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PET Recommendation Report 10

PET Imaging in Brain Cancer

N Laperriere and C Walker-Dilks

Report Date: January 19, 2009

PET Recommendation Report 10 is comprised of 2 sections and is available on the CCO Web site (https://www.cancercare.on.ca)
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Section 1: Recommendations
Section 2: Evidentiary Base

For further information about this report, please contact:

Dr. Normand Laperriere,
Princess Margaret Hospital, 610 University Avenue,
Toronto, Ontario, Canada M5G 2M9
Telephone: (416) 946-2127; Fax: (416) 946-2227; Email: norm.laperriere@rmp.uhn.on.ca

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please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Recommendation Report – PET #10: Section 1

PET Imaging in Brain Cancer: Recommendations

N Laperriere and C Walker-Dilks

Report Date: January 19, 2009

QUESTIONS

- What benefit to clinical management does positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) contribute to the diagnosis or staging of gliomas?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for gliomas?
- What benefit to clinical management does PET or PET/CT contribute when recurrence of gliomas is suspected but not proven?
- What benefit to clinical management does PET or PET/CT contribute to restaging at the time of documented recurrence for gliomas?
- What is the role of PET when a solitary metastasis is identified at the time of recurrence and a metastectomy is being contemplated?

TARGET POPULATION

Patients with gliomas.

INTENDED PURPOSE

- This recommendation report is primarily intended to guide the Ontario PET Steering Committee in their decision making concerning indications for the use of PET imaging.
- This recommendation report may also be useful in informing clinical decision making regarding the appropriate role of PET imaging and in guiding priorities for future PET imaging research.

RECOMMENDATIONS AND KEY EVIDENCE

These recommendations are based on an evidentiary foundation consisting of one recent high-quality systematic review from the U.S. Agency for Health Research and Quality (AHRQ) (1) that included primary study literature for the period from 2003 to March 2008.

Diagnosis/Staging

PET is not recommended for the determination of diagnosis or grading in gliomas.
Five studies (Chen et al [2], Cher et al [3], Liu et al [4], Potzi et al [5], Stockhammer et al [6]) assessed diagnostic accuracy and prognostic influence of PET scanning on survival, but none have demonstrated any additional diagnostic accuracy or prognostic influence over and above that provided by magnetic resonance imaging (MRI) and histology in a multivariate model.

Qualifying Statement

None.

Assessment of Treatment Response

A recommendation cannot be made for or against the use of PET for the assessment of treatment response in gliomas due to insufficient evidence.
None of the studies discuss this question.

Qualifying Statement

- Anecdotal evidence exists that PET/CT may differentiate radiation necrosis from tumour recurrence, but there is no gold standard for the diagnosis of radiation necrosis in glioblastoma multiforme.

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.
Two studies evaluating the use of PET included patients with recurrent gliomas (Chen et al [2], Potzi et al [5]). In both studies, fluorodeoxyglucose (FDG) PET was not the focus of the study but a comparison test for the tracer of interest, F-DOPA-PET in Chen et al (2) and Methionine-PET in Potzi et al (5). The evidence was insufficient to generate a recommendation on the use of FDG PET.

Qualifying Statements

- PET or PET/CT has not been examined in a prospective cohort of gliomas to assess the treatment effect on PET imaging before and after treatment and correlate this with survival.
- Radiation necrosis is a major factor in assessing recurrent gliomas.

Funding

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Contact Information

For further information about this report, please contact:

Dr. Normand Laperriere, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9, telephone (416) 946-2127, fax (416) 946-2227, email norm.laperriere@rmp.uhn.on.ca

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3. Cher LM, Murone C, Lawrentschuk N, Ramdave S, Papenfuss A, Hannah A, et al. Correlation of hypoxic cell fraction and angiogenesis with glucose metabolic rate in gliomas using 18F-fluoromisonidazole, 18F-FDG PET, and immunohistochemical studies. J Nucl Med 2006;47(3):410-8.
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Recommendation Report – PET #10: Section 2

PET Imaging in Brain Cancer: Evidentiary Base and Consensus Process

N Laperriere and C Walker-Dilks

Report Date: January 19, 2009

QUESTIONS

- What benefit to clinical management does positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) contribute to the diagnosis or staging of gliomas?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for gliomas?
- What benefit to clinical management does PET or PET/CT contribute when recurrence of gliomas is suspected but not proven?
- What benefit to clinical management does PET or PET/CT contribute to restaging at the time of documented recurrence for gliomas?
- What is the role of PET when a solitary metastasis is identified at the time of recurrence and a metastectomy is being contemplated?

INTRODUCTION

The Ontario PET Steering Committee made a special request to the Clinical Council of Cancer Care Ontario to co-lead the development of guidance regarding the clinical uses of PET imaging. The Program in Evidence-based Care (PEBC), working together with Provincial Cancer Disease Site Groups (DSGs), synthesized the clinical research and drafted recommendations for 10 disease sites. Recommendations for the use of PET in colorectal cancer, esophageal cancer, head and neck cancer, and melanoma were reviewed at a consensus meeting on 19 September 2008, and recommendations for the use of PET in brain, ovarian, cervical, testicular, small-cell lung, and pancreatic cancer were reviewed at a consensus meeting on 25 November 2008.

METHODS

Overview

In order to develop the recommendations and achieve consensus, a three-step methodology was undertaken.

Step 1 – Systematic review. A systematic review of the published literature was undertaken (see details below). This was conducted by one clinical lead author, a

member of the PEBC Neuro-oncology DSG, and a PEBC methodologist. The systematic review served as the evidentiary foundation for a set of draft recommendations developed by this team.

Step 2 – Consensus by the PEBC DSG. The Neuro-oncology DSG is currently not active, thus a teleconference did not occur.

Step 3 – Provincial PET imaging consensus meeting. The draft recommendations were vetted at a larger provincial PET imaging consensus meeting co-hosted by Cancer Care Ontario and the Provincial PET Steering Committee. The meeting was facilitated and supported by members of the PEBC team. Participants included representatives of the PEBC DSGs, other clinical experts in the areas of nuclear and diagnostic medicine, members of the Cancer Care Ontario clinical leadership team, and representatives from the Ontario PET Steering Committee and the Ontario Health Technology Assessment Committee.

The systematic review and companion recommendations are intended to promote evidence-based decisions in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

SYSTEMATIC REVIEW

Literature Search

The PEBC was aware of a technology assessment being produced by the University of Alberta Evidence-based Practice Center for the U.S. Agency for Healthcare Research and Quality (AHRQ) evaluating the use of PET imaging in nine cancers (1) (referred to as the AHRQ review from this point forward). This review updated a previous AHRQ report produced by Duke University in 2004 (2). The Alberta update included individual primary studies dating from 2003 to March 2008 on six of the 10 cancer sites targeted by this project. Because the AHRQ review sufficiently covered the questions and methodologies of interest to this recommendation report, a draft of the AHRQ review was made available to the PEBC, and its results were used for the evidentiary base.

Study Selection Criteria

All primary studies in the AHRQ review that addressed the questions of interest in this recommendation report (diagnosis, staging, treatment response, recurrence, and restaging) were included.

The inclusion criteria for primary studies included in the AHRQ review were:

- prospective or retrospective clinical study evaluating the use of FDG PET or FDG PET/CT in primary cancer;
- study not duplicated or superseded by a later study with the same purpose from the same institution;
- study reported numeric data on at least one objective outcome of interest for the key questions of the technology assessment (diagnostic performance, treatment decisions and management strategy, changes in therapy, patient-centred outcomes, and economic outcomes);
- study included ≥ 12 patients with the cancer of interest;
- study used a suitable reference standard (pathological confirmation and clinical follow-up) when appropriate.

Synthesizing the Evidence

In some cases where sufficient evidence existed, meta-analyses were included with pooled likelihood ratios. The AHRQ review included evidence tables that summarized the characteristics and results of each study according to the outcomes the study addressed. For diagnostic performance, the evidence tables recorded details on the source of the publication and the evidence grade, study design, patient characteristics, PET technical characteristics, criteria for interpretation, and results. In addition to the diagnostic performance of PET, the AHRQ review also sought to evaluate PET in terms of its impact on physician decision making approaches to diagnosis and management (referred to as diagnostic thinking) and its impact as part of a management strategy to improve patient-centred outcomes (referred to as management strategy). Full text and data extractions of the studies were provided to the clinical lead author to aid in the formulation of the recommendations. Telephone conferences and email correspondence between the clinical lead and the PEBC methodologist took place to clarify details and answer questions.

CONSENSUS

Provincial Consensus Process

The consensus meeting on 25 November 2008 was conducted as follows:

- Presentations by each of the clinical lead authors on the DRAFT DSG recommendations and supporting evidence were made to the meeting participants.
- The recommendations were refined by the large group and in some cases a revised recommendation was proposed resulting in a FINAL recommendation.
- The participants voted on the FINAL recommendations to indicate their extent of agreement on a scale from 1 to 7 (1 indicating strong agreement, 5 indicating no agreement or disagreement, and 7 indicating strong disagreement).

RESULTS

Literature Search Results

The AHRQ review results for brain cancer included 6 primary studies. Data from the evidence tables are summarized in Appendix 1. In addition to data for diagnostic performance, summaries of results for diagnostic thinking and management strategy are also presented where they apply. The key evidence is described below in an abbreviated fashion.

Key Evidence

Diagnosis/Staging

- Five studies (Chen et al [3], Cher et al [4], Liu et al [5], Potzi et al [6], Stockhammer et al [7]) assessed diagnostic accuracy and prognostic influence of PET scanning on survival, but none have demonstrated any additional diagnostic accuracy or prognostic influence over and above that provided by MRI and histology in a multivariate model.

Assessment of Treatment Response

- None of the studies addressed this question.

Recurrence/Restaging

- Two studies evaluating the use of PET included patients with recurrent gliomas (Chen et al [3], Potzi et al [6]). In both studies, FDG-PET was not the focus of the study but a comparison test for the tracer of interest, F-DOPA-PET in Chen et al (3), and Methionine-PET in Potzi et al (6). The evidence was insufficient to generate a recommendation on the use of FDG-PET.

RECOMMENDATIONS
DIAGNOSIS/STAGING
Clinical Question
What benefit to clinical management does PET or PET/CT contribute to the diagnosis or staging of gliomas?

DRAFT DSG Recommendation

PET or PET/CT is not recommended for the determination of diagnosis or prognosis in gliomas.

Provincial Consensus Meeting Deliberations

Dr. Laperriere explained that the challenge in brain tumours is to grade gliomas. It was agreed that "prognosis" should be changed to "grading." Otherwise, there was agreement with the recommendation.

FINAL Recommendation Put to Vote

PET is not recommended for the determination of diagnosis or grading in gliomas.

	1 – Strongly Agree		4 – Neither Agree nor Disagree			7 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	
Total	15	6						

Votes = 21

Qualifying Statement

None.

ASSESSMENT OF TREATMENT RESPONSE
Clinical Question
What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for gliomas?

DRAFT DSG Recommendation

PET or PET/CT is not recommended for treatment response in gliomas.

Provincial Consensus Meeting Deliberations

The group discussed the importance of pseudo progression and radiation necrosis. What is often detected is treatment effect, not treatment response. No evidence exists to support a recommendation, so the recommendation was changed to reflect this.

FINAL Recommendation Put to Vote

A recommendation cannot be made for or against the use of PET for the assessment of treatment response in gliomas due to insufficient evidence.

	1 – Strongly Agree		4 – Neither Agree nor Disagree			7 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	
Total	13	8						

Votes = 21

Qualifying statement

- Anecdotal evidence exists that PET/CT may differentiate radiation necrosis from tumour recurrence, but there is no gold standard for the diagnosis of radiation necrosis in glioblastoma multiforme.

RECURRENCE/RESTAGING

Clinical Question:

What benefit to clinical management does PET or PET/CT contribute when recurrence of gliomas is suspected but not proven? What benefit to clinical management does PET or PET/CT contribute to restaging at the time of documented recurrence for gliomas?

DRAFT DSG Recommendation

PET or PET/CT is not recommended in the assessment of patients with recurrent gliomas.

Provincial Consensus Meeting Deliberations

A discussion took place about the importance of radiation necrosis in the setting of tumour recurrence and it was recommended that it be added as a qualifying statement. It was also noted that the research in this area is quite dated. New research is being conducted on different tracers and instruments. It was decided that the recommendation be changed to reflect the current lack of evidence.

FINAL Recommendation Put to Vote

A recommendation cannot be made for or against the use of PET in the assessment of patients with recurrent gliomas due to insufficient evidence.

	1 – Strongly Agree			5 – Neither Agree nor Disagree				9 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	8	9	
Total	13	7	1							1

Votes = 21

Qualifying Statement

- PET or PET/CT has not been examined in a prospective cohort of gliomas to assess treatment effect on PET imaging before and after treatment and correlate this with survival.
- Radiation necrosis is a major factor in assessing recurrent gliomas.

Solitary Metastasis Identified at Time of Recurrence

Clinical Question

What is the role of PET when a solitary metastasis is identified at the time of recurrence and a metastectomy is being contemplated?

This question was not addressed in the brain cancer evidence review.

FUTURE RESEARCH

Mention was made during discussion that new research is focusing on other tracers (e.g., fluorothymidine [FLT] PET) and amino acid PET. PET is currently a research tool, rather than a diagnostic tool for brain tumours.

ACKNOWLEDGEMENTS

The PEBC would like to thank Dr. Normand Laperriere for taking the lead in drafting this systematic review.

For a complete list of the Neuro-oncology DSG (inactive) members, please visit the CCO Web site at http://www.cancercare.on.ca/

Funding

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Appendix 1. PET for brain cancer: summary of the evidence from 2003 to March 2008.

BRAIN Diagnostic performance						
Citation (ref #)	Study design	PET imaging	Reference std	Sens	Spec	Evidence grade
Primary diagnosis and recurrence						
Chen2006 (3)	Prospective	PET	Hist/bx or clin fup	60%	42%	B
Staging						
Cher2006 (4)	Prospective	PET	Hist/bx	62%	Not calc	B
Liu2006 (5)	Prospective	PET	Hist/bx	- Tumour uptake det'n – all: 63% - Tumour uptake det'n higher than contralateral grey matter: 19% - Tumour uptake det'n equal to contralateral grey matter: 84%	- Tumour uptake det'n – all: 100% - Tumour uptake det'n higher than contralateral grey matter: Not calc - Tumour uptake det'n equal to contralateral grey matter: Not calc	B
Stockhammer2007 (7)	Retrospective	PET	Hist/bx	75%	100%	B
Recurrence						
Potzi2007 (6)	Retrospective	PET	MRI, MET-PET	vs. MRI 11% vs. survival >12 mo 7%	vs. MRI 100% vs survival >12 mo 14%	B

Abbreviations: bx, biopsy; calc, calculated; clin, clinical; det'n, detection; fup, follow up; Hist, histology; MET, methionine; mo, months; MRI, magnetic resonance imaging; PET, positron emission tomography; Sens, sensitivity; Spec, specificity; std, standard.

Meta-analysis: Studies evaluating diagnostic performance with purpose of staging
Imaging: PET
Design: Prospective
Reference standard: Histology/biopsy
2 studies: Cher et al (4), Liu et al (5)
Pooled +LR = 10.00 (95% CI 0.67 to 149.57)
Pooled –LR = 0. 40 (95% CI 0.22 to 0.72)

<table>
<tr><td colspan="6">BRAIN
Management strategy</td></tr>
<tr><td>Citation (ref #)</td><td>Study design</td><td>PET imaging</td><td>Purpose of PET</td><td>Patient centred outcomes and prognosis</td><td>Evidence grade</td></tr>
<tr><td>Padma2003 (8)</td><td>Retrospective</td><td>PET</td><td>Predicting survival</td><td>Comparison groups: High FDG uptake (165 pts), low FDG uptake (166 pts)
<table><tr><td>Survival</td><td>High uptake</td><td>Low uptake</td></tr><tr><td><1 y</td><td>117/165</td><td>10/166</td></tr><tr><td>>1 y</td><td>48/165</td><td>156/166</td></tr><tr><td>>2 y</td><td>0/165</td><td>104/166</td></tr><tr><td>>3 y</td><td>0/165</td><td>65/166</td></tr><tr><td>4 y</td><td>0/165</td><td>49/166</td></tr><tr><td>5 y</td><td>0/65</td><td>26/166</td></tr></table>Any single scan with high uptake was associated with poor prognosis where serial scans were performed (37/40 pts with serial scans died over fup). Survival decreases steadily as grade of uptake increases.</td><td>D</td></tr>
</table>

Abbreviations: FDG, fluorodeoxyglucose; fup, follow up; PET, positron emission tomography; pts, patients; y, year.