TITLE: Positron Emission Tomography in Neurology and Cardiology: A Review of Guidelines and Recommendations

DATE: 27 January 2014

CONTEXT AND POLICY ISSUES

Positron emission tomography (PET) imaging, since the introduction of the concept of emission and transmission tomography in 1950, has been a major part of nuclear medicine and has proved to be a valuable non-invasive tool in the diagnosis and management of various disorders in many fields, from clinical oncology to neurology, from musculo-skeletal imaging to cardiology.1,2

PET has been used with success for the evaluation of neurological disorders such as cognitive function in Alzheimer's disease and diagnosis of brain tumours.3-5 PET also has shown its significant roles in the detection and prognosis of various cardiac disorders such as coronary artery disease (CAD), cardiac sarcoidosis, as well as in the assessment of myocardial perfusion and viability.6-11

This Rapid Response report aims to review the guidelines and recommendations associated with the use of PET in neurology and cardiology.

RESEARCH QUESTIONS

1. What are the evidence-based guidelines regarding the use of positron emission tomography in neurology?

2. What are the evidence-based guidelines regarding the use of positron emission tomography in cardiology?

KEY FINDINGS

The literature search identified a limited number of guidelines on the use of PET in neurology and cardiology. PET is not recommended for the diagnosis or grading of gliomas, and is recommended in typical cases of dementia and cranial neuropathy where diagnosis remains in

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doubt after magnetic resonance imaging (MRI) is equivocal or cannot be performed. The use of PET is reasonable to determine the presence of CAD in patients with hypertrophic cardiomyopathy (HCM) with chest discomfort and in patients with acute or chronic heart failure.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and December 18, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients referred to PET scanning for cardiology (e.g. coronary artery disease, myocardial viability, ischemia viability, ventricular function) or neurology indications (e.g. Alzheimer’s disease, Parkinson’s, epilepsy, brain tumours, dementia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>Comparator</td>
<td>None</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Guidelines and recommendations (diagnosis and management) - Patient indications</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Guidelines</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2009, or if they were duplicate publications of the same study.

Critical Appraisal of Individual Studies

The quality of the included guidelines was assessed using AGREE checklist. Numeric scores were not calculated. Instead, the strengths and limitations of the guidelines are summarized and presented.
SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 352 citations. After screening of abstracts from the literature search and from other sources, 52 potentially relevant studies were selected for full-text review. Five studies were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Critical Appraisal

The included guidelines\textsuperscript{13-17} had specific and unambiguous recommendations, with systematic and clearly described methods of searching for and selecting the evidence, and for formulating the recommendations. Health benefits and risks were stated, and procedures to update the guidelines were provided. It is unclear whether the guidelines were piloted among target users and whether patients’ view and preferences were sought. Potential cost implications of applying the recommendations were not included. Recommendations from Cancer Care Ontario on PET imaging on gliomas did not report strength of evidence.\textsuperscript{13}

Details of the strengths and limitations of the included studies are summarized in Appendix 2.

Summary of Findings

Main findings of included guidelines are summarized in detail in Appendix 3. Definitions of different levels of confidence and different classes of recommendations used in the included guidelines are in Appendix 4.

1. What are the evidence-based guidelines regarding the use of positron emission tomography in neurology?

Recommendations from Cancer Care Ontario\textsuperscript{13} stated that PET is not recommended for the determination of diagnosis or grading in gliomas, and that a recommendation cannot be made for or against the use of PET for the assessment of treatment response or in the assessment of patients with recurrent gliomas due to insufficient evidence.

Guidelines from the Agency for Healthcare Research and Quality (AHRQ)\textsuperscript{14} recommended that although typical cases of dementia may not benefit from routine PET imaging, PET is recommended in cases where diagnosis remains in doubt after MRI work-up and in particular clinical settings. In cases where dementia is suspected, normal findings from FDG-PET scan (fluorine-18 (\textsuperscript{18}F)-2-fluoro-2-deoxy-D-glucose-PET) make a neurodegenerative diagnosis less likely. These recommendations are classified as Class II (conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure) and with level A of confidence (data derived from multiple randomized clinical trials or meta-analyses).

Guidelines from the Agency for Healthcare Research and Quality (AHRQ)\textsuperscript{15} recommended that whole body FDG-PET/CT (computed tomography) is useful for the diagnosis of cranial neuropathy when MRI is equivocal or cannot be performed, especially in patients with
suspected or proven neoplastic process. The guidelines gave the recommendations a Rating Scale of 1 (the use of the procedure usually not appropriate).

2. What are the evidence-based guidelines regarding the use of positron emission tomography in cardiology?

Guidelines from the Agency for Healthcare Research and Quality (AHRQ)\textsuperscript{16} recommended that the use of PET or SPECT (single photon emission computed tomography) is useful to assess ischemia or perfusion abnormalities suggestive of CAD. The use of PET or SPECT is reasonable to rule out CAD in patients with HCM with chest discomfort. The recommendation is classified as Class IIa (benefit outweighs risk; weight of evidence/opinion is in favour of usefulness/efficacy) and with level C of confidence (data from consensus of opinion of the experts and/or small studies, retrospective studies, registries). PET is not indicated for the assessment of the presence of blunted flow reserve (microvascular ischemia) in the prognosis in patients with HCM. This recommendation is classified as Class III (no benefit) with level C of confidence (data from consensus of opinion of the experts and/or small studies, retrospective studies, registries).

Guidelines from the Agency for Healthcare Research and Quality (AHRQ)\textsuperscript{17} recommended that PET or other myocardial perfusion/ischemia techniques (such as SPECT, echocardiography) should be considered in patients with acute or chronic heart failure who may have CAD. The recommendation is classified as Class IIa (benefit $\gg$ risk; weight of evidence/opinion is in favour of usefulness/efficacy) and with level C of confidence (data from consensus of opinion of the experts and/or small studies, retrospective studies, registries).

Limitations

Guidelines on the use of PET in neurology and cardiology were limited to a number of clinical disorders (gliomas, dementia, cranial neuropathy, CAD in hypertrophic cardiomyopathy and heart failure). Guidelines and recommendations on the use of PET on other neurological and cardiac disorders are needed.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The literature search identified a limited number of guidelines on the use of PET in neurology and cardiology. PET is not recommended for the diagnosis or grading of gliomas, and is recommended in typical cases of dementia and cranial neuropathy where diagnosis remains in doubt after MRI is equivocal or cannot be performed. The use of PET is reasonable to determine the presence of CAD in patients with HCM with chest discomfort and in patients with acute or chronic heart failure.

Advancements in the field of nuclear medicine in the development of hybrid systems that combine PET with CT and MRI may further increase the indications of PET in clinical use. The hybrid systems may increase sensitivity, reduce radiation dose, decrease scanning time, and reduce motion artifact, and have been shown to be useful in diverse oncological, cardiac and neurological applications.\textsuperscript{18-21}

Further investigations are needed to increase the performances of non-invasive imaging techniques. Appropriate use of PET is recommended to increase its diagnostic value and its cost-effectiveness.
REFERENCES


18. Positron emission tomography (PET) and PET/CT fusion [Internet]. Indianapolis (IN): Anthem; 2013. [cited 2014 Jan 14]. (Medical policy). Available from: http://www.anthem.com/medicalpolicies/policies/mp_pw_a050587.htm


Appendix 1: Selection of Included Studies

352 citations identified from electronic literature search and screened

313 citations excluded

39 potentially relevant articles retrieved for scrutiny (full text, if available)

13 relevant reports retrieved from other sources (grey literature, hand search)

52 potentially relevant reports

47 reports excluded (irrelevant design, populations, interventions or outcomes)

5 reports included in review
### Appendix 2: Summary of Critical Appraisal of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical appraisal of included guidelines and recommendations (AGREE)”</strong></td>
<td></td>
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</tbody>
</table>
| Cancer Care Ontario, 13 2009 | • scope and purpose of the guidelines are clear  
• the recommendations are specific and unambiguous  
• the method for searching for and selecting the evidence are clear  
• methods used for formulating the recommendations are clearly described  
• health benefits, side effects and risks were stated in the recommendations  
• procedure for updating the guidelines provided  
• target users of the guideline are clearly defined | • unclear whether the guideline was piloted among target users  
• unclear whether patients’ views and preferences were sought  
• potential cost implications of applying the recommendation not included  
• strength of evidence not reported |
| AHRQ, 14 2012 | • scope and purpose of the guidelines are clear  
• the recommendations are specific and unambiguous  
• the method for searching for and selecting the evidence are clear  
• methods used for formulating the recommendations are clearly described  
• health benefits, side effects and risks were stated in the recommendations  
• procedure for updating the guidelines provided  
• target users of the guideline are clearly defined | • unclear whether the guideline was piloted among target users  
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| AHRQ, 15 2012 | • scope and purpose of the guidelines are clear  
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• potential cost implications of applying the recommendation not included  
• strength of evidence not reported |
| AHRQ, 16 2011 | • scope and purpose of the guidelines are clear  
• the recommendations are specific and unambiguous  
• the method for searching for and selecting the evidence are clear  
• methods used for formulating the recommendations are clearly described  
• health benefits, side effects and risks were stated in the recommendations  
• procedure for updating the guidelines provided  
• target users of the guideline are clearly defined | • unclear whether the guideline was piloted among target users  
• unclear whether patients’ views and preferences were sought  
• potential cost implications of applying the recommendation not included  
• strength of evidence not reported |
### Table A1: Summary of Critical Appraisal of Included Study

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>recommendations are clearly described</td>
<td>unclear whether the guideline was piloted among target users</td>
</tr>
<tr>
<td></td>
<td>• health benefits, side effects and risks were stated in the recommendations</td>
<td>• unclear whether patients’ views and preferences were sought</td>
</tr>
<tr>
<td></td>
<td>• procedure for updating the guidelines provided</td>
<td>• potential cost implications of applying the recommendation not included</td>
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<tr>
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<td>• scope and purpose of the guidelines are clear</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• procedure for updating the guidelines provided</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• target users of the guideline are clearly defined</td>
<td></td>
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</tbody>
</table>

AHRQ: Agency for Healthcare Research and Quality

PET in neurology and cardiology
# Appendix 3: Main Study Findings and Authors’ Conclusions

## Table A2: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research question 1 (evidence-based guidelines regarding the use of positron emission tomography in neurology)</strong></td>
<td></td>
</tr>
<tr>
<td>Cancer Care Ontario,13, 2009</td>
<td><strong>Clinical condition: gliomas</strong>&lt;br&gt;&quot;Diagnosis/Staging&lt;br&gt;PET is not recommended for the determination of diagnosis or grading in gliomas.**&lt;br&gt;<strong>Assessment of Treatment Response&lt;br&gt;A recommendation cannot be made for or against the use of PET for the assessment of treatment response in gliomas due to insufficient evidence.</strong>&lt;br&gt;**Recurrence/Restaging A recommendation cannot be made for or against the use of PET or PET/CT in the assessment of patients with recurrent gliomas due to insufficient evidence.&quot; (p 4, 5)</td>
</tr>
<tr>
<td>AHRQ,14, 2012</td>
<td><strong>Clinical condition: dementia</strong>&lt;br&gt;1. &quot;Although typical cases of dementia may not benefit from routine single positron emission computed tomography (SPECT) or positron emission tomography (PET) imaging, these tools are recommended in those cases where diagnosis remains in doubt after clinical and structural MRI work-up and in particular clinical settings (Class II, Level A).&quot; 2. Functional imaging can be of value to diagnose (or exclude) a neurodegenerative dementia in those subjects with cognitive impairment presenting with severe psychiatric disturbances (including depression and agitation) and in cases where proper cognitive testing is difficult, that is, with no language in common with the clinician (Good Practice Point). 3. Normal fluorine-18 ((^{18})F)-2-fluoro-2-deoxy-D-glucose (FDG) PET scan findings, in the presence of the suspicion of dementia, make a neurodegenerative diagnosis less likely (Class II, Level A).&quot; (p 5)</td>
</tr>
</tbody>
</table>
| AHRQ,15, 2012 | **Clinical Condition: Cranial Neuropathy**<br>**Variant 1: Anosmia and abnormalities of the sense of smell.**<br>"FDG-PET/CT whole body: Useful when MRI is equivocal or cannot be performed. Especially useful in patients with suspected or proven neoplastic process". (rating scale 1) (p 5)  
**Variant 2: Weakness or paralysis of the muscles of mastication; sensory abnormalities of the head and neck.**<br>"FDG-PET/CT whole body: Useful when MRI is equivocal or cannot be performed. Especially useful in patients with suspected or proven neoplastic process." (rating scale 1) (p 6)  
**Variant 3: Weakness or paralysis of facial expression.**<br>"FDG-PET/CT whole body: Useful when MRI is equivocal or cannot be performed. Especially useful in patients with suspected or proven neoplastic process." (rating scale 1) (p 7)  
**Variant 4: Palate weakness.**<br>"FDG-PET/CT whole body: Useful when MRI is equivocal or cannot be performed. Especially useful in patients with suspected or proven neoplastic process". (rating scale 1) (p 9)  
**Variant 5: Vocal cord paralysis.**<br>"FDG-PET/CT whole body: Useful when MRI is equivocal or cannot be performed. Especially useful in patients with suspected or proven neoplastic process". (rating scale 1) (p 10)  
**Variant 6: Weakness or paralysis of the sternocleidomastoid and trapezius muscles.**<br>"FDG-PET/CT whole body: Useful when MRI is equivocal or cannot be performed. Especially useful in patients with suspected or proven neoplastic process." (rating scale 1) (p 11) |

**PET in neurology and cardiology** 11
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Variant 7: Weakness or paralysis of the tongue.</strong></td>
</tr>
<tr>
<td></td>
<td>&quot;FDG-PET/CT whole body: Useful when MRI is equivocal or cannot be performed. Especially useful in patients with suspected or proven neoplastic process.&quot; (rating scale 1) (p 12)</td>
</tr>
<tr>
<td></td>
<td><strong>Variant 8: Perineural spread of tumor.</strong></td>
</tr>
<tr>
<td></td>
<td>&quot;FDG-PET/CT whole body: Useful when MRI is equivocal or cannot be performed. Especially useful in patients with suspected or proven neoplastic process.&quot; (rating scale 1) (p 13)</td>
</tr>
</tbody>
</table>

**Research question 2 (evidence-based guidelines regarding the use of positron emission tomography in cardiology)**

<table>
<thead>
<tr>
<th>AHRQ, 2011</th>
<th><strong>Clinical condition: Concomitant Coronary Disease in hypertrophic cardiomyopathy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Class IIa (Benefit &gt;&gt; Risk; Additional studies with focused objectives needed)</td>
</tr>
<tr>
<td></td>
<td>&quot;Assessment of ischemia or perfusion abnormalities suggestive of CAD with single photon emission computed tomography (SPECT) or positron emission tomography (PET) myocardial perfusion imaging (MPI; because of excellent negative predictive value) is reasonable in patients with HCM with chest discomfort and a low likelihood of CAD to rule out possible concomitant CAD. (Level of Evidence: C)&quot; (p 9)</td>
</tr>
<tr>
<td></td>
<td>Class III (no benefit)</td>
</tr>
<tr>
<td></td>
<td>&quot;Assessment for the presence of blunted flow reserve (microvascular ischemia) using quantitative myocardial blood flow measurements by PET is not indicated for the assessment of prognosis in patients with HCM. (Level of Evidence: C)&quot; (p 9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AHRQ, 2012</th>
<th><strong>Clinical condition: heart failure</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&quot;Myocardial perfusion/ischaemia imaging (echocardiography, CMR, single-photon emission computed tomography [SPECT], or positron emission tomography [PET]) should be considered in patients thought to have coronary artery disease (CAD), and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischaemia and viable myocardium. (Class of recommendation IIa, level of evidence C)&quot; (p 6)</td>
</tr>
</tbody>
</table>

AHRQ: Agency for Healthcare Research and Quality; CT: computed tomography; FDG-PET: fluorine-18 (¹⁸F)-2-fluoro-2-deoxy-D-glucose (FDG) - Positron Emission Tomography scan
Appendix 4: Summary of definitions of level of confidence and classes of recommendations used in included guidelines

Levels of Evidence

<table>
<thead>
<tr>
<th>Levels of Evidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Evidence A</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses.</td>
</tr>
<tr>
<td>Level of Evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of Evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>

Classes of Recommendations

<table>
<thead>
<tr>
<th>Classes of Recommendations</th>
<th>Definition</th>
<th>Suggested Wording to Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
<td>Is recommended/is indicated</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
<td></td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td>
<td>Should be considered</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion.</td>
<td>May be considered</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td>
<td>Is not recommended</td>
</tr>
</tbody>
</table>