Positron Emission Tomography (PET) in Oncology: A Systematic Review of Clinical Effectiveness and Indications for Use

[Adapted from Mujoomdar M, Moulton K, Nkansah E. *Positron Emission Tomography (PET) in Oncology: A Systematic Review of Clinical Effectiveness and Indications for Use*. (Health Technology Inquiry Service). Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010.]

Introduction

In 2008, approximately 166,400 new cases of cancer were diagnosed in Canada.[1] Accurate disease management along the continuum from diagnosis, staging, and monitoring treatment response, through to surveillance is critical to improving prognoses. Radiological imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are used in the management of cancers.[2]

PET is an imaging modality that is used to provide a three-dimensional image of functional changes in the body.[3] PET can be used to track the deposition of radioactive molecules to sites in the body.[4] The most common radioactive tracer is 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG).[5] FDG is a glucose analogue that accumulates in tissues with high metabolic activity, such as tumour tissue.[5] FDG uptake and accumulation is also increased in benign pathologies, including sites of inflammation, trauma, and infection. Therefore, precise anatomical information is critical to rule out areas of non-specific uptake of FDG and false-positives.[5] Hybrid scanners — PET/CT — that allow for the acquisition of information from the use of PET and CT simultaneously, are increasingly being used.[6] The hybrid scanners combine the functional information from PET with more precise structural and anatomical information from CT.[7] As of January 2008, 22 of the 24 publicly funded PET scanners that were operational or anticipated in Canada[8] were PET/CT.

PET is commonly used to detect and stage different types of cancer.[9] Accurate information about diagnosis and staging of disease is critical for planning the most appropriate treatment strategy.[4] PET has also been used to monitor therapy. The rationale for this is that the early detection of disease that is not responding to treatment could allow for a change to a more effective treatment strategy.[4] Whole-body PET has been used after first-line therapy to detect residual disease or sites of metastases.[10,11] Any sign of residual or recurrent disease could result in changes to the staging of disease and influence how the disease is treated.[4] The use of PET is on the rise, and the number of possible indications for PET use is increasing. This may be a challenge to the Canadian health care system and those responsible for coverage decisions. Access to PET varies across Canada. This report is a review of the evidence on the clinical effectiveness of PET for oncologic

conditions in adults compared with other imaging modalities, such as CT and MRI. Guidelines recommending indications for PET use in adults with cancer are also reviewed.

Objective

The objective of the report is to answer the following research questions:

- What is the clinical effectiveness of PET in oncology compared with CT and MRI when used as an adjunct to CT or MRI?
- What are the indications for PET use in oncology?

Methods

Published literature was obtained by cross-searching PubMed, MEDLINE, and Embase on the OVID search system between 2007 and December 4, 2008. Parallel searches were performed on The Cochrane Library (Issue 4, 2008) and the University of York's Centre for Reviews and Dissemination (CRD) databases. Results were limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews, health technology assessments (HTAs), meta-analyses, and guidelines. The websites of HTA and related agencies were searched, as were specialized databases, such as those of the National Institute for Health and Clinical Excellence (NICE), ECRI Institute, and EuroScan. The Google search engine was used to search for information on the Internet. Two independent reviewers screened articles for selection. This report was peer-reviewed by two clinical experts.

Results

Three HTAs, 10 systematic reviews, three meta-analyses, and 14 evidence-based guidelines were identified during the literature search.

Of the three HTAs identified in our literature search, the first[12] assessed the clinical effectiveness of PET in breast, colorectal, head and neck, lung, lymphoma, melanoma, esophageal, and thyroid cancers. The use of FDG-PET for diagnosis, staging or restaging, and monitoring recurrence and treatment for each cancer type was evaluated. The authors concluded that the highest quality evidence on the clinical effectiveness of PET was in the detection of distant metastases, staging or restaging of colorectal cancer, detection of solitary pulmonary nodules (SPNs), staging of non-small cell lung cancer (NSCLC), and restaging of Hodgkin disease.

The second HTA[13] reviewed the use of PET in monitoring the treatment response among women with breast cancer. The evidence suggested that PET may be useful in the identification of patients with advanced breast cancer who are not responding to neoadjuvant treatment and patients with metastatic disease who are responding to treatment.

The third HTA[14] examined the use of PET for monitoring the response to treatment of Hodgkin disease and non-Hodgkin lymphomas (NHLs). The authors concluded that a positive PET scan (specific uptake of FDG) during the monitoring of treatment of response is predictive of death or disease progression.

Ten systematic reviews and three meta-analyses were indentified in our literature search. Overall, the systematic reviews and meta-analyses concluded that PET had the highest accuracy for the detection of cancers originating in the lung, pancreas, and head and neck region, and cancers of unknown primary origin. PET was effective in the staging or restaging of breast, colorectal, esophageal, head and neck, lung, lymphoma, and melanoma cancers. The clinical effectiveness of PET for the detection of lymphoma, residual or recurrent breast cancer, colorectal cancer, head and neck cancer, and thyroid cancer was also demonstrated by the systematic reviews and meta-analyses. PET was neither effective in the staging of local lymph nodes in patients with melanoma, nor was it effective in the initial staging of lymphoma. Many systematic reviews concluded that PET was promising and that more research in the form of randomized controlled trials would help to define its use in the management of cancers.

Fourteen evidence-based guidelines were identified by the literature search on the use of PET in the management of cancers. Some guidelines did not grade the recommendations or did not report them. Of the guidelines that reported the grades, the highest recommendations for the use of PET were in the diagnosis of SPNs, in the staging of mediastinal lymph nodes in lung cancer, in the detection of extra-thoracic metastases in lung cancer, and in the detection of extra-hepatic metastases in colon cancer that spread to the liver. A quality assessment of these guidelines was not performed.

Limitations

This review has limitations. A limited literature search was conducted, and studies that were not cited in the databases searched may have been omitted. Evaluations of studies of PET use in children as well as economic evaluations were not included in this report. Recently published randomized controlled trials that were not reviewed in an HTA or a systematic review were not

included. Additional study types, including registries,[15] were also not included, because of the broad scope of this report.

Despite the large number of studies on the clinical effectiveness of PET for cancers, few studies compared PET with CT or with MRI. In addition, few studies evaluated the use of PET/CT. Because of the paucity of data on PET use in some cancers, studies that were deemed to be of low quality were often included.

In addition, reviews often combined prospective and retrospective data or the study type was not reported. Observational studies may not control for potential bias. Some of the studies that were included in the systematic reviews were subject to potential biases: the populations comprised patients with early- and late-stage disease, and the reference standard test was only used to validate a positive PET scan.

Conclusions

The studies that are included in this review suggest that PET may be similarly effective or more effective than CT or MRI for some cancer indications. There is moderate-quality evidence that PET is effective in the diagnosis or detection of cancer of the breast,[3] pancreas,[3] head and neck,[12] and lung (SPNs).[3] Consistent evidence reported as low quality suggests that PET may be useful in the diagnosis of cancer of unknown primary origin when conventional workup has failed.[3,16,17] Evidence, reported as high quality, is available for the use of PET in the staging of NSCLC.[3]

Staging or restaging in colorectal,[3] esophageal,[3] head and neck,[3,18] and breast cancers[3] is supported by moderate-quality evidence. Consistent evidence reported as low quality suggests that PET may be useful in the staging of lymphoma.[3,19] The use of PET to monitor treatment response in lymphoma[14] and metastatic breast cancer[13] is supported. PET that is used to restage or detect residual disease or recurrence (local or distant sites) in colorectal cancer,[3,12,20] head and neck cancer,[3,12] lymphoma (NHL),[3,12] and breast cancer[3,21] is supported by evidence reported to be of moderate quality.

There is limited evidence from studies with high internal validity (for example, studies that randomize the interventions being given to different groups of patients) to support PET use for some indications. In 2009, Ontario amended their PET coverage policy and continues to collect evidence on PET effectiveness.[22,23] There is an increased demand for the use of PET. Other considerations, including access to PET, costs of operating the scanner, appropriate space to

house the scanner, access to radiotracers, and appropriately trained staff will likely contribute to deciding the funding of PET use for various oncologic indications. A document referencing this current report was recently published by the Health Technology Policy Forum,[24] in addition to a Canadian Agency for Drugs and Technologies in Health environmental scanning report on PET scanning in Canada.[25]

The results of this review suggest that PET may be effective in aspects of the management of some cancers, including diagnosis, staging, and monitoring of treatment and recurrence. In some instances, PET may be more effective when compared with other imaging modalities currently used as standard-of-care. This information as well as the evidence from ongoing trials and field evaluations, an evaluation of the impact of PET on changes to treatment decisions, and assessments of cost-effectiveness would contribute to the decision-making process.

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