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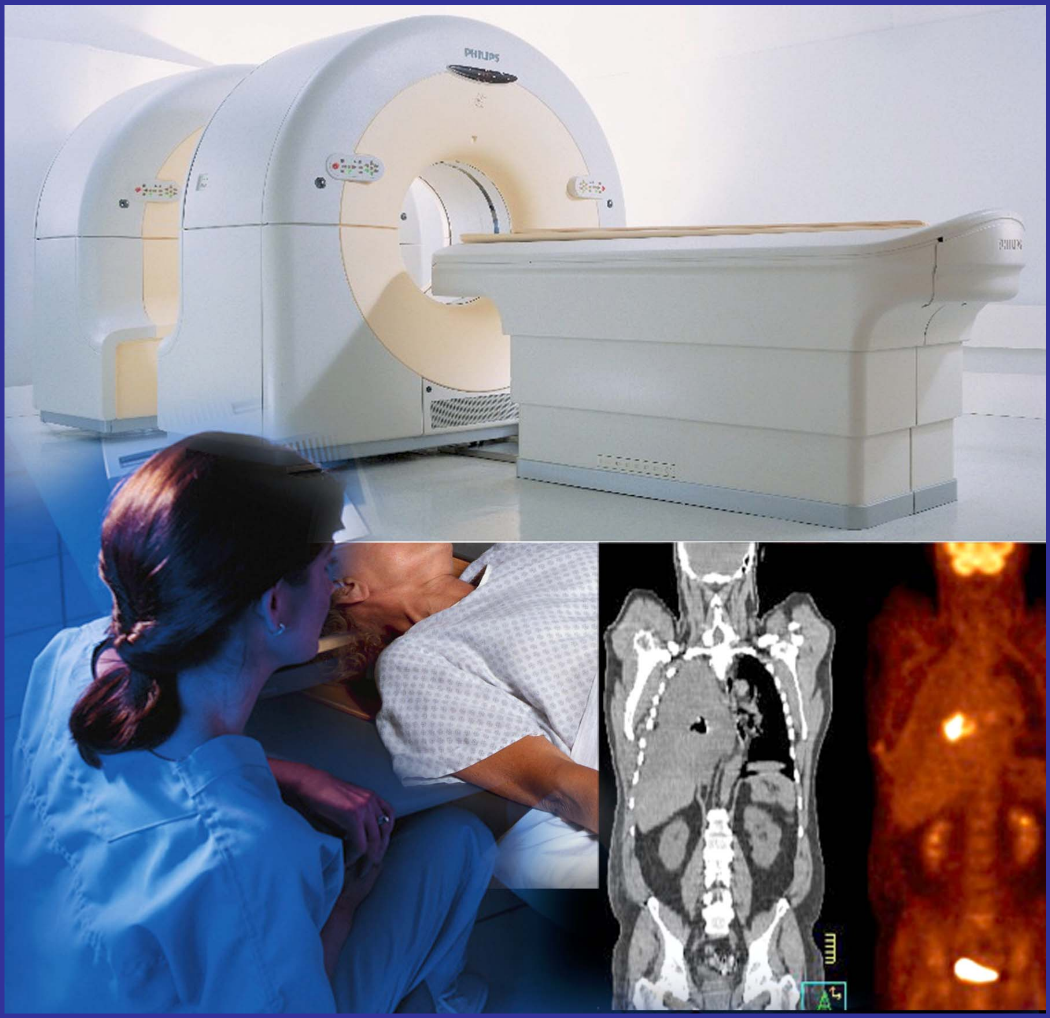
ICES Institute for Clinical Evaluative Sciences

Health Technology Assessment of Positron Emission Tomography (PET) - A Systematic Review -

Executive Summary



ICES Investigative Report

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Executive Summary

Purpose of this Report

This health technology assessment of Positron Emission Tomography (PET) was requested by the Committee on Technical Fees, a committee consisting of membership from the Ontario Ministry of Health and Long-Term Care (MOHL-TC), the Ontario Medical Association (OMA) and the Ontario Hospital Association (OHA). The Institute for Clinical Evaluative Sciences (ICES) was asked to a) review the existing literature about the diagnostic accuracy, effect upon patient outcomes and cost-effectiveness of PET, b) identify clinical indications for which PET is likely to be shown to be diagnostically accurate and cost-effective in the near future, c) estimate the number of patients in Ontario who may benefit from PET, given current information about its diagnostic accuracy, effectiveness and cost-effectiveness, and d) identify areas of clinical research related to PET that are of importance to Ontarians. This report was to consider the clinical use of PET only, not basic research using PET.

What is Positron Emission Tomography?

PET is an innovative technology that has been in use since the 1970s. In contrast to Computed Tomography or Magnetic Resonance Imaging which both provide images based upon anatomy, PET creates images that reflect biochemical processes and blood flow. Most radioisotopes used in clinical PET are combined with organic compounds. The most commonly used isotope is F18-fluorodeoxyglucose (FDG), which competes with glucose for absorption and metabolism in a wide variety of cells. Because cancer cells often use glucose at higher rates than normal or benign tissue, FDG can potentially identify a primary or metastatic cancer before structural evidence of disease is present. Similarly, metabolic activity within the brain, heart and other organs can be reflected by uptake of FDG.

A fully dedicated PET scanner has a sophisticated detection system that identifies photons of a specific energy that are traveling 180 degrees to each other, and complicated electronics that convert the photons that have been detected into a reconstructed image. Radioisotopes are used in this process and are produced by a cyclotron. Most radioisotopes used in PET have a short half-life, and therefore must be produced by a cyclotron located at the same site, or within a few hours travel from the scanner.

The average amount of time required for each scan varies from 30 minutes for a brain scan to 60 minutes for a whole body scan. PET has not been shown to have any side-effects in patients.

Cost of PET

The cost of PET scanning includes the cyclotron to produce the isotope (one cyclotron can supply more than one scanner, provided the off-site scanners are within a few hours travel from the cyclotron), the scanners themselves, the personnel needed to maintain the cyclotron and scanner, and the personnel required to ensure flow of patients through the scanner and to interpret the results. The costs of these items vary from region to region, but the best estimate, based upon expert opinion, of these costs in Ontario are: $3-4 million per cyclotron; $1.5-3 million per scanner; $600 thousand/year maintenance (per scanner and cyclotron); $600 thousand/year employee costs; and $250 thousand/year for other overhead costs.

Methodology of this Health Technology Assessment

An extensive systematic review of peer-reviewed, gray and web-based literature was undertaken, and updated until December 2000. Disorders of interest that were identified a priori were a) oncology (lung cancer, solitary pulmonary nodules, head and neck cancer, breast cancer, lymphoma or Hodgkin's disease, melanoma, colon cancer), b) cardiac disease (assessment of cardiac viability), and c) neurological disease (intractable epilepsy and dementia). Differentiating radionecrosis from recurrence in patients with brain tumours was subsequently added, at the suggestion of our Expert Panel. Because of the prevalence of coronary artery disease, a less systematic review of the usefulness of PET for the diagnosis of coronary artery disease was also undertaken.

The methodological quality of the articles that were identified was graded using a modification of a scheme used by the Veteran's Administration (VA) and the National Health Services Health Technology Assessments (NHS-HTA) of PET scanning. Studies received a score ranging from A (best quality) to C/D (poor quality). An a priori decision was made to concentrate upon A and B articles in this report.

Economic evaluations were identified by a separate literature search.

Administrative databases available at ICES, and the findings of a Canadian study in the case of epilepsy, were used to estimate the number of patients who might benefit from PET scanning, based upon the literature review.

An Expert Panel consisting of individuals with expertise in PET scanning, nuclear medicine, radiology, oncology, cardiology and cardiac surgery, neurology and neurosurgery, internal and family medicine, health economics and a representative of the public was formed. They were provided with a draft of the report and asked to provide written, detailed feedback, and also met face-to-face with the report's authors for a day. The Panel was then provided with a second draft of the report and asked to provide further feedback. The final decision about what to include in the report rested with the authors.

While in the process of writing the report, the authors became aware that L'Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AÉTMIS) in Quebec was also preparing a report on PET scanning. Both groups wrote their report independently, but shared drafts of their reports, and met once for a face-to-face meeting.

PET Scanning in Oncology

The number of Grade B articles found in oncology were solitary pulmonary nodule 2, lung cancer 12, colorectal cancer 2, squamous cancer of the head and neck 5, breast cancer 5, malignant lymphoma or Hodgkin's disease 5, malignant melanoma 3, and brain tumour 0. No Grade A articles were found. The most evidence available was for the diagnosis and staging of lung cancer. None of the studies in oncology assessed the impact of PET scanning on overall patient well being or quality of life. However, the effects of PET scanning upon a number of "intermediate outcomes" such as avoidance of thoracotomy in patients with metastatic or inoperable lung cancer was evaluated.

A review of the oncological literature suggests that PET scanning has a role for a) investigation of the solitary pulmonary nodule (some thoracotomies will likely be avoided), b) staging of primary lung cancer/evaluation of mediastinal lymph nodes (some thoracotomies and mediastinoscopies will likely be avoided), c) detection of residual or recurrent lung cancer (some bone scans may be avoided), d) detection of resectable recurrent/metastatic colorectal cancer, e) pre and post-therapy evaluation of squamous carcinoma of the head and neck (some CT scans may be avoided), f) axillary assessment in breast cancer if sentinal lymph node biopsy is not part of the evaluation, g) pre-therapy assessment of lymph node involvement, and evaluation of residual masses after completion of therapy in patients with lymphoma or Hodgkin's lymphoma (some CT scans will likely be avoided), and h) evaluation for silent metastases in malignant melanoma (some CT scans will likely be avoided). In addition to possibly decreasing the utilization of some other diagnostic tests or invasive procedures such as biopsies, more accurate knowledge of the extent of disease with PET scanning may change decisions about the aggressiveness of planned chemotherapy or radiotherapy, which can have important impacts upon mortality and quality of life. Decisions about clinical care vary from patient to patient - PET scanning should only be used if the results of the test will affect patient management.

PET Scanning in Cardiology

We did not review the literature regarding the use of PET to diagnose coronary artery disease with the same degree of rigor as we did evaluating its use to assess viability. A number of studies have shown that PET scanning is useful in diagnosing coronary artery disease, although its sensitivity and specificity is not much better than other non-invasive techniques such as SPECT in the overall population of patients referred for assessment of coronary artery disease. It has been suggested that PET may be superior to other non-invasive techniques in women, patients with left bundle branch block, and those with equivocal results with other non-invasive techniques. However, no studies of high methodological quality supporting this assertion were identified by ourselves or the Expert Panel. Therefore, given the cost of PET scanning, the availability of other non-invasive techniques for the investigation of coronary artery disease, and the poor quality of the evidence that PET scanning improves outcome in patients with suspected coronary artery disease, PET scanning cannot now be recommended for regular clinical use in the investigation of coronary artery disease.

PET scanning has been suggested as a method of identifying ischemic heart tissue in patients with moderate to severe heart failure that is reversible with revascularization procedures such as angioplasty or bypass surgery. One Grade A study was found evaluating the use of PET scanning for cardiac viability, and it failed to show any favourable effect upon outcome compared with SPECT. This study was relatively small (103 patients) and included a number of patients with only mild heart failure, and the generalizability to patients with severe heart failure is unknown. Other studies of poorer methodological quality have suggested potential benefits, although PET's incremental impact upon clinical outcomes (e.g., mortality, avoiding transplantation) compared with other non-invasive modalities was not investigated. Although in our opinion the available evidence does not support the routine use of PET for the assessment of viability at the present time, the state of evidence is evolving. Accordingly, we suggest that a re-evaluation of cardiac PET be conducted in 2-3 years.

PET Scanning in Neurology

The number of Grade A or B articles was 6 for intractable seizures and 8 for dementia. The literature suggests that PET scanning has a limited role in the investigation of patients with intractable seizures being considered for surgery (may help determine eligibility for surgery and avoid invasive diagnostic testing (e.g., intracranial electroencephalograms)). There is no evidence that PET scanning has a clinical role in the diagnosis or symptomatic management of dementia at the present time.

Economic Evaluations of PET

There were few high quality economic evaluations of PET, and none from Ontario or Canada. It is generally accepted that the sensitivity and specificity of a test are generalizable across borders. However, the costs of tests and interventions, and practice patterns vary widely among regions, making it very difficult to extrapolate cost-effectiveness ratios from one region to another. Therefore, the lack of economic evaluations from Ontario and Canada is unfortunate. The economic evaluations that were reviewed suggested that PET scanning is likely to have a favourable cost-effectiveness ratio in patients with lung cancer, those being investigated for a solitary pulmonary nodule, and patients with malignant lymphoma or Hodgkin's lymphoma. No high quality economic evaluations were found for other cancers, cardiac viability, or neurological indications. One high quality American economic evaluation found PET scanning to have an unfavourable cost-effectiveness profile for the routine diagnosis of coronary artery disease.

Numbers of Patients Who Might Benefit from PET Scanning in Ontario

A review of ICES databases suggest that in 2001 approximately 24,000 patients have the oncologic and seizure disorders that might benefit from PET.

Implementation of PET Scanning - Some Issues to Consider

Suggesting the number and location of PET scanners that should be introduced in Ontario, and the rapidity of their introduction, is not within the mandate of this report. However, planners will need to consider a number of issues including: a) the cost-effectiveness of PET scanning compared with other uses of limited health care resources, b) the number and location of cyclotrons relative to scanners (one cyclotron could serve more than one scanner), c) the need to train and retain highly skilled workers in PET (including physicists, maintenance personnel, and personnel to interpret the images), d) advances in the technology (e.g., the development of a combined CT and PET scanner), and e) how to determine which patients have access to a PET scanner.

Further Considerations

Despite the availability of PET scanning for almost three decades, the number of methodologically high quality studies (and the numbers of patients within those studies) is distressingly small. It is also possible that publication bias (the preferential publication of studies that show a benefit of PET scanning) may limit the evidence considered in this report. These two factors combine to make any conclusions about the usefulness of PET scanning less definitive than one would like.

Although better diagnostic techniques are welcome, in some instances the lack of dramatically effective therapy to complement the diagnostic tool is the more important issue.

In many instances PET is being compared with diagnostic technologies that themselves have not been rigorously evaluated, and it could be argued that PET is being held to a higher standard than some previous diagnostic tests. However, we believe that standards should improve over time, and given PET's expense and the competing demands for limited health care resources, that it is reasonable to expect the usefulness of PET to be supported by high quality studies prior to its introduction into routine clinical practice.

Clinical Research Priorities for PET Scanning in Ontario

The useful research that could be conducted to more definitively establish the role of PET scanning is substantial. However, three areas of clinical research appear to warrant immediate attention. First, rigorous cost-effectiveness studies using Ontario practice patterns and costs would be very helpful. Second, determining the usefulness of PET scanning for viability in patients with heart failure is a high priority, especially given the conflicting results in the literature and the increasing prevalence of heart failure (one randomized trial is already underway). Third, studies should be done on the optimal methods of managing waiting lists for PET scanning. Accessibility to expertise in clinical research design is mandatory for future research in PET in Ontario.

A registry of all patients having PET scans in Ontario should be developed which can be used for administrative and research purposes. The PET registry could be linked to other provincial databases. Although there are limits to the conclusions that can be drawn from registries, the information provided by such a registry would be very helpful in assessing the impact of PET scanning upon the use of other diagnostic modalities, patient management and outcome in Ontario.