Examining the Efficacy of Positron Emission Tomography (PET) in Cancer Diagnosis

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Diagnostic imaging has become the cornerstone of cancer diagnosis. Over the past twenty years, computed tomography (CT) has become the most widely adopted imaging method for detection and staging of a variety of cancers. However, there are many limitations to the use of CT in the diagnosis of cancer. For example, CT does not have the ability to distinguish between malignant and benign lesions. As such, functional imaging methods, such as positron emission tomography (PET), has gained an increased following in the medical community. PET allows clinicians to evaluate the functional characteristics of tumours and is superior to CT in the staging of a variety of cancers. Despite these benefits, the regulatory boards that govern the healthcare system in Canada have been slow to adopt PET as a standard of care due to some of the inherent limitations of the technology. New technology, such as multi-modal imaging involving PET in combination with CT, will undoubtedly address some of these inherent limitations. These developments will continue to increase the pressure on healthcare administrators to re-evaluate their positions on PET use in cancer care. Herein, we discuss some of the benefits and limitations of PET use in cancer diagnosis.

This article has been reviewed by Dr. Jean-Luc Urbain.

Introduction

Positron Emission Tomography (PET) is playing an increasing role in the diagnosis and staging of cancers since its development in 1973. However, the rate of adoption has not been equal throughout all nations and technology uptake has been limited by the approval of funding authorities. In Canada, as of June 2005, there is an installed base of 12 PET scanners, only 3 of which are available for clinical usage. This situation has created a dilemma for public health officials, nuclear medicine diagnosticians, and cancer patients alike as the debate continues over the clinical utility of PET scanning. This review describes the role of PET in oncology.

Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a medical imaging technique whereby a radioactive tracing compound is administered to a patient and the resulting radiation emissions detected by a detection array. These emissions are then analysed and reassembled into a three dimensional image of the target body region. The radioactive tracing agents all emit positrons (positively-charged electrons). When this emitted positron collides with a regular negatively-charged electron, two gamma rays are released at 180 degrees apart from each other. The PET detector array surrounds the patient in the shape of a ring. When two gamma rays are simultaneously detected on opposite sides of the ring, the trajectory of the rays can be traced back to their origin. A single trajectory is insufficient to compile an image. However, over the course of an acquisition, enough trajectories are detected to be analysed and compiled into an image. When these radioactive tracing agents are manufactured, they usually come in the form of modified molecules commonly found in the body. The most commonly used agent, $[^{18}\text{F}]$ fluorodeoxyglucose (FDG), is an analog of glucose that cannot be metabolized by the body. FDG tends to accumulate in tumour cells with higher metabolic rates, which uptake greater amounts of glucose. This allows for high-contrast differentiation between tumours and normal tissues as well as more accurate diagnosis and staging, especially with regards to metastasis.
Clinical and Economic Evidence Supporting Usage

The effectiveness of PET scanning in the diagnosis and staging of tumours has been strongly established for several types of cancer, namely lung cancer, breast cancer, and colorectal cancer. Research from Brink et al. found significant increases in the sensitivity of FDG-PET in detecting and staging small-cell lung cancer over conventional imaging methods. In breast cancer patients, FDG-PET was able to find distant metastases in “30% of patients who were thought only to have local-regional recurrence” ultimately suggesting that PET may be useful for patients suspected of having tumour recurrence as well as identifying distant sites of metastases. Also important in the treatment of breast cancer is axillary lymph node staging, identified as a key factor in patient survival. While the majority of Stage I/II Canadian breast cancer patients currently undergo axillary lymph node dissection as a diagnostic methodology, it has been suggested that PET could offer a less invasive option. Similar results have been found using PET in the initial diagnosis of colorectal cancers. Although PET performed similarly to X-Ray Computed Tomography (CT) in the diagnosis of local lymph node involvement, PET was found to be superior to CT in the detection of hepatic metastases, with significantly greater sensitivity (88% vs. 38%).

Equally important to the usage of PET are issues of expense and cost-effectiveness. In an article by Valk et al., the cost-effectiveness of whole-body PET staging of multiple cancers was determined with the main finding being that surgical procedures averted through PET use resulted in savings ratios of 2:1 to 4:1. An economic analysis using PET for the work-up of pulmonary nodules and small-cell lung cancer in Italy found an overall cost savings using PET with very high sensitivity (89% - 94%) and specificity (80% - 100%). Canadian economic analysis confirms the cost-effectiveness of PET for staging for cancers. In an Alberta study, the cost per scan was found to range from $1,231 if 3200 annual scans were performed to $7,869 if 400 annual scans were performed, with a large portion of the cost coming from regulatory requirements. These per scan costs represent a significant savings over current rates from the United States. Research from Newfoundland found an estimated cost per PET study of $2,195 and that each PET device would only require 740 cases per year to break even.

Limitations of FDG-PET in Oncology

The major drawback in the use of PET is the prevalence of false-positives. The stomach, colon and small intestine are capable of FDG uptake making it difficult to distinguish normal tissue from neoplasms. In addition, since FDG is excreted via the urinary tract, intense accumulations of FDG can be found in the kidney and bladder which can limit PET use in the evaluation in gynecologic malignancies as well as exclude its use for detecting tumours of the bladder, local pelvic lymph nodes and prostate.

Inflammation is another confounding process in the use of FDG-PET. This becomes particular important in cancer patients that have been treated with chemotherapy or radiotherapy in which tissue damage has occurred, and the possibility of inflammation is high which sometimes requires weeks to months for healing before PET-FDG can be used. Related to the inflammation-based false-positives, infections, such as tuberculosis, can result in elevated FDG uptake in local lymph nodes making it difficult to differentiate between a lymph node neoplasm and immune cell proliferation. Other forms of healing, such as bone and joint processes, can also give false-positives. Healing bone can show FDG uptake for up to 6 months after sustaining an injury. Degenerative joint disease can also show elevated FDG uptake resulting in an intense, asymmetric signal that could be misdiagnosed as an osseous neoplasm.

Another major problem area, in the use of PET in an oncology setting, relates to FDG-PET use in endocrine tumours. Gastropancreatic neuroendocrine tumours have had limited detection success rates such that only tumours that have very high proliferative rates and a low stage of differentiation have been identified using FDG-PET. Hyperglycemia is another major limitation in the use of FDG-PET. This is particularly prevalent in pancreatic tumours or small pancreatic masses in patients with diabetes mellitus. Finally, in patients with pheochromocytoma, a neuroendocrine tumour of the adrenal gland, FDG-PET is incapable of distinguishing between the malignant form and the benign forms of the disease.

The Future of PET

While FDG uptake is substantially higher in most types of tumours, there are many exceptions, some of which have already been mentioned. Another drawback in the use of FDG as a tumour detecting tracer is that it does not differentiate between specific types of cancer. As such, a variety of alternative tracers are currently being investigated for their application in cancer therapy. These alternative tracers are based on DNA analogs to detect rapidly proliferating cells, amino acid analogs that detect cells producing higher levels of proteins and receptor agonists that allow for the identification of tumours expressing...
specific markers. A good example of this, is $^{18}$F-fluoro-17-β-estradiol which binds to estrogen-receptor positive breast cancer cells which, in this case, would alter the course of treatment for the cancer.

Paralleling the development of these new tracers is the use of supplemental imaging technologies, such as CT, in conjunction with PET. PET/CT produces better body maps in less time and as such the higher initial equipment costs are offset by increased throughput. The improved anatomical localization achieved using PET/CT can lead to improved diagnostic certainty, better biopsy guidance and ultimately better treatment for the patient. The only major drawback of PET/CT is the increased dosage of radiation the patient receives. Researchers have started to experiment with the possibility of PET/MRI since MRI provides better anatomical information and excellent soft tissue contrast over CT with far less radiation exposure. However, currently the detection technology used in PET scanners does not function well within the magnetic field of the MRI machinery.

Conclusion

The use of PET in the diagnosis of cancer has been a controversial topic among the medical community in Canada. This review has touched upon some of the major arguments in this continuing debate. It is apparent that PET usage in lung, breast and colorectal cancer has clear clinical advantages over current imaging technologies. Combined with many studies that show the diagnostic value of PET in these cancers actually decreases medical expenses, it becomes evident that the provincial governments across Canada should adopt PET scans as a standard in patient care in these situations. Conversely, it should be noted that PET is not an imaging panacea as there are many limitations in a variety of cancers. With new tracers and new technologies, like PET/CT, it is expected that the breadth of diagnoses that can be made with PET will increase. This will provide further impetus to examine the adoption of PET in more medical centres across the country.

References