of protruded premalignant lesions between 1 and 1.9 cm, 17% of cancers smaller than 2 cm and only 23% of flat premalignant lesions. However, PET did detect 100% of all cancers greater than 2 cm.\textsuperscript{27}

PET is primarily used in the detection and localization of recurrent cancer in patients with rising carcinoembryonic antigen (CEA) levels and it can also be helpful in contributing to surgical decision making. In a comparison of one hundred whole-body PET scans of patients with colorectal cancer with CT, liver ultrasound, and a carcinoembryonic antigen test, PET had a sensitivity of 98% and a specificity of 90%. The respective sensitivity and specificity for CT was 91% and 72% and for the CEA test 76% and 90%. For the detection of liver metastases PET had a sensitivity of 100% and a specificity of 99% whereas ultrasound had a sensitivity of 87% and specificity of 96%.\textsuperscript{28}

**PET in Neurology**

Dementia is a neurodegenerative disease that can have a tremendous impact on the patient, their family and society in general. Management of patients with dementia relies on early recognition and accurate assessment of cognitive and behavioral symptoms. Through the combination of history and physical exam, laboratory tests and structural neuroimaging (CT and MRI), an appropriate management plan may be implemented. Over the past two decades studies have shown that neurodegenerative diseases can produce alterations in brain metabolism that can be measured with PET.\textsuperscript{29} PET can also distinguish normal degenerative changes due to aging versus dementia, and it can be used to assess very early stages of the disease. In a study of 284 patients undergoing evaluation for dementia with PET studies, progressive dementia was found with a sensitivity and specificity of 93% and 76% respectively. Regional brain metabolism is a sensitive indicator of Alzheimer’s dementia (AD) and neurodegenerative diseases in general.\textsuperscript{31}

Considerable data exists that supports the idea that the pattern of metabolism and perfusion abnormalities in AD is quite different from frontal lobe dementia, which is characterized by reduced frontal lobe metabolism and perfusion.\textsuperscript{31} In AD, there is temporoparietal hypometabolism.\textsuperscript{32} Dementia with Lewy Bodies is also clinically different than AD, displaying temporoparietal hypometabolism along with abnormalities in the visual association cortex of the occipital lobe.\textsuperscript{33}

Complex partial seizures remain uncontrolled in a significant proportion of patients despite medical therapy. Surgical removal of the epileptogenic foci in partial seizures results in significant improvement in control of the seizures.\textsuperscript{34} MRI is capable of detecting the source of the seizures in the majority of patients with partial seizures. However, about 20-30% of the patients with focal epilepsy have a normal MRI. The main clinical use of PET in epilepsy is the localization of the epileptogenic foci in surgical candidates with partial seizures and combining this with other investigational modalities such as electroencephalography. In partial seizures, there is an increase in glucose metabolism and
cerebral blood flow in the region of the epileptogenic foci during the ictal period.\textsuperscript{35} Due to the difficulties in injecting and imaging during the ictal period, most studies are done during the inter-ictal period when the area of interest actually shows hypometabolism on PET imaging.

Clinical detection of the various movement disorders can be very difficult, especially in the early stages. Furthermore, MRI often reveals no structural abnormalities. FDG PET in Parkinson’s disease shows normal to increased glucose metabolism in the striatum, but decreased metabolism in the temporoparietal areas.\textsuperscript{36} More novel radiopharmaceuticals have also been used. In particular, \textsuperscript{18}F-DOPA has shown promise in the evaluation of Parkinson’s disease.

**PET in Cardiology**

Cardiac nuclear imaging is performed on a regular basis with traditional (non-PET) radiopharmaceuticals and imaging with a single photon emission computed tomography (SPECT) camera. Although similar, cardiac imaging with PET offers potentially better capabilities. The two main applications are in assessing myocardial perfusion and myocardial viability.

**Figure 8.** PET images of the heart. Top two rows are short axis views through the left ventricle; bottom two rows are long axis views. In both sets, the upper row is a PET perfusion study using \textsuperscript{13}N-ammonia, while the lower row is a PET metabolism study using \textsuperscript{18}F-FDG. There are extensive, severe, perfusion abnormalities, but these areas show normal \textsuperscript{18}F-FDG uptake and hence are viable. Thus, the patient will likely benefit from a revascularization procedure.

**Figure 7.** PET images of the brain. The top row demonstrates normal brain metabolism. The bottom two images were taken from a patient with Alzheimer’s dementia and show marked hypometabolism of the parietal lobe bilaterally (arrows).
With respect to myocardial perfusion, the PET approach offers the potential to measure absolute coronary blood flow and coronary blood flow reserves, while SPECT only shows relative regional myocardial perfusion. Further advantages of PET include better resolution and accurate attenuation correction. When compared with the gold standard of invasive coronary angiography, cardiac PET, using 31N ammonia and 18RB, has demonstrated an overall sensitivity of 93% and specificity of 92% when diagnosing coronary artery disease.\(^\text{27}\) In comparison to SPECT, Go and colleagues showed a 95% sensitivity and 82% specificity for 82RB PET compared to a 79% and 76% respectively for SPECT.\(^\text{38}\)

In assessing myocardial viability, the intent is to determine whether areas of poorly perfused myocardium are still alive and hence may benefit from revascularization. Viability may be assessed with SPECT agents, MRI, dobutamine echo, or PET, with PET generally considered the gold standard. Viable myocardium metabolizes glucose, and hence viability assessment with PET is predicated on demonstrating 18F-FDG uptake in the areas of poorly perfused myocardium.

Conclusion

The impact of positron emission tomography on expected management of patients with cancer was recently studied by Hillner et al. They found that PET was associated with a change in management for 43.1% of patients.\(^\text{39}\) It has also been consistently demonstrated that PET finds more sites of active disease than CT or other imaging modalities. PET is a powerful tool in the management of cancer patients and shows significant promise in many other fields including neurology and cardiology.

References


PHYSICIANS
Laval QC, Kanata Ottawa, Vaughan Ontario, Edmonton Alberta, and Coquitlam BC

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