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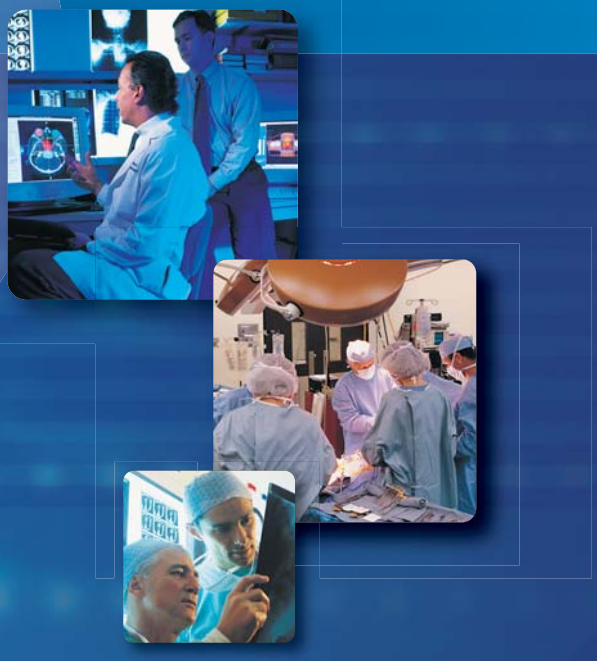
Positron Emission Tomography (PET) in Oncology: A Systematic Review of Clinical Effectiveness and Indications for Use



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

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April 2010

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision-making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision-makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision-makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

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CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of reviewers.

This document is prepared by the Health Technology Inquiry Service (HTIS), an information service of the Canadian Agency for Drugs and Technologies in Health. The service is provided to those involved in planning and providing health care in Canada. HTIS responses are based on a comprehensive and systematic search of literature available to CADTH at the time of preparation. The intent is to provide a list of sources, a summary, and a critical appraisal of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. This response has been peer-reviewed by clinical experts. The information in this document is intended to help Canadian health care decision-makers make well-informed decisions and thereby improve the quality of health care services. HTIS responses should be considered along with other types of information and health care considerations. It should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process or as a substitute for professional medical advice. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found but which may in future prove to be effective. While CADTH has taken care in the preparation of the document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

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Conflict of Interest: Dr. Steven Kymes has received research support and has done consulting for Pfizer Inc. and Allergan Inc.

ACRONYMS AND ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
ALND	axillary lymph node dissection
CI	confidence interval
CMM	cutaneous malignant melanoma
cN0	clinically node negative
CNS	central nervous system
CRD	Centre for Reviews and Dissemination
CT	computed tomography
DACEHTA	Danish Centre for Health Technology Assessment
FDG	2-[^{18}F] Fluoro-2-deoxy-D-glucose
HD	Hodgkin disease
HTA	health technology assessment
MRI	magnetic resonance imaging
NHL	non-Hodgkin lymphomas
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NSCLC	non-small cell lung cancer
PET	positron emission tomography
QADAS	quality assessment of studies of diagnostic accuracy
RCT	randomized controlled trial
SCLC	small cell lung cancer
SIGN	Scottish Intercollegiate Guidelines Network
SLNB	sentinel lymph node biopsy
SPN	solitary pulmonary nodule
sROC	summary receiver operating characteristic
UK	United Kingdom

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

DATE: April 2010

EXECUTIVE SUMMARY

Context and Policy Issues

In 2008, approximately 166,400 new cases of cancer were diagnosed in Canada. Radiological imaging modalities, including positron emission tomography (PET), are used in the diagnosis, staging, assessment of treatment response, and monitoring of recurrence of cancers.

PET is a modality that is used to provide a three-dimensional image of functional changes in the body. PET can be used to track the deposition of radioactive molecules to sites in the body. The most common radioactive tracer is 2-[^{18}F] Fluoro-2-deoxy-D-glucose (FDG). FDG is a glucose analogue that accumulates in tissues with high metabolic activity, such as tumour tissue. In addition to its use in cancer diagnosis, PET is commonly used to determine the stage or extent of disease for various types of cancers. The approach to treating the cancer will depend on the stage. Therefore, accurate information about diagnosis and staging is critical for planning the most appropriate treatment strategy. PET is also used to assess how a person is responding to treatment during or at the end of the treatment, and to monitor if the cancer has recurred after treatment.

The use of PET is on the rise, and the number of possible indications for PET use is increasing. Access to PET varies across Canada. With an increasing number of Canadians being diagnosed with cancer each year, there is a need to review the evidence on the clinical effectiveness of PET for oncologic conditions compared with other imaging modalities including computed tomography (CT) and magnetic resonance imaging (MRI).

Research Questions

1. What is the clinical effectiveness of positron emission tomography (PET) in oncology compared to computed tomography (CT) and magnetic resonance imaging (MRI) when used as an adjunct to CT or MRI?

2. 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.

Summary of Findings

Three HTAs were identified in our literature search. The first HTA 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, staging of non-small cell lung cancer (NSCLC), and restaging of Hodgkin disease.

The second HTA 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 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, head and neck region, and cancers of unknown primary origin. PET was effective in the staging or restaging of breast cancer, colorectal cancer, esophageal cancer, head and neck cancer, lung cancer, lymphoma, and melanoma. The systematic reviews and meta-analyses described the clinical effectiveness of PET for the detection of lymphoma, residual or recurrent breast cancer, colorectal cancer, head and neck cancer, and thyroid cancer. PET was not 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 (RCTs) 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 grade, the highest recommendations for the use of PET were in the diagnosis of solitary pulmonary nodules, 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 has spread to the liver. A quality assessment of these guidelines was not performed.

Conclusions and Implications for Decision- or Policy-Making

The studies that are included in this review suggest that PET may be similarly or more effective than other imaging modalities (CT or MRI) in some oncologic indications. There is moderate-quality evidence that PET is effective in the diagnosis or detection of cancer of the breast, pancreas, head and neck, and lung (solid pulmonary nodules). Low-quality, consistent evidence suggests that PET may be useful in the diagnosis of cancer of unknown primary origin when conventional workup has failed. Evidence that is reported to be of high quality is available for the use of PET in the staging of

NSCLC. Staging or restaging in colorectal, esophageal, head and neck, and breast cancer is supported by moderate-quality evidence. Some evidence suggests that PET may be useful in the staging of lymphoma. The use of PET to monitor treatment response in lymphoma and metastatic breast cancer is supported. PET that is used to restage or detect residual disease or recurrence (in local or distant sites) in colorectal cancer, head and neck cancer, lymphoma (NHLs), and breast cancer is supported by evidence that is reported to be of moderate quality. This information and an evaluation of the impact of PET on patient management and assessments of cost-effectiveness would contribute to informed decision-making.

1 CONTEXT AND POLICY ISSUES

In 2008, approximately 166,400 new cases of cancer were diagnosed in Canada.[1] Accurate disease management along the continuum from diagnosis, staging, 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 publically 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 including CT and MRI. Guidelines recommending indications for PET use in adults with cancer will also be reviewed.

2 RESEARCH QUESTIONS

1. What is the clinical effectiveness of positron emission tomography (PET) in oncology compared to computed tomography (CT) and magnetic resonance imaging (MRI) when used as an adjunct to CT or MRI?
2. What are the indications for PET use in oncology?

3 METHODS

3.1 Literature Search

Published literature was obtained by cross-searching PubMed, MEDLINE, and EMBASE on the Ovid search system between 2007 and October 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. Regular alerts were established on PubMed, MEDLINE, and Embase, and information retrieved via alerts is current to December 4, 2008. The 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, and EuroScan. The Google search engine was used to search for information on the Internet.

3.2 Study Selection

Two independent reviewers (MM and KM) reviewed the titles and abstracts that were retrieved during the literature search. Studies that were eligible for inclusion were HTAs with a systematic review, systematic reviews, systematic review-based meta-analyses, and evidence-based guidelines. Seventy-one studies were reviewed. The same two reviewers independently evaluated the full-text version of all articles. After initial screening, 71 articles were retrieved for consideration. Inclusion was limited to studies that reported diagnostic accuracy test characteristics (sensitivity and specificity). Studies assessing PET and PET/CT scanners were included. Only studies using FDG as a radiotracer were summarized. Thirty articles were included. We did not perform an independent quality assessment. Most of the included HTAs and systematic reviews had a quality assessment of the identified literature using assessment tools for which details are provided. The reasons for exclusion were that the reviews did not seem to be systematic, articles were in a language other than English, or the PET diagnostic accuracy was not assessed, but changes to patient management after the use of PET was the study's sole objective. Guidelines were included if they seemed to be evidence-based and included a systematic search. Guidelines that assessed the appropriateness of PET and clinical practice recommendations were not included in this report. Any differences in the selection of articles were resolved by discussion and consensus between reviewers. This report was peer-reviewed by two clinical experts.

4 SUMMARY OF FINDINGS

Three HTAs, 10 systematic reviews, three meta-analyses, and 14 evidence-based guidelines were identified during the literature search. Two articles identified by an external reviewer but which did not meet our inclusion criteria appear in Appendix 1. These two studies examine the role of PET in treatment decisions.

4.1 Health Technology Assessments

Three HTAs were retrieved during the literature search. The first HTA, which was conducted by the National Institute for Health Research (NIHR) HTA program in the United Kingdom (UK), examined the clinical effectiveness of FDG-PET imaging in selected cancers.[12] The objectives of this

HTA were to assess the clinical effectiveness of PET in breast cancer, colorectal cancer, head and neck cancer, lung cancer, lymphoma, melanoma, esophageal cancer, and thyroid cancer. Included in this assessment were studies on dedicated PET and PET/CT hybrid systems. This report was an update to a report that was published in May 2004.[13] The systematic literature search for the updated report was conducted in August 2005 and included English-language systematic reviews published since May 2004; systematic reviews published in French, German, Spanish, or Italian since 1966 (although those published before 2000 were unselected by investigators); and English and non–English-language primary studies published since 2000. After the study selection criteria were applied, six systematic reviews (four English and two non-English language) and 158 (152 English and six non-English language) primary studies were included in the report. The quality of the studies was assessed using the quality assessment of studies of diagnostic accuracy (QUADAS) tool. The authors of the HTA described studies as low, moderate, or high quality. The numerical scores that corresponded to the qualitative descriptions were not reported. Some of the systematic reviews discussed the effectiveness of PET for more than one type of cancer. Non-English language reports were professionally translated. The systematic reviews and primary studies that were included in the May 2004 report were discussed again by the authors of the updated report. The use of FDG-PET for diagnosis, staging or restaging, and monitoring recurrence and treatment for each cancer type was evaluated. An overview of the evidence that is included in this HTA on the parameters is stratified here by cancer type.

4.1.1 Breast Cancer

Only studies evaluating the use of dedicated PET (not PET/CT) for the management of breast cancer were identified. One systematic review evaluated 13 studies (606 participants) of women who were referred for biopsy, who were suspected of having breast cancer, and who did not have palpable lymph nodes. The intention in these studies was to use PET first and avoid biopsy if the PET result was negative. A summary receiver operating characteristic (sROC) analysis of PET sensitivity and specificity was 89% and 80% respectively. The authors of this systematic review considered the individual risk of a false-negative to be too high given that the opportunity to intervene early and treat the disease optimally would be missed for a gain of avoiding a biopsy. The authors suggested that the use of PET as an alternative to biopsy was insufficiently accurate to recommend in the diagnosis of breast cancer. The HTA included one study that was not part of the systematic review. This study compared the diagnostic capabilities of PET to MRI in 36 women with suspicious breast lesions on mammography. The sensitivity of PET was 76% compared with 95% for MRI. The specificity was identical for both imaging modalities (73%).

One systematic review (including eight primary studies with 337 participants) evaluated PET for staging axillary lymph nodes. Four of the studies that were included in the systematic review compared the sensitivity of PET to the reference standard of sentinel lymph node biopsy (SLNB) in combination with axillary lymph node dissection (ALND) in patients with clinically node negative (cN0) axillae. PET sensitivity ranged from 20% to 50%. The authors concluded that PET cannot be used to avoid the use of ALND in patients with

clinically negative axillae. An estimate of PET sensitivity was not reported in the remaining four studies. The HTA included four primary studies that were not part of the systematic review. The number of participants in these studies ranged from 24 women to 325 women. These studies compared the use of PET to ALND plus SLNB or to ALND alone for staging axillary lymph nodes. The reported sensitivities of PET were between 20% and 84%, and the reported specificities of PET ranged from 80% to 98%.

The HTA included one systematic review of three studies (142 participants). One additional primary study (32 participants) reported on the accuracy of PET compared with MRI or CT to detect disease recurrence at locoregional sites (and not recurrence at distant sites). The evidence from the systematic review suggested that PET had a lower sensitivity than CT or MRI. The specificities were similar. The additional primary study reported the sensitivity of PET to be higher than that of MRI (100% compared with 79%). The specificity was lower (72% compared with 94%).

One systematic review of 18 primary studies (the number of participants in each study was not reported) evaluated PET for the detection of metastases in primary, recurrent, or suspected recurrent cancers. Two studies were lesion-based instead of patient-based and were not assessed in the HTA. An sROC analysis of the remaining 16 studies showed that PET had a sensitivity of 86% and a specificity of 86%. Two of the studies that were included in the systematic review compared PET to CT or to MRI. PET was more accurate than CT in one study, and more sensitive and less specific than MRI in the second study. Four of the studies that were included in the systematic review reported that changes in patient management occurred. These changes were not reported. The HTA included two additional small studies (20 participants) that suggested that the use of mid-therapy PET can predict treatment response for neoadjuvant chemotherapy in locally advanced breast cancer.

4.1.2 Colorectal Cancer

Studies on the use of PET and PET/CT to diagnose, stage, or restage cancers, and monitor recurrence and treatment response were assessed in this HTA.[12] A systematic review of two studies (40 participants) using PET to detect the primary tumour in colorectal cancer reported a sensitivity greater than 85% and a specificity of 67% (reported for one study). Another study (45 participants) that was included in the HTA evaluated the use of PET to detect early-stage colon cancer or colonic adenoma. The sensitivity of PET in detecting malignant cases was 62%, with a specificity of 100%. The authors noted that PET could be used to detect one in six tumours that were less than 2 cm.

Overall, PET and PET/CT had high sensitivity to detect primary tumours and liver metastases. Compared with CT, PET could be used to detect primary tumours in 95% of patients compared to 49% with the use of CT. The sensitivity of PET in detecting lymph node metastases (29%) was lower than its sensitivity in detecting primary tumours. No lymph node metastases were detected using CT. The sensitivity of PET was 78% and that of CT was 67% in detecting liver metastases. The specificities were comparably high between imaging modalities. The sensitivity of PET to detect recurrence in suspect cases was approximately 90% compared with 73% using CT. One systematic review of

13 primary studies reported that PET had a similar diagnostic accuracy to MRI. One systematic review of 10 studies (741 participants) that addressed changes to patient management reported that 34% of participants had changes to their disease management after the use of PET (the changes were not reported). One primary study (46 participants) reported that 17% of patients had changes to their treatment program after the use of PET. Three retrospective studies that were included in the HTA compared PET with PET/CT in assessing recurrence accuracy. All three studies reported similar or higher sensitivities with the use of PET/CT compared with PET.

4.1.3 Head and Neck Cancers

Included in the HTA[12] was a systematic review of four studies (the study sizes were not reported) that compared PET to CT or MRI for the primary diagnosis of head and neck cancers. The sensitivity of PET ranged from 85% to 95% across studies, compared with a range of 67% to 88% for CT. The specificity of PET ranged from 80% to 100%, and was higher than that of CT and MRI (range 45% to 75%). The authors of the systematic review concluded that CT or MRI was needed for anatomical localization and that PET would be a valuable addition to the diagnostic strategy. One study (21 participants) evaluating the diagnostic accuracy of PET/CT reported that PET/CT could be used to detect more primary tumours than dedicated PET and CT technologies.

PET was less sensitive than SLNB in clinically node-negative cases. At other stages, it had comparable or higher accuracy than CT or MRI. Data from two systematic reviews (with a combined total of 25 studies) and from seven studies that were included in the HTA were used to estimate the sensitivity of PET for the detection of recurrence and restaging at approximately 80%, with a specificity of approximately 90%. The authors reported that PET has a statistically significantly ($P = 0.01$) higher sensitivity and specificity than CT or MRI for staging. The authors suggested that PET may be more accurate than CT or MRI for restaging or detecting recurrence. No value of the use of PET or PET/CT to monitor treatment response was reported.

4.1.4 Lung Cancer

This part of the HTA[12] was based on a clinical guideline for lung cancer that was prepared by the National Collaborating Centre for Acute Care for NICE.[14] The guideline, which is based on systematic reviews and input from clinical experts, includes only those topics that are relevant to England and Wales. Therefore, the authors of the HTA[12] included only the primary studies that were not part of the NICE clinical guideline. One of the studies was an HTA that was published by the Danish Centre for Health Technology Assessment (DACEHTA). The DACEHTA report assessed 10 studies (the total number of participants was not reported) in which PET was used to identify the primary tumour in patients with suspected non-small cell lung cancer (NSCLC). The results across studies varied. Several trials had sensitivities of 100% using PET alone or PET in combination with CT. Despite the high sensitivity, the authors of the HTA noted that it was unlikely that PET would be used in the absence of biopsy to diagnose NSCLC in the UK. A systematic review of 18 studies assessing PET for staging mediastinal disease was included in the HTA.[12] PET had a sensitivity of 84% (95% confidence interval [CI]; 78 to 89%) and a specificity of 89% (95% CI; 83 to 93%). Another systematic review that was included in the HTA (17 studies, 1202 participants)

reported that PET sensitivity and specificity for the detection of distant metastases were both more than 90%, except with metastases in the brain. Three studies (205 participants) that were evaluated in the HTA compared the accuracy of PET with that of PET/CT for staging. All the studies showed that patients were staged more accurately using PET/CT compared with PET. The largest of the three studies (129 patients) reported that 33% of patients were incorrectly staged using PET/CT, despite the greater anatomical information available from the use of CT.

The evidence on the use of PET for the diagnosis of small cell lung cancer (SCLC) was limited. Thus, no conclusions were drawn by the authors of the HTA. The HTA reported on five studies (the number of participants in each study ranged from three to 30) assessing the use of PET for the staging of SCLC. These small studies were included in a previous HTA by the Agency for Healthcare Research and Quality (AHRQ) and included populations with early and late-stage disease. The studies reported that PET had a sensitivity of approximately 89% and a specificity of 100%. In one study (120 participants) that was included in the NIHR HTA, PET had a high sensitivity and a specificity greater than 90% for detecting lymph node and distant metastases at sites other than the brain. This study reported that the use of PET resulted in the upstaging of 8% of patients to extensive disease and the downstaging of 3% of patients to limited disease. The AHRQ HTA included two small studies (58 participants) that evaluated the use of PET to restage or detect recurrent SCLC disease. The sensitivity was more than 95% in both studies. The specificity was as low as 41% in one study. No studies reporting on the use of PET/CT for the management of SCLC were included in the HTA by the UK group.

The only reported use of PET for the management of solitary pulmonary nodules (SPNs) was in the characterization of nodules as FDG-avid. A meta-analysis of 13 studies (450 participants) reported that the sensitivity of PET for diagnosis was 94% and that the specificity was 83%. In a second meta-analysis of 32 studies (the number of participants was not reported), an sROC analysis was performed, and PET was reported to have a sensitivity of 95% and a specificity of 77% to characterize SPNs.

4.1.5 Lymphoma

The results from one study (eight participants) on the diagnosis of primary gastric non-Hodgkin lymphomas (NHL) were limited, and the authors of the HTA were unable to draw conclusions from the data. The authors of the NIHR HTA suggested that it was unlikely PET would be used without histological confirmation for the routine diagnosis of lymphoma. PET and PET/CT were found to be equal to or more accurate than CT in staging and restaging to assess residual disease (Hodgkin disease [HD] and NHL) after induction therapy. Several studies that were presented in the HTA showed that PET was effective in predicting the mid-therapy response to chemotherapy. No evidence of a change in treatment strategy was presented.

4.1.6 Melanoma

The use of PET has been evaluated in melanoma for staging early and late-stage disease, and monitoring recurrence. The HTA reports on 12 studies presented by stage. For early-stage disease (528 participants), PET sensitivity was poor (typically less than 20%). Additional studies evaluated the effectiveness of PET in the staging of late-stage disease (127 participants). In one study, PET (83%) was less sensitive than MRI (100%) in detecting liver metastases. A second study estimated the sensitivity of PET

in detecting lesions greater than 1 cm to be 100% (specificity 75%) and 13% (specificity 33%) for lesions less than 1 cm. This was greater than the sensitivity of MRI. No studies evaluating the use of PET/CT in the management of melanoma were included in the HTA.

4.1.7 Esophageal

The HTA included a systematic review of eight studies (the number of participants was not reported) that reported PET had a high sensitivity in the diagnosis of esophageal malignancies, except in early-stage disease. The authors of the HTA concluded that it was unlikely PET would replace the standard practice of endoscopy in combination with ultrasound in the UK. To evaluate the role of PET in staging, two systematic reviews with a combined total of 21 studies (the number of participants was unclear from data abstraction tables) were assessed for the HTA. The sensitivity of PET to detect locoregional lymph nodes was low at 51%, which was greater than that estimated for CT. The specificities of PET and CT were comparable at approximately 85%. The sensitivity of PET for detecting distant metastases was 67%, with 97% specificity. Several studies reported that PET seemed to be more sensitive than CT at detecting distant metastases. Four studies that were included in the HTA were not included in the systematic review. Three of these studies confirmed the lower sensitivity of PET for detecting locoregional lymph-node metastases than for detecting distant metastases, and a single study reported a low sensitivity of 53% for detecting distant metastases. Another systematic review (of four studies) and one study (the number of participants was not reported) that was included in the HTA found that PET may be useful for the assessment of treatment response and prognosis after neoadjuvant treatment. These findings and one study (48 participants) of PET/CT that was included in the HTA suggested that PET and PET/CT may outperform CT for monitoring treatment response.

4.1.8 Thyroid Cancer

The use of PET for diagnosis, restaging, recurrence, and monitoring treatment response in thyroid cancer was assessed in the HTA. One study (43 participants) examining the use of PET for diagnosis in patients with suspect thyroid nodules found that the specificity of PET was low at 63%. No studies on the initial staging of thyroid cancer using PET were identified in the HTA. Four studies of PET for restaging found that CT could be used to detect more tumours than PET. Included in the HTA was a meta-analysis of 11 (244 patients) studies of patients with a suspected recurrence of epithelial thyroid cancer and concomitant elevated biomarkers (not confirmed by ^{131}I scintigraphy). In the meta-analysis, it was estimated that the sensitivity to detect recurrence was 84% (95% CI, 73% to 91%) with a specificity of 56% (95% CI, 27% to 82%). Four studies that were not included in the meta-analysis assessed the use of PET to detect recurrent thyroid cancer in patients with elevated biomarkers and reported that PET sensitivity was at least 80%. The authors of the HTA sought to assess the ability of PET to detect a recurrence of medullary thyroid cancer. Limited data were available. Two studies (50 participants) that were included in the HTA assessed the use of PET/CT for the detection of recurrence with an estimated sensitivity of 66%.

Most of the studies in the HTA evaluated PET and not PET/CT. Generally, studies that evaluated both imaging modalities found that the effectiveness of PET/CT was equal to or greater than that of PET, and therefore trends of findings of PET likely represent anticipated results with PET/CT.

Overall, the diagnostic accuracy of PET for the detection of distant metastases was high. PET had variable sensitivity for the detection of lymph node metastases and low sensitivity for the detection of early-stage disease. Some evidence in the HTA suggested that PET imaging could be correlated with treatment response, although most of the studies were small, and the assessment points varied across studies. The authors concluded that the highest quality evidence for the clinical effectiveness of PET was in the staging or restaging of colorectal cancer, detection of SPN, staging of NSCLC, and restaging of HD.

A second HTA, which was prepared by ECRI, reviewed the use of PET for monitoring treatment response and recurrence of breast cancer.[15] The use of PET was considered in four patient populations: women with locally advanced breast cancer who were being treated with neo-adjuvant therapy and whose assessment of response to treatment was made during therapy; women with primary, recurrent, or metastatic breast cancer, whose response to treatment was assessed using PET during therapy; women who had completed primary therapy, and PET was used to monitor local recurrence and distant metastases; and women with suspected recurrence after primary therapy to confirm or reject the suspicion. Eleven studies were identified during the systematic literature search (seven studies of the response to neo-adjuvant therapy, three studies of the response to treatment, and one study of the detection of recurrence), and a meta-analysis was performed on data from these studies. The quality of the studies was assessed using a quality tool for diagnostic studies that was developed by ECRI. The scores ranged from 0 to 10 with scores of less than 5 representing very low quality; scores of 5 to 6.6 representing low quality; scores of 6.7 to 8.3 representing moderate quality; and scores of 8.7 to 10 representing high quality. The outcomes from very low quality studies were excluded from the analyses. No studies of the detection of recurrences on routine surveillance were identified. The authors reported that the PET scans that were performed after one cycle of neo-adjuvant chemotherapy have a sensitivity of 100% for detecting tumours that are responsive to treatment, and a specificity of 64.8% (95% CI, 53% to 76%). This evidence suggested that PET may be useful in the identification of patients who are not responding to neo-adjuvant treatment and of patients with metastatic disease who are responding to treatment. No conclusion could be drawn about the use of PET for assessing the response in primary and recurrent cancer and for detecting recurrence after treatment.

A third HTA, which was produced by ECRI, examined the use of PET for monitoring the response to the treatment of HD and NHL.[16] The objectives were to determine the accuracy of PET for monitoring treatment response and to compare the performance of PET to that of a standard test for monitoring treatment response. Sixteen studies (915 patients) were included in the HTA. The quality of the included studies was evaluated. Thirty-six per cent of the patients had HD, and the remainder had NHL. All the studies addressed the diagnostic accuracy of PET, and seven studies compared the diagnostic performance with that of other tests, including CT. The authors interpreted accuracy by determining whether or not PET could accurately predict survival and whether or not monitoring treatment response using PET can extend a patient's life. The authors assessed overall survival at one, two, three, and four years. They showed that patients who were monitored for treatment response and had a PET scan

that detected disease were more likely to die within one to four years after treatment than those who had a negative PET scan. The authors concluded that a positive PET scan during the monitoring of treatment response is predictive of death or disease progression. No conclusion was reached about the relationship between the use of PET and the extension of patient life. The authors concluded that the evidence was insufficient to estimate any difference in diagnostic accuracy when PET was compared with CT. An analysis of four low-quality studies showed that the prognostic ability of PET to detect cancer progression was greater than that of CT at one year.

4.2 Systematic Reviews and Meta-Analyses

Brouwer et al. performed a systematic review of the evidence on the diagnostic accuracy of PET for recurrent laryngeal carcinoma in 2008.[17] Eight studies (191 participants) were eligible for inclusion (five were prospective studies, and three did not report the study design). The methodological quality of the included studies was assessed using the criteria list for diagnostic tests recommended by the Cochrane Methods Group for screening and diagnostic tests. The authors reported that the quality of the included studies varied. The pooled estimates for sensitivity and specificity were 89% (95% CI, 80% to 94%) and 74% (95% CI, 64% to 83%) respectively. The authors concluded that the diagnostic accuracy of PET was promising and that more research in the form of prospective randomized controlled trials would help to define PET's role in the management of laryngeal cancer.

A meta-analysis by Dong et al. in 2008[18] evaluated the diagnostic accuracy of PET and PET/CT in the detection of primary tumours among patients who were presenting with cancers of which the primary sites were unknown (cancer of unknown primary). Of the 28 studies (910 patients) that were included in this meta-analysis, 13 were retrospective, 13 were prospective, and two were of a study type that was not specified. The authors evaluated study quality using an approach that was reported by Delgado-Bolton et al. in 2003 and Huebner et al. in 2000. Seven areas relating to study quality were assessed. These included the description of study design, patient characteristics, and technologies used. A score was assigned based on how well the study addressed all seven areas. High-quality studies received a score of greater than 70%. Twenty-four of the 28 included studies were deemed to be high quality. The pooled sensitivity estimate was 0.78 (95% CI, 0.72 to 0.84) and the pooled specificity estimate was 0.79 (95% CI, 0.74 to 0.83). The pooled sensitivity estimate of PET/CT was 0.91 (95% CI, 0.74 to 0.87) and the pooled specificity estimate of PET/CT was 0.83 (95% CI, 0.78 to 0.87). The authors noted that PET was used to detect 28.5% of tumours and PET/CT 31.4% of tumours that were not detected using conventional clinical means. They concluded that PET and PET/CT were useful tools in the detection of cancer of unknown primary when conventional workup has failed.

In 2008, El-Maraghi and Kielar conducted a systematic review to evaluate the use of PET or PET/CT compared with SLNB for the staging of melanoma.[19] Twenty studies were included in the review. The articles were evaluated for levels of evidence as described by the Oxford Centre for Evidence-Based Medicine. Fourteen studies reported the number of participants (1,000 participants). The authors noted an overall lack of high-quality evidence on this topic. No articles fulfilled the criteria for Level I evidence. All the included studies concluded that SLNB

outperformed PET or PET/CT in the staging of local lymph nodes.

In 2008, Fletcher et al. performed a systematic review of the role of PET in oncology[3] with the objective of developing recommendations on the use of PET in cancer. Recommendations were made based on evidence on the clinical effectiveness of PET for a particular indication. The authors evaluated evidence on the use of PET for diagnosing, staging, and detecting recurrence in breast cancer, colorectal cancer, esophageal cancer, head and neck cancer, lung cancer, pancreatic cancer, thyroid cancer, lymphoma, melanoma, sarcoma, and cancer of unknown primary tumour. Thirty-six systematic reviews and three RCTs met the inclusion criteria. The methodological quality of the studies was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation tool. All the studies used dedicated PET.

A summary of the recommendations that were made by the authors appears in Table 1.

Table 1: Conclusions on Use of PET for Diagnosis, Staging, and Detecting Cancer Recurrence[3]

	Purpose of PET Use		
Cancer Type	**Diagnosis**	**Staging or Re-staging**	**Detecting Metastases or Recurrence**
Breast	Not useful for routine diagnosis; may be useful in high-risk patients with lesions >2 cm and elevation in serum tumour markers	Not useful for routine axillary staging	Not useful for routine detection of metastases or recurrence
Colorectal	Not useful for routine detection of primary colorectal cancer	Useful for evaluation of resectable liver metastases	May be useful addition to clinical workup if carcinoembryonic antigen marker elevated
Esophageal	Not reported	Useful for pre-operative staging (some effectiveness at detecting local nodal metastases)	Useful for detecting distant metastases
Head and neck	Not useful as addition to CT or MRI	PET in combination with CT or MRI improves nodal or distant disease staging	May be useful addition to conventional workup strategies to detect recurrences
NSCLC	Useful in differentiation between benign and malignant lesions in patients with SPN	Useful	Useful in diagnostic workup for detecting distant metastases
SCLC	No conclusions, insufficient evidence	No conclusions, insufficient evidence	No conclusions, insufficient evidence
Lymphoma	Not reported	Useful in pre-treatment staging of	Useful

Table 1: Conclusions on Use of PET for Diagnosis, Staging, and Detecting Cancer Recurrence[3]			
	Purpose of PET Use		
Cancer Type	**Diagnosis**	**Staging or Re-staging**	**Detecting Metastases or Recurrence**
		lymphoma. Also evidence of effectiveness in staging or restaging lymphoma after treatment (HD and NHL)	
Melanoma	Not reported	Useful	Useful
Pancreatic	Useful when conventional imaging results are inconclusive	Not reported	Not reported
Sarcomas	No conclusions, insufficient evidence	No conclusions, insufficient evidence	No conclusions, insufficient evidence
Thyroid	Not reported	Not reported	Useful for detecting recurrence in patients treated for well-differentiated thyroid cancer when findings of ^{131}I scintigraphy negative and serum thyroglobulin marker elevated
Unknown primary	Useful in detection of primary tumours not detected by conventional clinical workup means	Not reported	Not reported

CT = computed tomography; HD = Hodgkin disease; MRI = magnetic resonance imaging; NHL = non-Hodgkin lymphomas; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SPN = solitary pulmonary nodule; SCLC = small cell lung cancer.

A systematic review and meta-analysis was prepared by Isles et al. in 2007[20] to assess the effectiveness of PET in the detection of recurrent head and neck squamous cell cancer after chemotherapy or radiotherapy. Among the 27 studies (1,871 patients) that were eligible for inclusion, 21 prospective studies and six retrospective studies were included in the analysis. The quality of included studies was assessed using the QUADAS tool. Overall, the quality score of the included studies ranged from eight to 12 (out of a maximum score of 14). The pooled estimates of sensitivity and specificity of PET for detecting recurrent disease were 94% (95% CI, 87% to 97%) and 82% (95% CI, 76% to 86%) respectively. The studies suggested that the sensitivity was greater when scans were performed at least 10 weeks after treatment. The authors of this systematic review concluded that PET has high sensitivity for the detection of recurrent or resistant head and neck cancer.

In 2008, Krug et al.[21] conducted a systematic review of the role of PET and diagnostic performance in the initial staging of cutaneous malignant melanoma (CMM). Twenty-eight prospective and retrospective studies (2,905 patients) were included in the review. The quality of included studies was assessed using the QUADAS tool. A range for the quality scores was not reported. The authors stated that the quality assessment revealed several potential sources of bias in the included studies. Table 2 describes the pooled estimates of PET for the detection of metastases in the initial staging of CMM. From these data, the authors concluded that PET is useful for the initial staging of patients with CMM, and noted that research including more prospective studies and cost-effectiveness analyses would clarify the role that PET may have in the staging of CMM and disease management.

Table 2: Pooled estimates of PET for Cutaneous Malignant Melanoma[21]

Diagnostic Performance Characteristic	Estimate
Sensitivity	83% (95% CI, 81% to 84%)
Specificity	85% (95% CI, 83% to 87%)
Positive likelihood ratio	4.56 (3.12 to 6.64)
Negative likelihood ratio	0.27 (0.18 to 0.40)
Diagnostic odds ratio	19.8 (10.8 to 36.4)

CI = confidence interval: PET = positron emission tomography.

A 2008 systematic review by Kwee and Kwee[22] assessed the use of PET/CT for the detection of unknown primary tumours. Unknown primary tumours occur in patients with metastatic disease that has been detected and confirmed histologically, and the site or origin of disease is unknown. Eleven studies (433 participants) were evaluated and meta-analyzed. Eight studies were retrospective, and the study type was not reported in three. The included studies were deemed to be of moderate methodological quality using a modified version of the QUADAS tool. The range of scores (expressed as percentages of the maximum score) was 42% to 75%. The overall primary tumour detection rate, pooled sensitivity, and pooled specificity of PET/CT were 37%, 84% (95% CI, 78% to 88%), and 84% (95% CI, 78% to 89%) respectively. The authors concluded that PET/CT could be a useful modality for the detection of cancers of unknown primary.

In 2008, Kwee and Kwee[23] systematically reviewed the use of PET, PET/CT, CT, and whole-body MRI for the staging of malignant lymphoma (HD and NHL). Seventeen studies assessing PET (832 participants), four studies evaluating PET/CT (234 participants), and three studies examining CT (94 participants) were included in the review. The methodological quality of the included studies was assessed using a modified version of published quality checklists (QUADAS and Kelly et al. in 1997). No studies assessing whole-body MRI were eligible for inclusion. None of the included studies compared PET or PET/CT with CT. Instead, comparisons were made between studies. The authors noted that the studies used different systems to stage disease. From the systematic literature review, it was concluded that CT is the standard method for the initial staging of lymphoma, and PET is a valuable tool in restaging after treatment. The included

studies suggested that PET/CT had a superior performance compared with dedicated PET or CT.

A systematic review by Samson et al. in 2007[24] addressed the management of SCLC including the use of PET for disease staging. Six studies (277 participants) that were included in the review addressed the use of PET specifically. The types of studies that were included were not indicated, and the authors noted that the evidence was limited and of poor quality. The quality of included studies was assessed using the QUADAS tool. Reference standards were mentioned sometimes, and the reporting was incomplete. Despite the paucity of data, the authors concluded that PET in conjunction with conventional means of assessing stage is more sensitive at detecting disease except brain metastases.

In 2008, Shie et al.[25] conducted a meta-analysis of six studies (four prospective cohort studies and two retrospective cohort studies) comparing the diagnostic performance of PET with that of bone scintigraphy in the detection of bone metastases in patients with breast cancer. Details about the assessment of methodological quality were not provided. The pooled estimates of sensitivity and specificity for both imaging modalities appear in Table 3. The sensitivities of PET and bone scintigraphy were comparable. PET had a higher specificity. The area under the curve was 0.08 for PET and 0.43 for bone scintigraphy. The authors suggested that PET could be used as a confirmatory test and could potentially be used in monitoring treatment response.

Table 3: Pooled Estimates of PET and Bone Scintigraphy for Breast Cancer[25]

Imaging Modality	Diagnostic Performance Characteristic	Estimate	95% CI
PET	Sensitivity	81%	70% to 89%
	Specificity	93%	84% to 97%
Bone scintigraphy	Sensitivity	78%	67% to 86%
	Specificity	79%	40% to 95%

CI = confidence interval; PET = positron emission tomography.

The diagnostic accuracy of PET to detect recurrent or residual HD and NHL after first-line therapy was assessed in a systematic review by Terasawa et al. in 2008.[26] Nineteen studies (five prospective studies and 14 retrospective studies) were included (474 patients with HD and 245 patients with NHL respectively). The authors of the systematic review noted that the methodological quality was suboptimal and that the patient populations were heterogeneous (pediatric, adolescent, and adult patients). The quality of included studies was assessed using the QUADAS tool and a second checklist reported by Kent et al. in 1992. The range of sensitivity and specificity across studies for PET to detect recurrent or residual HL were 0.50 to 1.00 and 0.67 to 1.00 respectively. For NHL, the sensitivity range was 0.33 to 0.77, and the specificity range was 0.82 to 1.00. Data on the diagnostic accuracy of PET for HD suggested that PET may be useful in monitoring recurrence after treatment. Data on the diagnostic accuracy of PET for NHL were more limited.

In a 2008 meta-analysis, Zhang et al.[27] evaluated the diagnostic performance of PET for recurrent colorectal cancer. Of the

27 studies (1,639 participants) that were included in the meta-analysis, 16 were retrospective, 10 were prospective, and one was a double-blind comparative study. All were of acceptable methodological quality. The quality of included studies was assessed using criteria originally proposed by Huebner et al. in 2000. The pooled estimates of sensitivity and specificity for detecting distant metastases (or whole-body disease) were 0.91 (95% CI, 0.88 to 0.92) and 0.83 (95% CI, 0.79 to 0.87) respectively. The pooled sensitivity and specificity of PET for the detection of liver metastases was 0.97 (95% CI, 0.95 to 0.98) and 0.98 (95% CI, 0.97 to 0.99) respectively. The pooled sensitivity and specificity of detecting pelvic metastases or local regional recurrence were 0.94 (95% CI, 0.91 to 0.97) and 0.94 (95% CI, 0.92 to 0.96). The authors concluded that PET was useful in the detection of recurrent colorectal cancer.

In 2007, Liu et al.[28] conducted a systematic review in which PET, CT, and MRI were compared for the detection of residual or recurrent nasopharyngeal carcinoma. Twenty-one studies met the inclusion criteria. The quality of included studies was assessed using the QUADAS tool. All the included studies had, at minimum, a score of nine out of a maximum of 14 on the quality assessment checklist. PET had a higher pooled sensitivity estimate at 95% (95% CI, 90% to 97%) compared with CT at 76% (95% CI, 70% to 81%) and MRI at 78% (95% CI, 71% to 84%). The pooled specificity estimate for PET was higher at 90% (95% CI, 87% to 93%) compared with CT at 59% (95% CI, 55% to 63%) and MRI at 76% (95% CI, 71% to 80%). The diagnostic odds ratio was greater for PET at 96.51 (95% CI, 47.62 to 195.57) compared with CT or MRI at 7.01 (95% CI, 3.53 to 13.93) and 8.68 (95% CI, 6.0 to 12.60) respectively. The results of this analysis showed that PET was the superior imaging modality for the detection of local residual or recurrent disease.

4.3 Evidence-Based Guidelines

Fourteen evidence-based guidelines were identified during the literature search. Only those guidelines reporting that a systematic literature search was conducted were selected for inclusion. The guideline objectives, methods of development, and recommendations appear in Table 4.

Table 4: Evidence-Based Guidelines on Use of PET in Various Cancers			
Cancer Type, Author, and Year	**Objective**	**Methods**	**Recommendations**
Lung (all types), Jazieh et al. (2008)[10]	Develop guidelines on diagnosis, workup, treatment, and follow-up of lung cancer	• systematic review • 13 member panel • consensus development	• Obtain total body PET/CT scan for staging of all lung cancers (grading of recommendations not reported)
Lung (solitary pulmonary nodules, [SPN]), Gould et al. (2007)[29]	Develop guidelines for identifying and managing malignant SPNs	• systematic review • consultation with experts and stakeholders	• PET can be used to characterize indeterminate SPNs (8 mm to 10 mm in diameter) with a low-to-moderate pre-test malignancy probability (grade 1B) • PET should not be used to characterize subcentimeter SPNs with high pretest malignancy probability (grade 2C)*
Lung (special treatment issues), Shen et al. (2007)[11]	Develop guidelines for lung cancers needing special treatment consideration	• systematic review • consultation with experts and stakeholders	• whole-body PET recommended for patients being considered for curative resection where involvement of mediastinal nodes or disease is contraindicated (grade 1C)*
Lung, Rubin et al. (2007)[30]	Develop guidelines for follow-up and surveillance of patients after curative intent therapy	• systematic review • consultation with experts and stakeholders	• PET as means of surveillance not recommended for patients with lung cancer after curative-intent therapy (grade 2C)*
Lung (NSCLC), Silvestri et al. (2007)[31]	Develop guidelines regarding non-invasive staging of NSCLC	• systematic review • consultation with experts and stakeholders	• PET, to evaluate for mediastinal and extrathoracic staging, should be considered in patients with clinical 1A lung cancer being treated with curative intent (grade 2C) • Patients with clinical IB-IIIB lung cancer being treated with curative intent should undergo PET for mediastinal and extra-thoracic staging (grade 1B) • Patients with abnormal clinical evaluations should undergo imaging for extra-thoracic metastasis. This may include PET (grade 1B)

Table 4: Evidence-Based Guidelines on Use of PET in Various Cancers			
Cancer Type, Author, and Year	**Objective**	**Methods**	**Recommendations**
			• Routine imaging, which may include PET, should be performed on patients with clinical stage IIIA and IIIB disease even if clinical evaluation findings are negative (grade 2C)*
Lung (SCLC), Samson et al. (2007)[24]	Develop guidelines for management of SCLC	• systematic review • consultation with experts and stakeholders	• PET not recommended for routine staging of SCLC (grade 2B)*
Lung (SPN, NSCLC, and SCLC), Ung et al. (2008)[32]	Develop guidelines on use of PET in diagnosis of SPN, staging of primary NSCLC, and staging of primary SCLC	• systematic review • consultation with experts • consensus development	• PET may be used in diagnosis of SPN when fine-needle biopsy inconclusive or contraindicated • PET may be useful in detection of distant metastases in NSCLC cases • PET may be useful in staging of SCLC • (Grading of recommendations not reported)
Lymphoma, Juweid et al. (2007)[33]	Develop guidelines on use of PET to assess treatment response	• systematic review • consensus development	• PET should be performed at least 3 weeks after treatment (preferably after 6 to 8 weeks) • Use of PET with attenuation correction (PET/CT) strongly encouraged • PET for monitoring of treatment response during course of therapy should only be performed in context of trial or as part of registry • (Grading of recommendations not reported)
Myeloma, D'Sa et al. (2007)[34]	Develop guidelines on use of imaging for diagnosis and management of myeloma	• systematic review • consultation with other specialists • consensus development	• PET not recommended for routine use in management of myeloma patients. PET can be used to clarify previous imaging findings, preferably in clinical trial context (grade C recommendation; Level IV evidence)* • PET can be considered in context of extramedullary disease to clarify extent of

Table 4: Evidence-Based Guidelines on Use of PET in Various Cancers			
Cancer Type, Author, and Year	**Objective**	**Methods**	**Recommendations**
			disease present (grade B recommendation; Level III evidence) • PET should not be performed within 4 weeks of chemotherapy and within 3 weeks of radiotherapy (grade B recommendation, Level III evidence) • PET not recommended for routine follow-up of treated myeloma patients (grade C recommendation; Level IV evidence)
CNS cancers, Brem et al. (2008)[35]	Develop guidelines on management of adults with CNS cancers	• systematic review • consensus development	• PET may be considered if >3 metastatic lesions found on CT or MRI and no primary tumour identified • PET may be useful in differentiation between tumour and radiation-induced necrosis and for deciding optimal area to biopsy • (Grading of recommendations not reported)
Cervical, SIGN (2008)[36]	Develop guidelines for management of cervical cancer by multi-disciplinary teams	• systematic review • consensus development	• For staging, patients not suitable for surgery should have PET scan • (Grading of recommendations not reported)
Metastatic colon (to liver), Bipat et al. (2007)[37]	Develop guidelines for diagnosis, treatment, and follow-up of patients with colorectal liver metastases	• systematic review • consultation with experts	• PET should not be used for routine detection of liver metastases or for determining resectability (Level of evidence: I) • PET may be useful in detection of extrahepatic disease (Level of evidence: I)*
Thyroid (well- differentiated), Working Group Thyroid Carcinoma (2007)[38]	Develop guidelines on diagnosis, referral, treatment, overall and disease-free survival, and quality of life	• systematic review • consultation with other specialists • consensus development	• PET does not have role in follow-up • (Grading of recommendations not reported)

Table 4: Evidence-Based Guidelines on Use of PET in Various Cancers			
Cancer Type, Author, and Year	**Objective**	**Methods**	**Recommendations**
Cutaneous melanoma, American Society of Plastic Surgeons (2007)[39]	Develop guidelines that fairly reflect accepted medical standards for assessment and treatment of cutaneous melanoma	• systematic review • consensus development	• Radiological assessment of patients with more advanced disease may include PET (grade C). • (For this study, grade C equates to option, not recommendation; therefore, grading scale will not be discussed further)

CNS = Central Nervous System; CT = computed tomography; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SCLC = small cell lung cancer; SIGN = Scottish Intercollegiate Guidelines Network; SPN = solitary pulmonary module.
*Schemes for grading of recommendations and levels of evidence appear in Appendix 2.

4.4 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. In addition, articles that were published from 2007 to October 2008 and in the English language were eligible for inclusion. As a result, potentially relevant evidence that was published before 2007 would have been excluded. The HTAs and systematic reviews that were included in this report included papers that were

published before 2007. Despite this, date restriction is a limitation of this report. We relied exclusively on the methodological details in the article, so eligible reports could have been excluded based on omission of details about methods. The evaluation of studies of PET use in children and economic evaluations were not included in this report.

Recently published RCTs that were not reviewed in an HTA or a systematic review were not included in this report. Additional study types, including registries,[40] were not included because of the broad scope of this report. Data from RCTs and from other study types that were not included in this review may provide information on the clinical effectiveness of PET for specific cancer indications. The scope of this report included all cancer types. The objective of this report was to review the evidence on the diagnostic accuracy of PET for cancers. Studies that discussed changes to patient management only, in the absence of details about diagnostic performance, were omitted. We recognize this as a limitation.

Despite the large number of studies on the clinical effectiveness of PET for cancers, few studies compared PET to CT or to MRI. In addition, few studies evaluated the use of PET/CT. PET/CT hybrid systems are used in some centres across Canada.[8] Studies suggest that PET/CT, with the added benefit of precise anatomical imaging that is provided by CT, performs equally well as or better than PET alone.[3] With the increased use of PET/CT systems, it is expected that more data on the clinical effectiveness of PET/CT will be available.

Thirteen systematic reviews and meta-analyses were identified. Most of the studies that were included in these articles were observational studies and not RCTs. Because of the paucity of data on PET use in some cancers, often studies that were deemed to be of low quality were 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.

The impact of using PET, in terms of how the imaging results influenced treatment decisions, was not discussed in most of the included studies.

One HTA that was included in this report assessed the use of PET for monitoring treatment response among patients with lymphoma. Studies on patients with HD and patients with NHL were included in the HTA. Thirty-six per cent of the included patients had HD. This is likely to be an over-representation of the percentage of lymphomas that are HD.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

The studies that are included in this review suggest that PET may be similarly or more effective than CT or MRI for some cancer indications. There is evidence of moderate quality 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] Evidence reported as low quality and consistent evidence suggests that PET may be useful in the diagnosis of cancer of unknown primary when conventional workup has failed.[3,18,22] Evidence that is 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,[3,20] and breast cancer[3] is supported by moderate-quality evidence. Evidence reported as low quality and consistent evidence suggests that PET may be useful in the staging of lymphoma.[3,23] The use of PET to monitor treatment response in lymphoma[16] and metastatic breast cancer[15] is supported. PET that is used to restage or detect residual disease or recurrence (local or distant sites) in colorectal cancer,[3,12,27] head and neck cancer,[3,12] lymphoma (NHL), [3,12] and breast cancer[3,25] 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.[41,42] 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,[43] in addition to a CADTH environmental scanning report on PET scanning in Canada.[44]

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 standards-of-care. This information,

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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APPENDIX 1: ADDITIONAL STUDIES (NOT MEETING INCLUSION CRITERIA) ABOUT PET THAT MAY BE OF INTEREST

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APPENDIX 2: GRADING AND LEVELS OF EVIDENCE FOR GUIDELINES ON USE OF PET IN ONCOLOGY

Table 1: American College of Chest Physicians (ACCP) Grading System for Guideline Recommendations[45]

Grade	Remarks
1A	• strong recommendation • strength of evidence high • benefits and risks not evenly balanced
1B	• strong recommendation • strength of evidence moderate • benefits and risks not evenly balanced
1C	• strong recommendation • strength of evidence low or very low • benefits and risks not evenly balanced
2A	• weak recommendation • strength of evidence high • benefits and risks evenly balanced
2B	• weak recommendation • strength of evidence moderate • benefits and risks evenly balanced
2C	• weak recommendation • strength of evidence low or very low • benefits and risks evenly balanced or uncertain

Table 2: Levels of Evidence and Grades of Recommendations*

Grade	Evidence Level	Remarks
B	**III**	Recommendation based on well-conducted studies but does not include randomized controlled trials on topic
C	**IV**	Evidence from expert committee reports or opinions and/or reputable clinical expertise

*Adapted from D'Sa et al.,[34] page 50.

Table 3: Levels of Evidence Used to Develop Guidelines*	
Level of Evidence	
1	Systematic review (category A_1) or minimum of 2 independent studies from category A_2
2	Systematic review (B1) or at least two independently performed studies of category B2
3	1 study of category A2, B2, or C
4	Expert opinion (category D)
Categories of Literature	
A_1	Systematic reviews of category A2 studies with consistent findings
A_2	Diagnostic accuracy study (index test compared with reference test) of high quality (prospectively performed with blinded interpretation of index test and reference test and large number of consecutive patients undergoing complete verification), or treatment-related randomized controlled trials of high quality (randomized, blinded, complete follow-up, similar baseline characteristics, intention-to-treat analysis)
B_1	Systematic reviews of category B2 studies with consistent findings
B_2	Diagnostic accuracy study (index test compared with reference test) with poor quality (missing aforementioned characteristics), or treatment-related randomized controlled trial of low quality or other comparative studies including non-randomized, cohort, and case-control studies
C	Diagnostic non-comparative study (index test not compared with reference test), or treatment-related non-randomized, cohort, and case-control studies with poor quality or descriptive studies (non-comparative studies)
D	Opinion from expert committee or clinical experience

*Adapted from Bipat et al.,[37] page 6.