



PET Recommendation Report 9

PET Imaging in Small Cell Lung Cancer

Y Ung and C Walker-Dilks

Report Date: January 19, 2009

PET Recommendation Report 9 is comprised of 2 sections and is available on the CCO Web site (<https://www.cancercare.on.ca>)
PEBC PET Recommendation Reports page at:
<https://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/petrecs/>

Section 1: Recommendations

Section 2: Evidentiary Base

For further information about this report, please contact:

Dr. Yee Ung,
Odette Cancer Centre, 2075 Bayview Avenue,
Toronto, Ontario Canada M4N 3M5
Telephone (416) 480-4951; Fax (416) 480-6002; Email: yee.ung@sunnybrook.ca

For information about the PEBC and the most current version of all reports, 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

Citation (Vancouver Style): Ung Y, Walker-Dilks C. PET Imaging in small cell cancer. Toronto (ON): Cancer Care Ontario; 2009 Jan 19. Program in Evidence-based Care PET Recommendation Report No.: 9.



Recommendation Report - PET #9: Section 1

PET Imaging in Small Cell Lung Cancer: Recommendations

Y Ung 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 small cell lung cancer (SCLC)?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for SCLC?
- What benefit to clinical management does PET or PET/CT contribute when recurrence of SCLC 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 SCLC?
- 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 SCLC.

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 recommended for staging in patients with SCLC who are potential candidates for the addition of thoracic radiotherapy to chemotherapy.

Six studies were based on PET alone (Bradley et al [2], Brink et al [3], Kut et al [4], Pandit et al [5], Vinjamuri et al [6], Blum et al [7]). Two studies were based on PET/CT (Fischer et al [8], Fischer et al [9]).

Overall higher sensitivity and specificity is achieved with PET/CT versus PET versus conventional imaging (Fischer et al [8]).

In terms of diagnostic accuracy, the diagnostic performance of PET compared with CT for extrathoracic lymph node metastases was 100% versus (vs) 70% sensitivity and 98% vs 94% specificity; for distant metastases 98% vs 83% sensitivity and 92% vs 79% specificity; and for brain mets (compared with MRI) was 46% vs 100% sensitivity and 97% vs 100% specificity (Brink et al [3]).

For the differentiation of extensive disease (ED) from limited disease (LD), PET/CT had sensitivity and specificity of 93% and 100%, PET had sens and specificity of 93% and 83%, and standard staging had sensitivity and specificity of 79% and 100% (Fischer et al [8]).

SCLC has a high metabolic rate and invariably the primary site is fluorodeoxyglucose (FDG) avid (Bradley et al [2], Brink et al [3], Kut et al [4], Niho et al [10], Blum et al [7]).

The rate of upstaging from limited to extensive disease varies from 0% to 33%. The sample size of the reported studies varies from four to 63 patients with limited disease. Only two studies specifically evaluated the role of PET in LD SCLC (Bradley et al [2], Niho et al [10]). In these two studies, upstaging ranged from 8.3% to 9.5%, with the most common sites for detected metastases being in the bone, liver, and lymph nodes (bilateral supraclavicular, cervical, and axillary).

The remaining seven studies had a mixture of LD and ED SCLC, with varying percentages of upstaging LD to ED SCLC from 0% to 33% (Brink et al [3], Fischer et al [8], Kut et al [4], Pandit et al [5], Vinjamuri et al [6], Blum et al [7], Kamel et al [11]).

Some downstaging of ED SCLC occurred but primarily in cases where conventional imaging found suspected adrenal metastases (Brink et al [3], Vinjamuri et al [6]) or contralateral lung nodule (Vinjamuri et al [6], Kamel et al [11]) as the only site for ED SCLC, and PET downstaged some of these patients.

The impact of PET imaging is seen in cases where the unsuspected lymph nodes metastases (FDG-avid disease) is found and causes a change in the thoracic radiation treatment volume. The thoracic radiation treatment volumes were altered from 19% to 34% (Bradley et al [2], Vinjamuri et al [6], Blum et al [7], Niho et al [10], Kamel et al [11]).

Qualifying Statement

- PET or PET/CT performs better for staging the primary tumour in SCLC than for areas outside the chest, including the extrathoracic lymph nodes and distant metastases. There is greater discordance between PET and conventional imaging results in the evaluation of the mediastinal nodes, extrathoracic nodes, and distant sites.

Assessment of Treatment Response

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

Only one study addressed the issue of change in therapy or continuation of therapy based on response (Kamel et al [11]). In this study, restaging with PET after therapy was available in 20 patients. PET correctly identified the five patients with CR, 11 of 12 patients with residual disease, and three patients with progressive disease. CR was verified by clinical and radiological follow-up. Discordance was found between PET and CT in three patients where no FDG uptake was seen in abnormally enlarged nodes and further chemotherapy was deemed unnecessary due to a metabolic CR. In one patient, PET detected residual disease that CT had missed, and further chemotherapy was given.

Two studies evaluated the concordance of response evaluation of PET with conventional imaging (Fischer et al [9], Kut et al [4]). In the study by Fischer et al (9), PET/CT was performed after one cycle of chemotherapy in 12 patients (early response assessment). Major disagreement between PET/CT and CT was seen in one patient, and minor disagreement was seen in six patients. The one-year survival rate for patients responding on PET/CT was 64%. One nonresponder on PET/CT and CT died after eight months. PET/CT was also performed after six cycles of chemotherapy (final response assessment) in 19 patients. Overall, disagreement between CT and PET/CT was found in eight patients (42%) and major disagreement in two patients (11%). One-year survival was 65% for responders and 50% for nonresponders. No changes in therapy were made based on early or final response assessment.

In the study by Kut et al (4), nine of 21 patients had a response assessment. Based on both PET and conventional imaging, there were seven partial responses (PR), one complete response (CR), and 1 stable disease (SD). PET failed to identify liver progression as PET indicated SD but CT showed new liver lesions. In two cases, PET showed CR while CT showed persistent lymphadenopathy.

The prognostic value of PET response was evaluated in two studies (Pandit2003 [5], Blum2004 [7]). In the study by Pandit et al (5), the two-year survival in nine of 10 PET-negative patients was 67%, and in four of 27 PET-positive patients it was 23% (p=0.0108). In the study by Blum et al (7), the median time to progression in PET CR was 13.7 vs 9.7 months in no CR.

The role for PCI only in complete responders was not addressed in any of these studies but was raised for discussion by Kamel et al (11).

None of the studies addressed the issue of whether change in therapy affected patient outcomes.

Qualifying Statements

- Response evaluation may be used for various reasons:
 - a) to determine if a change in therapy is needed in non-responders or those with progressive disease
 - b) to determine if additional consolidation therapy is needed
 - c) to determine prognosis
 - d) to determine the role for PCI
- Issues in SCLC that need to be addressed before changing therapy include:
 - 1) what effective salvage or second line treatment is available?
 - 2) do we know that additional consolidation therapy is needed beyond four to six cycles?
 - 3) what is the optimal time to do response assessment?
 - 4) do we only give prophylactic cranial irradiation (PCI) to CR and exclude PR?

Recurrence/Restaging

A recommendation cannot be made for or against the use of PET for evaluation of recurrence or restaging due to insufficient evidence.

None of the studies address these questions but rather address the concordance of PET vs conventional imaging in evaluating response.

Qualifying Statement

- Detecting early recurrence is useful if there is effective salvage therapy, but in SCLC second-line chemotherapy has a low response rate.

Solitary Metastasis Identified at Time of Recurrence

A recommendation cannot be made for or against the use of PET when metastectomy or stereotactic body radiation therapy is being contemplated for solitary metastases due to insufficient evidence.

None of the studies address this question.

In the uncommon setting where there is persistent localized disease after treatment with CT radiation therapy (RT), surgical resection may be a possibility or with newer RT techniques, stereotactic body radiation therapy may be possible, and in this unusual scenario, there may be a role for PET/CT, but currently there are no data to support this.

Qualifying Statement

None.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario 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.

Copyright

This report is copyrighted by Cancer Care Ontario; the report and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information

For further information about this report, please contact:

Dr. Yee Ung, Odette Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario Canada M4N 3M5, telephone (416) 480-4951, fax (416) 480-6002, email yee.ung@sunnybrook.ca

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at <http://www.cancercare.on.ca/> or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

REFERENCES

1. McEwan AJ, Gulenchyn K, Ospina M, Horton J, Seida J, Vandermeer B, et al. Positron emission tomography for nine cancers (bladder, brain, cervical, kidney, ovarian, pancreatic, prostate, small cell lung, testicular). Rockville, Maryland: Agency for Healthcare Research and Quality; August 2008. Draft.
2. Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004;22(16):3248-54.
3. Brink I, Schumacher T, Mix M, Ruhland S, Stoelben E, Digel W, et al. Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. *Eur J Nucl Med Mol Imaging* 2004;31(12):1614-20.
4. Kut V, Spies W, Spies S, Gooding W, Argiris A. Staging and monitoring of small cell lung cancer using [18F]fluoro-2-deoxy-Dglucose-positron emission tomography (FDG-PET). *Am J Clin Oncol* 2007;30(1):45-50.
5. Pandit N, Gonen M, Krug L, Larson SM. Prognostic value of [18F]FDG-PET imaging in small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2003;30(1):78-84.
6. Vinjamuri M , Craig M, Campbell-Fontaine A, Almubarak M, Gupta N, Rogers JS. Can positron emission tomography be used as a staging tool for small-cell lung cancer? *Clin Lung Cancer* 2008;9(1):30-4.
7. Blum R, MacManus MP, Rischin D, Michael M, Ball D, Hicks RJ. Impact of positron emission tomography on the management of patients with small-cell lung cancer: preliminary experience. *Am J Clin Oncol* 2004;27(2):164-71.
8. Fischer BM, Mortensen J, Langer SW, Loft A, Berthelsen AK, Petersen BI, et al. A prospective study of PET/CT in initial staging of small cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. *Ann Oncol* 2007;18(2):338-45.
9. Fischer BM, Mortensen J, Langer SW, Loft A, Berthelsen AK, Daugaard G, et al. PET/CT imaging in response evaluation of patients with small cell lung cancer. *Lung Cancer* 2006;54(1):41-9.
10. Niho S, Fujii H, Murakami K, Nagase S, Yoh K, Goto K, et al. Detection of unsuspected distant metastases and/or regional nodes by FDG-PET [corrected] scan in apparent limited-disease small-cell lung cancer.[erratum appears in *Lung Cancer*. 2007 Dec;58(3):432]. *Lung Cancer* 2007;57(3):328-33.
11. Kamel EM, Zwahlen D, Wyss MT, Stumpe KD, von Schulthess GK, Steinert HC. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. *J Nucl Med* 2003;44(12):1911-7.



Recommendation Report - PET #9: Section 2

PET Imaging in Small Cell Lung Cancer: Evidentiary Base and Consensus Process

Y Ung 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 small cell lung cancer (SCLC)?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for SCLC?
- What benefit to clinical management does PET or PET/CT contribute when recurrence of SCLC 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 small cell lung cancer?
- 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 the PEBC 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, nominated by the PEBC Lung 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 Lung DSG. The draft recommendations were refined during a DSG teleconference. The Lung DSG is comprised of medical and radiation oncologists and surgeons and supported by a PEBC research methodologist.

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

DSG Consensus Process

The clinical lead author wrote summaries of the key evidence, draft recommendations, and qualifying statements for the questions pertaining to diagnosis/staging, assessment of treatment response, and recurrence/restaging. The ensuing documents were circulated to all members of the Lung DSG and discussed during a teleconference. The recommendations that were generated during this process are referred to below as the DRAFT DSG Recommendations. The intent of these recommendations was to guide discussion at the consensus meeting.

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 SCLC included 10 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

- Six studies were based on PET alone (Bradley et al [3], Brink et al [4], Kut et al [5], Pandit et al [6], Vinjamuri et al [7], Blum et al [8]). Two studies were based on PET/CT (Fischer et al [9], Fischer et al [10]).
- Overall higher sensitivity and specificity is achieved with PET/CT versus PET versus conventional imaging (Fischer et al [9]).

- In terms of diagnostic accuracy, the diagnostic performance of PET compared with CT for extrathoracic lymph node metastases was 100% vs 70% sensitivity and 98% vs 94% specificity; for distant metastases 98% vs 83% sensitivity and 92% vs 79% specificity; and for brain mets (compared with MRI) was 46% vs 100% sensitivity and 97% vs 100% specificity (Brink et al [4]).
- For the differentiation of ED from LD, PET/CT had sensitivity and specificity of 93% and 100%, PET had sensitivity and specificity of 93% and 83%, and standard staging had sensitivity and specificity of 79% and 100% (Fischer et al [9]).
- SCLC has a high metabolic rate and invariably the primary site is FDG avid (Bradley et al [3], Brink et al [4], Kut et al [5], Niho et al [11], Blum et al [8]).
- The rate of upstaging from limited to extensive disease varies from 0% to 33%. The sample size of the reported studies varies from four to 63 patients with limited disease. Only two studies specifically evaluated the role of PET in LD SCLC (Bradley et al [3], Niho et al [11]). In these two studies upstaging ranged from 8.3% to 9.5%, with the most common sites for detected metastases being in the bone, liver, and lymph nodes (bilateral supraclavicular, cervical, and axillary).
- The remaining seven studies had a mixture of LD and ED SCLC with varying percentages of upstaging LD to ED SCLC from 0% to 33% (Brink et al [4], Fischer et al [9], Kut et al [5], Pandit et al [6], Vinjamuri et al [7], Blum et al [8], Kamel et al [12]).
- Some downstaging of ED SCLC occurred but primarily in cases where conventional imaging found suspected adrenal metastases (Brink et al [4], Vinjamuri et al [7]) or contralateral lung nodule (Vinjamuri et al [7], Kamel et al [12]) as the only site for ED SCLC, and PET downstaged some of these patients.
- The impact of PET imaging is seen in cases where the unsuspected lymph nodes metastases (FDG-avid disease) is found and causes a change in the thoracic radiation treatment volume. The thoracic radiation treatment volumes were altered from 19% to 34% (Bradley et al [3], Vinjamuri et al [7], Blum et al [8], Niho et al [11], Kamel et al [12]).

Assessment of Treatment Response

- Only one study addressed the issue of change in therapy or continuation of therapy based on response (Kamel et al [12]). In this study, restaging with PET after therapy was available in 20 patients. PET correctly identified the five patients with CR, 11 of 12 patients with residual disease, and three patients with progressive disease. CR was verified by clinical and radiological follow-up. Discordance was found between PET and CT in three patients where no FDG uptake was seen in abnormally enlarged nodes, and further chemotherapy was deemed unnecessary due to a metabolic CR. In one patient, PET detected residual disease that CT had missed, and further chemotherapy was given.
- Two studies evaluated the concordance of response evaluation of PET with conventional imaging (Fischer et al [10], Kut et al [5]). In the study by Fischer et al (10), PET/CT was performed after one cycle of chemotherapy in 12 patients (early response assessment). Major disagreement between PET/CT and CT was seen in one patient, and minor disagreement was seen in six patients. The one-year survival rate for patients responding on PET/CT was 64%. One nonresponder on PET/CT and CT died after eight months. PET/CT was also performed after six cycles of chemotherapy (final response assessment) in 19 patients. Overall disagreement between CT and PET/CT was found in eight patients (42%) and major disagreement in two patients (11%). One-year survival was 65% for responders and 50% for nonresponders. No changes in therapy were made based on early or final response assessment.

- In the study by Kut et al (5), nine of 21 patients had response assessment. Based on both PET and conventional imaging, there were seven PR, one CR, and one SD. PET failed to identify liver progression as PET indicated SD but CT showed new liver lesions. In two cases, PET showed CR, while CT showed persistent lymphadenopathy.
- The prognostic value of PET response was evaluated in two studies (Pandit2003 [6], Blum et al [8]). In the study by Pandit et al (6), the two-year survival in nine of 10 PET-negative patients was 67% and in four of 27 PET-positive patients it was 23% (p=0.0108). In the study by Blum et al (8), the median time to progression in PET CR was 13.7 vs 9.7 months in no CR.
- The role for PCI only in complete responders was not addressed in any of these studies but was raised for discussion by Kamel et al (12).
- None of the studies addressed the issue of whether a change in therapy affected patient outcomes.

Recurrence/Restaging

- None of the studies address these questions but instead address the concordance of PET vs conventional imaging in evaluating response.

Solitary Metastasis Identified at Time of Recurrence

- None of the studies address this question.
- In the uncommon setting where there is persistent localized disease after treatment with CT RT, surgical resection may be a possibility or with newer RT techniques, stereotactic body radiation therapy may be possible and in this unusual scenario, there may be a role for PET/CT, but currently there are no data to support this.

RECOMMENDATIONS

DIAGNOSIS/STAGING

Clinical Question

What benefit to clinical management does PET or PET/CT contribute to the diagnosis or staging of SCLC?

DRAFT DSG Recommendation

PET is recommended for staging in patients with SCLC who are potential candidates for radiotherapy but for whom conventional staging is ambiguous or inconclusive with respect to extent of disease.

Provincial Consensus Meeting Deliberations

There was some discussion in the large group about what constituted conventional staging. As a result, the recommendation was modified.

FINAL Recommendation Put to Vote

PET is recommended for staging in patients with SCLC who are potential candidates for the addition of thoracic radiotherapy to chemotherapy.

	1 - Strongly Agree		4 - Neither Agree nor Disagree			7 - Strongly Disagree		N/A
	1	2	3	4	5	6	7	
Total	10	9		2				

Votes = 21

Issues raised on voting questionnaire:

- In light of the “weak evidence” for use in staging, one could consider using a weaker recommendation (i.e., “suggest”).
- Not sure if upstaging rate is high enough to warrant routine use.

Qualifying Statement

- PET or PET/CT performs better for staging the primary tumour in SCLC than for areas outside the chest, including the extrathoracic lymph nodes and distant metastases. There is greater discordance between PET and conventional imaging results in the evaluation of the mediastinal nodes, extrathoracic nodes, and distant sites.

ASSESSMENT OF TREATMENT RESPONSE

Clinical Question

What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for SCLC?

DRAFT DSG Recommendation

A recommendation cannot be made for or against the use of PET for the assessment of treatment response, for either LD SCLC or ED SCLC due to insufficient evidence.

Provincial Consensus Meeting Deliberations

No major issues were raised during discussion of these recommendations, but it was agreed to remove LD and ED from the recommendation.

FINAL Recommendation Put to Vote:

A recommendation cannot be made for or against the use of PET for the assessment of treatment response in SCLC 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	9	10	1	1				

Votes = 21

Issues raised on voting questionnaires:

- Many possible situations, however - see qualifying statements.
- I recommend no PET at present.

Qualifying Statements

- Response evaluation may be used for various reasons:
 - a) to determine if a change in therapy is needed in non-responders or those with progressive disease
 - b) to determine if additional consolidation therapy is needed
 - c) to determine prognosis
 - d) to determine the role for PCI
- Issues in SCLC that need to be addressed before changing therapy include:
 - 1) what effective salvage or second line treatment is available?
 - 2) do we know that additional consolidation therapy is needed beyond 4 to 6 cycles?
 - 3) what is the optimal time to do response assessment?
 - 4) do we only give PCI to CR and exclude PR?

RECURRENCE/RESTAGING

Clinical Question

What benefit to clinical management does PET or PET/CT contribute when recurrence of SCLC 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 SCLC?

DRAFT DSG Recommendation

A recommendation cannot be made for or against the use of PET for evaluation of recurrence or restaging due to insufficient evidence.

Provincial Consensus Meeting Deliberations

No major issues were raised during discussion of this recommendation.

FINAL Recommendation Put to Vote

A recommendation cannot be made for or against the use of PET for evaluation of recurrence or restaging 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	9	12								1

Votes = 21

Qualifying Statement

- Detecting early recurrence is useful if there is effective salvage therapy but in SCLC second-line chemotherapy has a low response rate.

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?

DRAFT DSG Recommendation

PET or PET/CT is recommended when metastectomy or stereotactic body radiation therapy is being contemplated for solitary metastases.

Provincial Consensus Meeting Deliberations

During discussion, a large number of participants felt it was unjustified to make a recommendation for PET in the absence of any evidence. In a situation such as this, the special access system would be used.

FINAL Recommendation Put to Vote

A recommendation cannot be made for or against the use of PET when metastectomy or stereotactic body radiation therapy is being contemplated for solitary metastases 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	11	8		2						1

Votes = 21

Qualifying Statement

None.

FUTURE RESEARCH

Areas for future research were not discussed in the process of drafting these recommendations.

ACKNOWLEDGEMENTS

The Lung DSG would like to thank Dr. Yee Ung for taking the lead in drafting this systematic review.

For a complete list of the Gynecology DSG members, please visit the CCO Web site at <http://www.cancercare.on.ca/>

Funding

The PEBC is a provincial initiative of Cancer Care Ontario 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.

Copyright

This report is copyrighted by Cancer Care Ontario; the report and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information

For further information about this report, please contact:

Dr. Yee Ung, Odette Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario Canada M4N 3M5, telephone (416) 480-4951, fax (416) 480-6002, email yee.ung@sunnybrook.ca

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at <http://www.cancercare.on.ca/> or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

REFERENCES

1. McEwan AJ, Gulenchyn K, Ospina M, Horton J, Seida J, Vandermeer B, et al. Positron emission tomography for nine cancers (bladder, brain, cervical, kidney, ovarian, pancreatic, prostate, small cell lung, testicular). Rockville, Maryland: Agency for Healthcare Research and Quality; 2008 Aug. [Draft].
2. Matchar DB, Kulasingam SL, Havrilesky L, Mann LO, Myers ER, McCrory DC, et al. Positron emission tomography for six cancers (brain, cervical, small cell lung, ovarian, pancreatic, and testicular). Rockville, Maryland: Agency for Healthcare Research and Quality; 2004 Feb [cited 2009 Jan 19]. Available from: <http://www.cms.hhs.gov/mcd/viewtechassess.asp?where=search&tid=21>
3. Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004;22(16):3248-54.
4. Brink I, Schumacher T, Mix M, Ruhland S, Stoelben E, Digel W, et al. Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. *Eur J Nucl Med Mol Imaging* 2004;31(12):1614-20.
5. Kut V, Spies W, Spies S, Gooding W, Argiris A. Staging and monitoring of small cell lung cancer using [18F]fluoro-2-deoxy-Dglucose-positron emission tomography (FDG-PET). *Am J Clin Oncol* 2007;30(1):45-50.
6. Pandit N, Gonen M, Krug L, Larson SM. Prognostic value of [18F]FDG-PET imaging in small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2003;30(1):78-84.
7. Vinjamuri M, Craig M, Campbell-Fontaine A, Almubarak M, Gupta N, Rogers JS. Can positron emission tomography be used as a staging tool for small-cell lung cancer? *Clin Lung Cancer* 2008;9(1):30-4.
8. Blum R, MacManus MP, Rischin D, Michael M, Ball D, Hicks RJ. Impact of positron emission tomography on the management of patients with small-cell lung cancer: preliminary experience. *Am J Clin Oncol* 2004;27(2):164-71.
9. Fischer BM, Mortensen J, Langer SW, Loft A, Berthelsen AK, Petersen BI, et al. A prospective study of PET/CT in initial staging of small cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. *Ann Oncol* 2007;18(2):338-45.
10. Fischer BM, Mortensen J, Langer SW, Loft A, Berthelsen AK, Daugaard G, et al. PET/CT imaging in response evaluation of patients with small cell lung cancer. *Lung Cancer* 2006;54(1):41-9.
11. Niho S, Fujii H, Murakami K, Nagase S, Yoh K, Goto K, et al. Detection of unsuspected distant metastases and/or regional nodes by FDG-PET [corrected] scan in apparent limited-disease small-cell lung cancer.[erratum appears in *Lung Cancer*. 2007 Dec;58(3):432]. *Lung Cancer* 2007;57(3):328-33.
12. Kamel EM, Zwahlen D, Wyss MT, Stumpe KD, von Schulthess GK, Steinert HC. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. *J Nucl Med* 2003;44(12):1911-7.

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

SMALL CELL LUNG Diagnostic performance						
Citation (ref #)	Study design	PET imaging	Reference std	Sens	Spec	Evidence grade
Staging						
Bradley2004 (3)	Prospective	PET	Hist/bx or clin fup	100%	Not calc	B
Brink2004 (4)	Prospective	PET	Hist/bx or conv staging	100%	Not calc	B
*Fischer2007 (9)	Prospective	PET/CT	Hist/bx	PET 93% PET/CT 93% for ED	PET 83% PET/CT 100% for ED	B
Kut2007 (5)	Prospective	PET	Conv staging	100%	Not calc	C
Niho2007 (11)	Retrospective	PET & PET/CT	Clin fup or conv staging	14%	Not calc	C
Pandit2003 (6)	Retrospective	PET	Hist/bx or clin fup	vs. hist/bx (30 scans) 100% vs. clin fup (62 scans) 97%	vs. hist/bx (30 scans) 63% vs. clin fup (62 scans) 78%	C
Vinjamuri2008 (7)	Retrospective	PET	Clin fup	100%	Not calc	C
Staging and restaging						
Blum2004 (8)	Retrospective	PET	Hist/bx or clin fup	100%	Not calc	C
Fischer2006 (10)	Prospective	PET/CT	Clin fup	92%	Not calc	C
*Kamel2003 (12)	Prospective	PET	Hist/bx or clin fup	93% for LD	66% for LD	C

*Results in Fischer2007 are differentiating extensive disease from limited disease. Results in Kamel2003 are differentiating limited disease from extensive disease.

Abbreviations: bx, biopsy; calc, calculated; clin, clinical; conv, conventional; CT, computed tomography; ED, extensive disease; fup, follow up; Hist, histology; LD, limited disease; PET, positron emission tomography; Sens, sensitivity; Spec, specificity; std, standard.

SMALL CELL LUNG Diagnostic thinking					
Citation (ref #)	Study design	PET imaging	Purpose of PET	Management decision	Evidence grade
Blum2004 (8)	Retrospective	PET	Staging & restaging	Rx strategy changed for 17/36 pts: Initial staging: -7/15 plans upstaged -From radical concurrent chemo to palliative (5 pts) -RT target vol increased (2 pts)	C

PET REPORT 9 IN REVIEW

				<p>Restaging: -10/25 plans changed (3 upstaged, 5 downstaged, 2 not described) Complete metabolic responders on PET had longer median time to progression (13.7 vs 9.7 mo)</p>	
Bradley2004 (3)	Prospective	PET	Staging	<p>-7/25 pts (29%) upstaged. -Unsuspected 1° tumour id'd in 6 pts (not detected by CT) led to change to RT portal. -Id of extensive disease in 2 pts who were dx as limited stage SCLC by conv staging.</p>	B
Kamel2003 (12)	Prospective	PET & PET/CT	Staging & restaging	<p>Rx strategy changed for 12/42 pts (29%). Initial staging: -Upstaged & palliative chemo (3 pts) -Downstaged & curative resection (1 pt) -Minor change to dx & rad'n field altered (5 pts) Restaging: -chemo reinstated (1 pt) -Discontinued (2 pts)</p>	C

Abbreviations: conv, conventional; CT, computed tomography; id, identified; PET, positron emission tomography; pts, patients; RT, radiation therapy; Rx, treatment; SCLC, small cell lung cancer.