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PET Recommendation Report 4 Version 2

PET Imaging in Esophageal Cancer

R. Wong, C. Walker-Dilks, and A.O. Raifu

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: January 19, 2009

Update: November 30, 2010

The full PET Recommendation Report 4 Version 2 consists of 2 sections and is available on the CCO website (http://www.cancercare.on.ca)
PEBC PET Recommendations Reports page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/petrecs/

Section 1: Recommendations
Section 2: Evidentiary Base and Consensus Process

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PET Recommendation Report 4 Version 2: Section 1

PET Imaging in Esophageal Cancer: Recommendations

R. Wong, C. Walker-Dilks, and A.O. Raifu

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: January 19, 2009
Update: November 30, 2010

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 esophageal cancer?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for esophageal cancer?
- What benefit to clinical management does PET or PET/CT contribute when recurrence of esophageal cancer 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 esophageal cancer?
- What is the role of PET when a solitary metastasis is identified at the time of recurrence and the metastectomy is being contemplated?

TARGET POPULATION

Patients with esophageal cancer.

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 to inform clinical decision making regarding the appropriate role of PET imaging and to guide priorities for future PET imaging research.

RECOMMENDATIONS AND KEY EVIDENCE

These recommendations are based on an evidentiary foundation consisting of one recent high-quality United Kingdom (U.K.) Health Technology Assessment (HTA) systematic review (1) that included systematic review and primary study literature for the period from 2000 to August 2005 and update searches based on those in that original systematic review

and undertaken to retrieve the same level of evidence for the period from August 2005 to May 2010.

Diagnosis/Staging

For the staging workup of patients with esophageal cancer who are potential candidates for curative therapy, PET is recommended to improve the accuracy of M staging.

There is a significant role for PET for its incremental value in detecting distant disease, in addition to CT +/- endoscopic ultrasound (EUS). Especially in the absence of EUS, PET provides an incremental benefit.

HTA review (1): One systematic review containing three primary studies showed the superiority of PET to CT or EUS in detecting distant metastases. Another systematic review of 12 primary studies showed that PET had a sensitivity of 67% and a specificity of 97%, corroborating the first systematic review. One additional primary study showed the incremental benefit of adding PET to CT and EUS, giving a sensitivity of 74% compared with 53% for PET alone and 64% for PET plus CT.

A 2008 systematic review by van Vliet et al, 2008 (2), with two primary studies not included in Facey et al, 2007 (1), and two studies from the update search (Kato et al, 2005 [3] and Katsoulis et al, 2007 [4]) showed higher detection rates for distant metastases with PET than with CT, but the difference was not statistically significant.

When the effect of PET is evaluated, based on whether staging is changed, a correct change occurred in approximately 30% of cases in two studies (one in van Vliet et al [2], and one in Katsoulis et al [4] from the updated search).

There is some evidence that PET/CT is superior to PET alone for nodal staging (Yuan et al, 2006 [5]).

2008-2010 update: Seven primary studies (Chatterton et al, 2009 [6], Cheze-Le Rest et al, 2008 [7], Hsu et al, 2009 [8], Hu et al, 2009 [9], Noble et al, 2009 [10], Okada et al, 2009 [11], and Shimizu et al, 2009 [12]) also showed the significant impact of PET and PET/CT on the clinical management, prognostic stratification of patients with newly diagnosed esophageal cancer, prediction of regional and locoregional lymph nodes, and improvement on the accuracy of pretreatment staging compared to CT and EUS alone.

Qualifying Statement

- The data supporting this recommendation are compelling but sparse. The recommendation is based on patients with a new diagnosis of esophageal cancer.

Assessment of Treatment Response

A recommendation cannot be made for or against the use of PET (post or neoadjuvant therapy) for the purpose of predicting response to neoadjuvant therapy due to insufficient evidence.

There is some evidence that PET, either early in treatment or at the completion of neoadjuvant therapy, can predict complete pathologic response, and therefore, predict the longer-term outcome in terms of survival and event-free survival.

HTA 2007 review (1): One systematic review of four primary studies plus one additional study showed that PET may be superior to CT and comparable to EUS in the assessment of response and of prognosis after neoadjuvant therapy. One additional study showed PET/CT to be more sensitive for the evaluation of response than either CT or endoscopic ultrasound.

2005-2010 update: Thirteen primary studies were identified in the update search. The change in PET parameters before and after neoadjuvant therapy provided a reasonable diagnostic accuracy (68% to 86%) for the prediction of pathological response (Song et al, 2005 [13], Levine et al, 2006 [14], Duong et al, 2006 [15], Kim et al, 2007 [16], Wieder et al, 2007

[17], Smithers et al, 2008 [18], Higuchi et al, 2008 [19], Klaeser et al, 2009 [20], and Shenfine et al, 2009 [21]). Perhaps more importantly, there is evidence that PET response is related to longer-term clinical outcomes, including disease-free survival and overall survival (Duong et al [15], Kim et al [16], Wieder et al [17], Higuchi et al [19], and Shenfine et al [21]). The best cutoff point to use for defining responder versus non-responder remains to be defined. Data derived from the receiver operating characteristic (ROC) curves would suggest a 30% to 50% reduction as a useful parameter (Wieder et al [17], Smithers et al [18],). The prognostic value of PET is further supported by the fact that responders and nonresponders have significantly different SUV change profiles.

The value of PET as an early indicator for future response was evaluated in three studies (Gillham et al, 2006 [22], Westerterp et al, 2006 [23], Wieder et al, 2007 [17b], and Vallbohmer et al, 2009 [24]). While a significant difference existed between pathological responders and nonresponders, further study is required to establish the best criteria and standardized conditions to use if this modality is to be routinely incorporated into clinical practice to guide treatment decisions.

One study evaluated PET as an early tool to predict a response allowing neoadjuvant therapy to be abandoned in favour of early surgery (Lordick et al, 2007 [25]). This study confirmed that responders had better outcomes in terms of survival and disease-free survival.

Qualifying Statement

- Whether the use of PET to assess treatment response would translate into an improved outcome remains to be established, but it is potentially useful in minimizing toxicity related to futile treatment. The optimal parameters to use for defining responders require further validation.

Recurrence/Restaging

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

Two studies from the 2005-2010 update (Guo et al, 2007 [26] and Jingu et al, 2010 [27]) showed PET/CT to be accurate in detecting regional and distant recurrence and in predicting the prognosis in patients with postoperative recurrent esophageal cancer. The findings of these studies require corroboration before a recommendation can be made.

Qualifying Statement

None.

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REFERENCES

1. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technol Assess. 2007 Oct;11(44):iii-iv, xi-267. [cited 2009 Jan 19]. Available from: http://www.hta.ac.uk/1487
2. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer. 2008 Feb 12;98(3):547-57. Epub 2008 Jan 22.
3. Kato H, Miyazaki T, Nakajima M, Takita J, Kimura H, Faried A, et al. Comparison between whole-body positron emission tomography and bone scintigraphy in evaluating bony metastases of esophageal carcinomas. Anticancer Res. 2005 Nov-Dec;25(6C):4439-44.
4. Katsoulis IE, Wong WL, Mattheou AK, Damani N, Chambers J, Livingstone JI. Fluorine-18 fluorodeoxyglucose positron emission tomography in the reoperative staging of thoracic oesophageal and gastro-oesophageal junction cancer: a prospective study. Int J Surg. 2007 Dec;5(6):399-403. Epub 2007 Jun 3.
5. Yuan S, Yu Y, Chao KS, Fu Z, Yin Y, Liu T, et al. Additional value of PET/CT over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. J Nucl Med. 2006 Aug;47(8):1255-9.
6. Chatterton BE, Ho Shon I, Baldey A, Lenzo N, Patrikeos A, Kelley B, et al. Positron emission tomography changes management and prognostic stratification in patients with oesophageal cancer: Results of a multicentre prospective study. Eur J Nucl Med Mol Imag. 2009:36(3):354-61.
7. Cheze-Le Rest C, Metges JP, Teyton P, Jestin-Le Tallec V, Lozac'h P, Volant A, et al. Prognostic value of initial fluorodeoxyglucose-PET in esophageal cancer: a prospective study. Nucl Med Commun. 2008:29(7):628-35.
8. Hsu W-H, Hsu P-K, Wang S-J, Lin K-H, Huang C-S, Hsieh CC, et al. Positron emission tomography-computed tomography in predicting locoregional invasion in esophageal squamous cell carcinoma. Ann Thorac Surg. 2009:87(5):1564-8.
9. Hu Q, Wang W, Zhong X, Yuan S, Fu Z, Guo H, et al. Dual-time-point FDG PET for the evaluation of locoregional lymph nodes in thoracic esophageal squamous cell cancer. Eur J Radiol. 2009;70(2):320-4.
10. Noble F, Bailey D, Tung K, Byrne JP. Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study. Clin Radiol. 2009;64(7):699-705.
11. Okada M, Murakami T, Kumano S, Kuwabara M, Shimono T, Hosono M, et al. Integrated FDG-PET/CT compared with intravenous contrast-enhanced CT for evaluation of metastatic regional lymph nodes in patients with resectable early stage esophageal cancer. Ann Nucl Med. 2009;23(1):73-80.
12. Shimizu S, Hosokawa M, Itoh K, Fujita M, Takahashi H, Shirato H. Can hybrid FDG-PET/CT detect subclinical lymph node metastasis of esophageal cancer appropriately and contribute to radiation treatment planning? A comparison of image-based and pathological findings. Int J Clin Oncol. 2009;14(5):421-5.
13. Song SY, Kim JH, Ryu JS, Lee GH, Kim SB, Park SI, et al. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. Int J Radiat Oncol Biol Phys. 2005 Nov 15;63(4):1053-9. Epub 2005 Jun 20.
14. Levine EA, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, et al. Predictive value of 18-fluoro-deoxy-glucose-positron emission tomography (F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. Ann Surg. 2006 Apr:243(4):472-8.

15. Duong CP, Hicks RJ, Weih L, Drummond E, Leong T, Michael M, et al. FDG-PET status following chemoradiotherapy provides high management impact and powerful prognostic stratification in oesophageal cancer. Eur J Nucl Med Mol Imaging. 2006 Jul;33(7):770-8. Epub 2006 Mar 21.
16. Kim MK, Ryu JS, Kim SB, Ahn JH, Kim SY, Park SI, et al. Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer. 2007 Jun;43(9):1385-91. Epub 2007 May 23.
17. Wieder HA, Ott K, Lordick F, Becker K, Stahl A, Herrmann K, et al. Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. Eur J Nucl Med Mol Imaging. 2007 Dec;34(12):1925-32. Epub 2007 Aug 7.
18. Smithers BM, Couper GC, Thomas JM, Wong D, Gotley DC, Martin I, et al. Positron emission tomography and pathological evidence of response to neoadjuvant therapy in adenocarcinoma of the esophagus. Dis Esophagus. 2008;21(2):151-8.
19. Higuchi I, Yasuda T, Yano M, Doki Y, Miyata H, Tatsumi M, et al. Lack of fludeoxyglucose F 18 uptake in posttreatment positron emission tomography as a significant predictor of survival after subsequent surgery in multimodality treatment for patients with locally advanced esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg. 2008;136(1):205-12.e3.
20. Klaeser B, Nitzsche E, Schuller JC, Köberle D, Widmer L, Balmer-Majno S, et al. Limited predictive value of FDG-PET for response assessment in the preoperative treatment of esophageal cancer: Results of a prospective multi-center trial (SAKK 75/02). Onkologie. 2009;32(12):724-30.
21. Shenfine J, Barbour AP, Wong D, Thomas J, Martin I, Gotley DC, et al. Prognostic value of maximum standardized uptake values from preoperative positron emission tomography in resectable adenocarcinoma of the esophagus treated by surgery alone. Dis Esophagus. 2009;22(8):668-75.
22. Gillham CM, Lucey JA, Keogan M, Duffy GJ, Malik V, Raouf AA, et al. (18)FDG uptake during induction chemoradiation for oesophageal cancer fails to predict histomorphological tumour response. Br J Cancer. 2006 Nov 6;95(9):1174-9. Epub 2006 Oct 3.
23. Westerterp M, Omloo JM, Sloof GW, Hulshof MC, Hoekstra OS, Crezee H, et al. Monitoring of response to pre-operative chemoradiation in combination with hyperthermia in oesophageal cancer by FDG-PET. Int J Hyperthermia. 2006 Mar;22(2):149-60.
24. Vallböhmer D, Hölscher AH, Dietlein M, Bollschweiler E, Baldus SE, Mönig SP, et al. 18F-Fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg. 2009;250(6):888-94.
25. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007 Sep;8(9):797-805.
26. Guo H, Zhu H, Xi Y, Zhang B, Li L, Huang Y, et al. Diagnostic and prognostic value of 18F-FDG PET/CT for patients with suspected recurrence from squamous cell carcinoma of the esophagus. J Nucl Med. 2007 Aug;48(8):1251-8. Epub 2007 Jul 13.
27. Jingu K, Kaneta T, Nemoto K, Takeda K, Ogawa Y, Ariga H, et al. 18F-fluorodeoxyglucose positron emission tomography immediately after chemoradiotherapy predicts prognosis in patients with locoregional postoperative recurrent esophageal cancer. Int J Clin Oncol. 2010;15(2):184-90.

28. Lowe VJ, Booya F, Fletcher JG, Nathan M, Jensen E, Mullan B, et al. Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal cancer. Mol Imaging Biol. 2005 Nov-Dec;7(6):422-30.
29. Duong CP, Demitriou H, Weih L, Thompson A, Williams D, Thomas RJ, et al. Significant clinical impact and prognostic stratification provided by FDG-PET in the staging of oesophageal cancer. Eur J Nucl Med Mol Imaging. 2006 Jul;33(7):759-69. Epub 2006 Feb 10.
30. Buchmann I, Hansen T, Brochhausen C, Kneist W, Oberholzer K, Junginger T, et al. FDG-PET in the initial staging of squamous cell oesophageal carcinoma. Nuklearmedizin. 2006;45(6):235-41.
31. van Westreenen HL, Westerterp M, Sloof GW, Groen H, Bossuyt PM, Jager PL, et al. Limited additional value of positron emission tomography in staging oesophageal cancer. Br J Surg. 2007 Dec;94(12):1515-20.
32. Chung HW, Lee KH, Lee EJ, Lee SJ, Cho YS, Choi JY, et al. Comparison of uptake characteristics and prognostic value of 201Tl and 18F-FDG in esophageal cancer. World J Surg. 2008 Jan;32(1):69-75.
33. McDonough PB, Jones DR, Shen KR, Northup PG, Galysh RL, Hernandez A, et al. Does FDG-PET add information to EUS and CT in the initial management of esophageal cancer? A prospective single center study. Am J Gastroenterol. 2008 Mar;103(3):570-4. Epub 2007 Oct 17.
34. Ott K, Weber WA, Lordick F, Becker K, Busch R, Herrmann K, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol. 2006 Oct 10;24(29):4692-8. Epub 2006 Sep 11.

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PET Recommendation Report 4 Version 2: Section 2

PET Imaging in Esophageal Cancer: Evidentiary Base and Consensus Process

R. Wong, C. Walker-Dilks, and A.O. Raifu

Report Date: January 19, 2009
Update: November 30, 2010

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 esophageal cancer?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for esophageal cancer?
- What benefit to clinical management does PET or PET/CT contribute when recurrence of esophageal cancer 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 esophageal cancer?
- What is the role of PET when a solitary metastasis is identified at the time of recurrence and the 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, nominated by the Provincial Gastrointestinal (GI) 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 Provincial GI DSG. The draft recommendations were refined during a DSG teleconference. The GI 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

A scoping review undertaken by the PEBC methodologist to identify any existing systematic reviews on PET imaging in the cancers of interest yielded one such review. The U.K. HTA systematic review (1) (referred to as the HTA review from this point forward) evaluated the effectiveness of Fluoro-deoxy-glucose (FDG) PET imaging in several selected cancers, including esophageal. The document included systematic reviews and individual primary studies dating from 2000 to August 2005. Because the HTA review sufficiently covered the questions and methodologies of interest to this recommendation report, its results were used for the evidence base from 2000 to August 2005, and its search strategies were performed in MEDLINE and EMBASE to update the literature to May 2010. The update strategies for MEDLINE and EMBASE are in Appendices 1 and 2 for 2005 to 2008 search and Appendices 3 and 4 for 2008 to 2010 search.

Study Selection Criteria

All systematic reviews and primary studies in the HTA review that addressed the questions of interest in this recommendation report (diagnosis, staging, treatment response, recurrence, and restaging) were included. The inclusion criteria of the HTA review were employed to select systematic reviews and primary studies identified in the update search.

The inclusion criteria for systematic reviews included in the HTA review and used in the update are:

- dedicated to FDG PET in the selected cancers in humans;

- contained evidence related to diagnostic accuracy, change in patient management, clinical outcomes, or treatment response.

The inclusion criteria for primary studies included in the HTA review and used in the update were:

- prospective clinical study of dedicated FDG PET in a single cancer of interest;
- study published after the search date of a robust systematic review covering that cancer management decision;
- study published as a full article in a peer-reviewed journal;
- study reported evidence related to diagnostic accuracy, change in patient management, or clinical outcomes;
- study included ≥ 12 patients with the cancer of interest;
- study used a suitable reference standard (pathological confirmation and clinical follow-up) when appropriate.

The citations and abstracts from the update searches were reviewed by the PEBC research coordinator and marked as relevant or not relevant according to the inclusion criteria from the HTA review, and were classified by disease site. The research coordinator and the clinical lead for each DSG reviewed the relevant citations and full text of the articles for final decision on inclusion.

Synthesizing the Evidence

The HTA review did not pool individual studies. Data were extracted into separate tables for systematic reviews and primary studies for each type of management decision. The same approach was used for data extraction for the evidence from August 2005 to May 2010. Full text and data extractions of the studies from the update search 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 GI 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 19 September 2008 was conducted as follows:

- Consensus meeting participants sat at tables specifically set up to discuss a particular disease site (colorectal, esophageal, head & neck, and melanoma). The esophageal table held the clinical lead and any other GI DSG members attending, in addition to other invited health professionals.
- The recommendations and summary of key evidence drafted by the clinical lead and refined and confirmed by the GI DSG were presented by the clinical lead to the group at the Esophageal table.

- During small-group discussion at the Esophageal table in the morning and discussion among the entire consensus meeting participants in the afternoon, the recommendations underwent further refinement and modification. The attendees voted on the revised recommendations to indicate their extent of agreement on a scale from 1 to 9 (1 indicating strong agreement, 5 indicating no agreement or disagreement, and 9 indicating strong disagreement).

After the consensus meeting, the exact wording of the recommendations was slightly modified for consistency with the recommendations resulting from the other disease discussions. These modifications included using emphatic, unambiguous language (i.e., *PET is recommended*...) and removing the need to distinguish between PET and PET/CT. It was made clear at the consensus meetings that PET imaging alone is being phased out and PET/CT imaging is the current standard. Thus, the term PET is used to cover PET and PET/CT imaging. These recommendations are referred to below as the FINAL RECOMMENDATIONS and are provided in Section 1 of this report.

RESULTS

Literature Search Results

The HTA review results for esophageal cancer included four systematic reviews and six primary studies. The 2005 to 2010 update included two systematic reviews and 29 primary studies. Five of the 29 primary studies were already included in the two systematic reviews and the summary of evidence from these five studies are not further discussed but presented in Appendix 5 and referenced.

Data extracted from the systematic reviews and primary studies in the HTA review (1) are available on the HTA website (pages 223-232). Data extracted from the primary studies from the updated search are in Appendices 5 and 6. The key evidence identified by the search is described below in an abbreviated fashion.

Key Evidence

Diagnosis/Staging

- There is a significant role for PET because of its incremental value in detecting distant disease, in addition to CT +/- endoscopic ultrasound (EUS). PET provides incremental benefit especially in the absence of EUS.
- **HTA review** (1): One systematic review containing three primary studies showed the superiority of PET to CT or EUS in detecting distant metastases. Another systematic review of 12 primary studies showed that PET had a sensitivity of 67% and a specificity of 97%, corroborating the first systematic review. One additional primary study showed the incremental benefit of adding PET to CT and EUS, giving a sensitivity of 74% compared with 53% for PET alone and 64% for PET plus CT.
- A 2008 systematic review by van Vliet et al, 2008 (2) with two primary studies not included in Facey et al, 2007(1) and two studies from the update search (Kato et al, 2005 [3] and Katsoulis et al, 2007 [4]) showed higher detection rates for distant metastases with PET than CT, but the difference was not statistically significant.
- When the effect of PET is evaluated based on whether staging is changed, a correct change occurred in approximately 30% of cases in two studies (one in the van Vliet et al systematic review [2], and one from the updated search, Katsoulis et al [4]).
- There is some evidence that PET/CT is superior to PET alone for nodal staging (Yuan et al, 2006 [5]).
- **2008-2010 update search:** Seven primary studies from the update search (Chatterton et al, 2009 [6], Cheze-Le Rest et al, 2008 [7], Hsu et al, 2009 [8], Hu et al, 2009 [9], Noble et

al, 2009 [10], Okada et al, 2009 [11], and Shimizu et al, 2009 [12]) also showed the significant impact of PET and PET/CT on the clinical management, prognostic stratification of patients with newly diagnosed esophageal cancer, prediction of regional and locoregional lymph nodes, and improvement the accuracy of pre-treatment staging compared to CT and EUS alone.

Assessment of Treatment Response

- There is some evidence that PET, either early in treatment or at the completion of neoadjuvant therapy, can predict complete pathologic response, and therefore predict the longer-term outcome in terms of survival and event-free survival.
- **HTA review** (1): One systematic review of four primary studies plus one additional study showed that PET may be superior to CT and comparable to EUS in the assessment of response and of prognosis after neoadjuvant therapy. One additional study showed PET/CT to be more sensitive for the evaluation of response than were CT or endoscopic ultrasound.
- **2005-2010 update**: Thirteen primary studies were identified in the update search. The change in PET parameters before and after neoadjuvant therapy provided a reasonable diagnostic accuracy (68% to 86%) for the prediction of pathological response (Song et al, 2005 [13], Levine et al, 2006 [14], Duong et al, 2006 [15], Kim et al, 2007 [16], Wieder et al, 2007 [17], Smithers et al, 2008 [18], Higuchi et al, 2008 [19], Klaeser et al, 2009 [20], Shenfine et al, 2009 [21]). Perhaps more importantly, there is evidence that PET response is related to longer-term clinical outcomes, including disease-free survival and overall survival (Duong et al [15], Kim et al [16], Wieder et al [17], Higuchi et al [19], and Shenfine et al [21]). The best cutoff point to use for defining responder versus nonresponder remains to be defined. Data derived from the receiver operating characteristic (ROC) curves would suggest a 30% to 50% reduction as a useful parameter (Wieder et al [17], Smithers et al [18]). The prognostic value of PET is further supported by the fact that responders and nonresponders have significantly different SUV change profiles.
- The value of PET as an early indicator for future response was evaluated in four studies (Wieder et al, 2007 [17], Gillham et al, 2006 [22], Westerterp et al, 2006 [23], and Vallbohmer et al, 2009 [24]). While a significant difference existed between pathological responders and nonresponders, further study is required to establish the best criteria and standardized conditions to use if this modality is to be routinely incorporated into clinical practice to guide treatment decisions.
- One study evaluated PET as an early tool to predict a response allowing neoadjuvant therapy to be abandoned in favour of early surgery (Lordick et al, 2007 [25]). This study confirmed that responders had better outcomes in terms of survival and disease-free survival.

Recurrence/Restaging

- Two studies from the 2005-2010 update (Guo et al, 2007 [26] and Jingu et al, 2010 [27]) showed PET/CT to be accurate in detecting regional and distant recurrence and in predicting the prognosis in patients with postoperative recurrent esophageal cancer. The findings of these studies require corroboration before a recommendation can be made.

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

DRAFT DSG Recommendation

For the staging workup of patients with esophageal cancer who are potential candidates for curative therapy, PET is recommended as an adjunct to standard diagnostic imaging (CT) in improving the accuracy of M staging.

Provincial Consensus Meeting Deliberations

There was general agreement with this recommendation. Discussions took place around what constitutes minimum workup before the use of PET and the level at which distant metastases could be detected.

Recommendation Put to Vote

For the staging workup of patients with esophageal cancer who are potential candidates for curative therapy, PET is recommended in improving the accuracy of M staging.

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

Votes = 20

FINAL RECOMMENDATION

For the staging workup of patients with esophageal cancer who are potential candidates for curative therapy, PET is recommended to improve the accuracy of M staging.

Qualifying Statement

- The data supporting this recommendation are compelling but sparse. Prospective data through the provincial registries should be collected in order to provide additional information on this issue.

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

DRAFT DSG Recommendation

There is insufficient evidence to support the routine use of PET (either post or early during neoadjuvant therapy) for the purpose of predicting the response to neoadjuvant therapy.

Provincial Consensus Meeting Deliberations

No major issues were raised during discussions about this recommendation. The observation was made that, while there is a relation between nonresponse and poor outcome, there is insufficient evidence to indicate that prediction of this by PET would change treatment.

Recommendation Put to Vote

There is insufficient evidence to support the routine use of PET (post or early during neoadjuvant therapy) for the purpose of predicting the response to neoadjuvant therapy.

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

Votes = 20

Issues raised on voting questionnaire:

-Can't predict nonresponders.

FINAL RECOMMENDATION

A recommendation cannot be made for or against the routine use of PET (post or early during neoadjuvant therapy) for the purpose of predicting the response to neoadjuvant therapy due to insufficient evidence.

Qualifying Statement

- Whether the use of PET to assess treatment response would translate into improved outcome remains to be established. It is potentially useful in minimizing toxicity related to futile treatment. Optimal parameters to use for defining responders require further validation.

RECURRENCE/RESTAGING

Clinical Question

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

DRAFT DSG Recommendation

Insufficient evidence exists to recommend PET or PET/CT for evaluation of suspected recurrence.

Provincial Consensus Meeting Deliberations

No major issues were raised during discussions about this recommendation.

Recommendations Put to Vote

Insufficient evidence exists to recommend PET or PET/CT for the evaluation of suspected recurrence.

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

Votes = 20

FINAL RECOMMENDATION

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

Qualifying Statement

None.

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 the metastectomy is being contemplated?

This question was not addressed in the esophageal evidence review.

FUTURE RESEARCH

Areas for future research were not discussed in the process of drafting these recommendations. However, during the small and large group discussions, the following suggestions were made:

- Implement standards for PET reporting
- Have the PET Steering Committee hold an education workshop on standards
- Clarify what constitutes conventional treatment against which to measure PET
- Consider establishing a prospective registry to capture use and/or outcomes

JOURNAL REFERENCE

The following guideline recommendations article was published in Clinical Oncology (© 2011 The Royal College of Radiologists. Published by Elsevier Ltd.; http://www.rcr.ac.uk/content.aspx?PageID=153):

- Wong R, Walker-Dilks C, Raifu A. Evidence-based guideline recommendations on the use of positron emission tomography imaging in oesophageal cancer. Clin Oncol. doi:10.1016/j.clon.2011.09.006. Epub 2011 Sep 29.

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For a complete list of the Gastrointestinal DSG members, please visit the CCO website at http://www.cancercare.on.ca/

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REFERENCES

1. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technol Assess. 2007 Oct;11(44):iii-iv, xi-267. [cited 2009 Jan 19]. Available from: http://www.hta.ac.uk/1487
2. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer. 2008 Feb 12;98(3):547-57. Epub 2008 Jan 22.
3. Kato H, Miyazaki T, Nakajima M, Takita J, Kimura H, Faried A, et al. Comparison between whole-body positron emission tomography and bone scintigraphy in evaluating bony metastases of esophageal carcinomas. Anticancer Res. 2005 Nov-Dec;25(6C):4439-44.
4. Katsoulis IE, Wong WL, Mattheou AK, Damani N, Chambers J, Livingstone JI. Fluorine-18 fluorodeoxyglucose positron emission tomography in the reoperative staging of thoracic oesophageal and gastro-oesophageal junction cancer: a prospective study. Int J Surg. 2007 Dec;5(6):399-403. Epub 2007 Jun 3.
5. Yuan S, Yu Y, Chao KS, Fu Z, Yin Y, Liu T, et al. Additional value of PET/CT over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. J Nucl Med. 2006 Aug;47(8):1255-9.
6. Chatterton BE, Ho Shon I, Baldey A, Lenzo N, Patrikeos A, Kelley B, et al. Positron emission tomography changes management and prognostic stratification in patients with oesophageal cancer: Results of a multicentre prospective study. Eur J Nucl Med Mol Imag. 2009:36(3):354-61.
7. Cheze-Le Rest C, Metges JP, Teyton P, Jestin-Le Tallec V, Lozac'h P, Volant A, et al. Prognostic value of initial fluorodeoxyglucose-PET in esophageal cancer: a prospective study. Nucl Med Commun. 2008:29(7):628-35.
8. Hsu W-H, Hsu P-K, Wang S-J, Lin K-H, Huang C-S, Hsieh CC, et al. Positron emission tomography-computed tomography in predicting locoregional invasion in esophageal squamous cell carcinoma. Ann Thorac Surg. 2009:87(5):1564-8.
9. Hu Q, Wang W, Zhong X, Yuan S, Fu Z, Guo H, et al. Dual-time-point FDG PET for the evaluation of locoregional lymph nodes in thoracic esophageal squamous cell cancer. Eur J Radiol. 2009;70(2):320-4.
10. Noble F, Bailey D, Tung K, Byrne JP. Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study. Clin Radiol. 2009;64(7):699-705.
11. Okada M, Murakami T, Kumano S, Kuwabara M, Shimono T, Hosono M, et al. Integrated FDG-PET/CT compared with intravenous contrast-enhanced CT for evaluation of metastatic regional lymph nodes in patients with resectable early stage esophageal cancer. Ann Nucl Med. 2009;23(1):73-80.
12. Shimizu S, Hosokawa M, Itoh K, Fujita M, Takahashi H, Shirato H. Can hybrid FDG-PET/CT detect subclinical lymph node metastasis of esophageal cancer appropriately and contribute to radiation treatment planning? A comparison of image-based and pathological findings. Int J Clin Oncol. 2009;14(5):421-5.
13. Song SY, Kim JH, Ryu JS, Lee GH, Kim SB, Park SI, et al. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. Int J Radiat Oncol Biol Phys. 2005 Nov 15;63(4):1053-9. Epub 2005 Jun 20.
14. Levine EA, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, et al. Predictive value of 18-fluoro-deoxy-glucose-positron emission tomography (F-FDG-PET) in the

identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. Ann Surg. 2006 Apr:243(4):472-8.
15. Duong CP, Hicks RJ, Weih L, Drummond E, Leong T, Michael M, et al. FDG-PET status following chemoradiotherapy provides high management impact and powerful prognostic stratification in oesophageal cancer. Eur J Nucl Med Mol Imaging. 2006 Jul;33(7):770-8. Epub 2006 Mar 21.
16. Kim MK, Ryu JS, Kim SB, Ahn JH, Kim SY, Park SI, et al. Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer. 2007 Jun;43(9):1385-91. Epub 2007 May 23.
17. Wieder HA, Ott K, Lordick F, Becker K, Stahl A, Herrmann K, et al. Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. Eur J Nucl Med Mol Imaging. 2007 Dec;34(12):1925-32. Epub 2007 Aug 7.
18. Smithers BM, Couper GC, Thomas JM, Wong D, Gotley DC, Martin I, et al. Positron emission tomography and pathological evidence of response to neoadjuvant therapy in adenocarcinoma of the esophagus. Dis Esophagus. 2008;21(2):151-8.
19. Higuchi I, Yasuda T, Yano M, Doki Y, Miyata H, Tatsumi M, et al. Lack of fludeoxyglucose F 18 uptake in posttreatment positron emission tomography as a significant predictor of survival after subsequent surgery in multimodality treatment for patients with locally advanced esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg. 2008;136(1):205-12.e3.
20. Klaeser B, Nitzsche E, Schuller JC, Köberle D, Widmer L, Balmer-Majno S, et al. Limited predictive value of FDG-PET for response assessment in the preoperative treatment of esophageal cancer: Results of a prospective multi-center trial (SAKK 75/02). Onkologie. 2009;32(12):724-30.
21. Shenfine J, Barbour AP, Wong D, Thomas J, Martin I, Gotley DC, et al. Prognostic value of maximum standardized uptake values from preoperative positron emission tomography in resectable adenocarcinoma of the esophagus treated by surgery alone. Dis Esophagus. 2009;22(8):668-75.
22. Gillham CM, Lucey JA, Keogan M, Duffy GJ, Malik V, Raouf AA, et al. (18)FDG uptake during induction chemoradiation for oesophageal cancer fails to predict histomorphological tumour response. Br J Cancer. 2006 Nov 6;95(9):1174-9. Epub 2006 Oct 3.
23. Westerterp M, Omloo JM, Sloof GW, Hulshof MC, Hoekstra OS, Crezee H, et al. Monitoring of response to pre-operative chemoradiation in combination with hyperthermia in oesophageal cancer by FDG-PET. Int J Hyperthermia. 2006 Mar;22(2):149-60.
24. Vallböhmer D, Hölscher AH, Dietlein M, Bollschweiler E, Baldus SE, Mönig SP, et al. 18F-Fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg. 2009;250(6):888-94.
25. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007 Sep;8(9):797-805.
26. Guo H, Zhu H, Xi Y, Zhang B, Li L, Huang Y, et al. Diagnostic and prognostic value of 18F-FDG PET/CT for patients with suspected recurrence from squamous cell carcinoma of the esophagus. J Nucl Med. 2007 Aug;48(8):1251-8. Epub 2007 Jul 13.

27. Jingu K, Kaneta T, Nemoto K, Takeda K, Ogawa Y, Ariga H, et al. 18F-fluorodeoxyglucose positron emission tomography immediately after chemoradiotherapy predicts prognosis in patients with locoregional postoperative recurrent esophageal cancer. Int J Clin Oncol. 2010;15(2):184-90.

28. Lowe VJ, Booya F, Fletcher JG, Nathan M, Jensen E, Mullan B, et al. Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal cancer. Mol Imaging Biol. 2005 Nov-Dec;7(6):422-30.
29. Duong CP, Demitriou H, Weih L, Thompson A, Williams D, Thomas RJ, et al. Significant clinical impact and prognostic stratification provided by FDG-PET in the staging of oesophageal cancer. Eur J Nucl Med Mol Imaging. 2006 Jul;33(7):759-69. Epub 2006 Feb 10.
30. Buchmann I, Hansen T, Brochhausen C, Kneist W, Oberholzer K, Junginger T, et al. FDG-PET in the initial staging of squamous cell oesophageal carcinoma. Nuklearmedizin. 2006;45(6):235-41.
31. van Westreenen HL, Westerterp M, Sloof GW, Groen H, Bossuyt PM, Jager PL, et al. Limited additional value of positron emission tomography in staging oesophageal cancer. Br J Surg. 2007 Dec;94(12):1515-20.
32. Chung HW, Lee KH, Lee EJ, Lee SJ, Cho YS, Choi JY, et al. Comparison of uptake characteristics and prognostic value of 201Tl and 18F-FDG in esophageal cancer. World J Surg. 2008 Jan;32(1):69-75.
33. McDonough PB, Jones DR, Shen KR, Northup PG, Galysh RL, Hernandez A, et al. Does FDG-PET add information to EUS and CT in the initial management of esophageal cancer? A prospective single center study. Am J Gastroenterol. 2008 Mar;103(3):570-4. Epub 2007 Oct 17.
34. Ott K, Weber WA, Lordick F, Becker K, Busch R, Herrmann K, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol. 2006 Oct 10;24(29):4692-8. Epub 2006 Sep 11.

Appendix 1. MEDLINE search strategy update U.K. Health Technology Assessment systematic review on PET imaging in selected cancers.

Search run 24 June 2008

Combines basic FDG PET strategy with Mijnhout FDG PET strategy and includes primary studies (n=2060) and systematic reviews (n=856)
Retrieval period from August 2005 to June 2008

Ovid MEDLINE(R) 1996 to June Week 2 2008

#	Searches	Results
1	Tomography, Emission-Computed/	14196
2	(positron adj emission adj tomography).ti,ab.	14193
3	PET.ti,ab.	21371
4	PET-FDG.ti,ab.	155
5	Fluorodeoxyglucose F18/	7990
6	18f fluorodeoxyglucose.ti,ab.	1118
7	18fdg.ti,ab.	330
8	2-fluoro-2-deoxy-d-glucose.ti,ab.	250
9	2-fluoro-2-deoxyglucose.ti,ab.	59
10	18f-fdg.ti,ab.	1351
11	fluorine-18-fluorodeoxyglucose.ti,ab.	524
12	positron-emission tomography/	8899
13	PET-CT.ti,ab.	1772
14	PET$CT.ti,ab.	2
15	or/1-14	31518
16	deoxyglucose/	2869
17	deoxyglucose.ti,ab.	2574
18	desoxyglucose.ti,ab.	16
19	desoxy-glucose.ti,ab.	11
20	deoxy-d-glucose.ti,ab.	1977
21	desoxy-d-glucose.ti,ab.	12
22	2deoxyglucose.ti,ab.	2
23	2deoxy-d-glucose.ti,ab.	6
24	fluorodeoxyglucose.ti,ab.	3420
25	fluorodesoxyglucose.ti,ab.	16
26	fludeoxyglucose.ti,ab.	42
27	fluordeoxyglucose.ti,ab.	23
28	fluordesoxyglucose.ti,ab.	3
29	18fluorodeoxyglucose.ti,ab.	49
30	18fluorodesoxyglucose.ti,ab.	1
31	18fluordeoxyglucose.ti,ab.	0
32	fdg$.ti,ab.	6977
33	18fdg$.ti,ab.	331
34	18f-dg$.ti,ab.	5
35	or/16-34	12309
36	fluor.ti,ab.	472
37	2fluor$.ti,ab.	12
38	fluoro.ti,ab.	6187
39	fluorodeoxy.ti,ab.	67
40	fludeoxy.ti,ab.	3
41	fluorine.ti,ab.	2680

42	18f.ti,ab.	4596
43	18flu$.ti,ab.	98
44	or/36-43	11911
45	glucose.ti,ab.	103645
46	pet.ti,ab.	21371
47	petscan$.ti,ab.	5
48	Tomography, Emission-Computed/	14196
49	pet ct.ti,ab.	1772
50	emission.ti,ab.	37628
51	tomograph.ti,ab.	751
52	tomographs.ti,ab.	165
53	tomographic$.ti,ab.	11313
54	tomography.ti,ab.	76598
55	tomographies.ti,ab.	116
56	or/51-55	85792
57	50 and 56	20590
58	46 or 47 or 48 or 49 or 57	35054
59	44 and 45	2573
60	35 or 59	12507
61	58 and 60	8366
62	exp neoplasms/	806680
63	neoplasm staging/	49856
64	cancer$.ti,ab.	389251
65	tumor$.ti,ab.	349790
66	tumour$.ti,ab.	75060
67	carcinoma$.ti,ab.	165074
68	neoplasm$.ti,ab.	32308
69	lymphoma.ti,ab.	41481
70	melanoma.ti,ab.	27108
71	staging.ti,ab.	20085
72	metastas$.ti,ab.	81288
73	metastatic.ti,ab.	53184
74	exp neoplasm metastasis/	46034
75	exp neoplastic processes/	109110
76	neoplastic process$.ti,ab.	884
77	non small cell.ti,ab.	13022
78	adenocarcinoma$.ti,ab.	35985
79	squamous cell.ti,ab.	25718
80	nsclc.ti,ab.	7274
81	osteosarcoma$.ti,ab.	5515
82	phyllodes.ti,ab.	477
83	cytosarcoma$.ti,ab.	0
84	fibroadenoma$.ti,ab.	1061
85	(non adj small adj cell).ti,ab.	13022
86	(non adj2 small adj2 cell).ti,ab.	13100
87	(nonsmall adj2 cell).ti,ab.	853
88	plasmacytoma$.ti,ab.	1308
89	myeloma.ti,ab.	11218
90	multiple myeloma.ti,ab.	8668
91	lymphomblastoma$.ti,ab.	0

92	lymphocytoma$.ti,ab.	72
93	lymphosarcoma$.ti,ab.	344
94	immunocytoma.ti,ab.	110
95	sarcoma$.ti,ab.	20984
96	hodgkin$.ti,ab.	18282
97	(nonhodgkin$ or non hodgkin$).ti,ab.	12659
98	or/62-97	972317
99	15 and 98	11146
100	61 and 98	5465
101	99 or 100	11152
102	limit 101 to (english language and humans and yr="2005 - 2008")	4528
103	(comment or editorial or letter or case reports).pt.	978402
104	102 not 103	3145
105	(integrative research review$ or research integration).ti,ab.	37
106	(methodologic$ adj10 review$).ti,ab.	2371
107	(methodologic$ adj10 overview$).ti,ab.	130
108	(quantitativ$ adj10 review$).ti,ab.	1548
109	(quantitativ$ adj10 overview$).ti,ab.	124
110	(quantitativ$ adj10 synthes$).ti,ab.	875
111	(systematic adj10 review$).ti,ab.	15200
112	(systematic adj10 overview$).ti,ab.	404
113	(metaanal$ or meta anal$).ti,ab.	18450
114	meta-analysis/	15791
115	meta analysis.pt.	15791
116	or/105-115	38409
117	(review-tutorial or review-academic or review).pt.	835243
118	(pooling or pooled analys$ or mantel haenszel$).ti,ab.	5302
119	(peto$ or der simonian or dersimonian or fixed effect$).ti,ab.	2655
120	116 or 117 or 118 or 119	857219
121	104 and 120	920
122	104 not 120	2225
123	(200508: or 200509: or 20051: or 2006: or 2007: or 2008:).ed.	1865975
124	121 and 123	856
125	122 and 123	2060
126	from 124 keep 1-856	856
127	from 125 keep 1-1000	1000
128	from 125 keep 1001-2000	1000
129	from 125 keep 2001-2060	60

Appendix 2. EMBASE search strategy update U.K. Health Technology Assessment systematic review on PET imaging in selected cancers.

Search run 2 July 2008

Combines basic FDG PE strategy with Mijnhout FDG PET strategy and includes primary studies (n=4285) and systematic reviews (n=1497)
Retrieval period from 2005 to July 2008

EMBASE 1996 to 2008 Week 26

#	Searches	Results
1	deoxyglucose/	2417
2	deoxyglucose.ti,ab.	2570
3	desoxyglucose.ti,ab.	13
4	desoxy-glucose.ti,ab.	15
5	deoxy-d-glucose.ti,ab.	1947
6	desoxy-d-glucose.ti,ab.	10
7	2deoxyglucose.ti,ab.	3
8	2-deoxy-d-glucose.ti,ab.	1815
9	fluorodeoxyglucose.ti,ab.	3629
10	fluorodesoxyglucose.ti,ab.	20
11	fludeoxyglucose.ti,ab.	46
12	fluordeoxyglucose.ti,ab.	27
13	fluordesoxyglucose.ti,ab.	5
14	18fluorodeoxyglucose.ti,ab.	63
15	18fluorodesoxyglucose.ti,ab.	3
16	18fluordeoxyglucose.ti,ab.	0
17	fdg$.ti,ab.	7410
18	18fdg$.ti,ab.	472
19	18f-dg$.ti,ab.	9
20	or/1-19	12333
21	fluor.ti,ab.	440
22	2fluor$.ti,ab.	10
23	fluoro.ti,ab.	7009
24	fluorodeoxy.ti,ab.	90
25	fludeoxy.ti,ab.	1
26	fluorine.ti,ab.	3221
27	18f.ti,ab.	6816
28	18flu$.ti,ab.	143
29	or/21-28	14709
30	glucose.ti,ab.	104283
31	pet.ti,ab.	22197
32	petscan$.ti,ab.	9
33	computer assisted emission tomography/	1421
34	pet ct.ti,ab.	2023
35	emission.ti,ab.	42287
36	tomograph.ti,ab.	755
37	tomographs.ti,ab.	141
38	tomographic$.ti,ab.	10759
39	tomography.ti,ab.	75334
40	tomographies.ti,ab.	108
41	or/36-40	84118

42	35 and 41	21289
43	31 or 32 or 33 or 34 or 42	33404
44	29 and 30	2956
45	20 or 44	12557
46	43 and 45	8790
47	cancer$.ti,ab.	385221
48	tumor$.ti,ab.	340943
49	tumour$.ti,ab.	76396
50	carcinoma$.ti,ab.	162315
51	neoplasm$.ti,ab.	30388
52	lymphoma.ti,ab.	40473
53	melanoma.ti,ab.	27301
54	staging.ti,ab.	20100
55	metastas$.ti,ab.	79569
56	metastatic.ti,ab.	52902
57	neoplastic process$.ti,ab.	827
58	neoplas$.ti,ab.	66122
59	exp neoplasm/	874595
60	cancer staging/	62622
61	exp metastasis/	110090
62	exp "oncogenesis and malignant transformation"/	74028
63	or/47-62	1009399
64	46 and 63	5802
65	(editorial or letter or review).pt.	1107915
66	64 not 65	4890
67	limit 66 to (human and english language and yr="2005 - 2008")	1987
68	(integrative research review$ or research integration).ti,ab.	20
69	(methodologic$ adj10 review$).ti,ab.	1824
70	(methodologic$ adj10 overview$).ti,ab.	138
71	(quantitativ$ adj10 review$).ti,ab.	1467
72	(quantitativ$ adj10 overview$).ti,ab.	124
73	(quantitativ$ adj10 synthes$).ti,ab.	915
74	(systematic adj10 review$).ti,ab.	14736
75	(systematic adj10 overview$).ti,ab.	402
76	(metaanal$ or meta anal$).ti,ab.	18093
77	meta-analysis/	30401
78	(pooling or pooled analys$ or mantel haenszel$).ti,ab.	4802
79	(peto$ or der simonian or dersimonian or fixed effect$).ti,ab.	1566
80	or/68-79	55380
81	46 and 63 and 80	107
82	(editorial or letter).pt.	441971
83	81 not 82	107
84	limit 83 to (human and english language and yr="2005 - 2008")	38
85	(positron adj emission adj tomography).ti,ab.	14828
86	PET.ti,ab.	22197
87	PET-FDG.ti,ab.	163
88	FDG-PET.ti,ab.	5206
89	fludeoxyglucose F 18/	10204
90	18f fluorodeoxyglucose.ti,ab.	1594
91	18fdg.ti,ab.	471

92	2-fluoro-2-deoxy-d-glucose.ti,ab.	252
93	2-fluoro-2-deoxyglucose.ti,ab.	56
94	18f-fdg.ti,ab.	2013
95	fluorine-18-fluorodeoxyglucose.ti,ab.	539
96	positron emission tomography/	30927
97	or/85-96	37717
98	cancer$.ti,ab.	385221
99	tumor$.ti,ab.	340943
100	tumour$.ti,ab.	76396
101	carcinoma$.ti,ab.	162315
102	neoplasm$.ti,ab.	30388
103	lymphoma.ti,ab.	40473
104	melanoma.ti,ab.	27301
105	staging.ti,ab.	20100
106	metastas$.ti,ab.	79569
107	metastatic.ti,ab.	52902
108	neoplastic process$.ti,ab.	827
109	neoplas$.ti,ab.	66122
110	exp neoplasm/	874595
111	cancer staging/	62622
112	exp metastasis/	110090
113	exp "oncogenesis and malignant transformation"/	74028
114	or/98-113	1009399
115	97 and 114	14319
116	115 not 65	10146
117	limit 116 to (human and english language and yr="2005 - 2008")	4284
118	80 or review.pt.	696716
119	115 and 118	3275
120	119 not 82	3269
121	limit 120 to (human and english language and yr="2005 - 2008")	1497
122	67 or 117	4285
123	84 or 121	1497

Appendix 3. MEDLINE search strategy update U.K. Health Technology Assessment systematic review on PET imaging in selected cancers.

Search run 26 May 2010

Combines basic FDG PET strategy with Mijnhout FDG PET strategy and includes primary studies (n=1485) and systematic reviews (n=483)
Retrieval period from June 2008 to May 2010

#	Searches	Results
1	Tomography, Emission-Computed/ or (positron adj emission adj tomography).ti,ab. or PET.ti,ab. or PET-FDG.ti,ab. or Fluorodeoxyglucose F18/ or 18f fluorodeoxyglucose.ti,ab. or 18f fluorodeoxyglucose.ti,ab. or 18fdg.ti,ab. or 2-fluoro-2-deoxy-d-glucose.ti,ab. or 2-fluoro-2-deoxyglucose.ti,ab. or 18f-fdg.ti,ab. or fluorine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluorodeoxyglucose.ti,ab. or flourine-18-fluorodeoxyglucose.ti,ab. or flourine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluordeoxyglucose.ti,ab. or positron emission tomography/ or PET-CT.ti,ab. or PET$CT.ti,ab.	42153
2	deoxyglucose/ or deoxyglucose.ti,ab. or desoxyglucose.ti,ab. or desoxy-glucose.ti,ab. or desoxy-d-glucose.ti,ab. or deoxy-d-glucose.ti,ab. or 2deoxyglucose.ti,ab. or 2deoxy-d-glucose.ti,ab. or fluorodeoxyglucose.ti,ab. or fluorodesoxyglucose.ti,ab. or fludeoxyglucose.ti,ab. or fluordeoxyglucose.ti,ab. or fluodeoxyglucose.ti,ab. or fluordesoxyglucose.ti,ab. or 18fluorodeoxyglucose.ti,ab. or 18fluorodesoxyglucose.ti,ab. or fdg$.ti,ab. or 18fdg$.ti,ab. or 18f-dg$.ti,ab.	16184
3	(fluor or 2fluor$ or fluoro or flouro or fluorodeoxy or fludeoxy or flourodeoxy or fluorine or 18f or 18flu$ or 18fluo$).ti,ab.	15438
4	glucose.ti,ab.	132234
5	(pet or petscan$ or pet ct).ti,ab.	28884
6	Tomography, Emission-Computed/	14603
7	emission.ti,ab.	49767
8	(tomograph or tomographs or tomographic$ or tomogrpahy or tomographies).ti,ab.	15532
9	7 and 8	1606
10	5 or 6 or 9	35319
11	3 and 4	3268
12	2 or 11	16458
13	10 and 12	10752
14	exp neoplasm/ or neoplasm staging/ or cancer$.ti,ab. or tumor$.ti,ab. or tumour$.ti,ab. or carcinoma$.ti,ab. or neoplasm$.ti,ab. or lymphoma.ti,ab. or melanoma.ti,ab. or staging.ti,ab. or metastas$.ti,ab. or metastatic.ti,ab. or exp neoplasm metastasis/ or exp neoplastic processes/ or neoplastic process$.ti,ab. or non small cell.ti,ab. or adenocarcinoma$.ti,ab. or squamous cell.ti,ab. or nsclc.ti,ab. or osteosarcoma$.ti,ab. or thymoma.ti,ab. or phyllodes.ti,ab. or cytosarcoma$.ti,ab. or fibroadenoma$.ti,ab. or (non adj small adj cell).ti,ab. or (non adj2 small adj2 cell).ti,ab. or (nonsmall adj2 cell).ti,ab. or myeloma.ti,ab. or multiple	1218982

	myeloma.ti,ab. or lymphoblastoma$.ti,ab. or lymphocytoma$.ti,ab. or lymphosarcoma$.ti,ab. or immunocytoma.ti,ab. or sarcoma$.ti,ab. or hodgkin$.ti,ab. or (nonhodgkin$ or non hodgkin$).ti,ab.	
15	1 and 14	16334
16	13 and 14	7370
17	15 or 16	16335
18	limit 17 to (human and english language and yr="2008 - 2010")	4706
19	(comment or editorial or letter or case reports).pt.	1206499
20	18 not 19	3224
21	(integrative research review$ or research integration or (methodologic$ adj10 review$) or (methodologic$ adj10 overview$) or (quantitativ$ adj10 review$) or (quantitativ$ adj10 overview$) or (quantitativ$ adj10 synthes$) or (systematic adj10 review$) or (systematic adj10 overview$) or (metaanal or meta anal$)).ti,ab. or meta-analysis/	55401
22	(review-tutorial or review-academic or review).pt. or (pooling or pooled analys$ or mantel heanszel$).ti,ab.	1016357
23	(peto$ or der simonian or dersimonian or fixed effect$).ti,ab.	3731
24	21 or 22	1039311
25	20 and 24	834
26	20 not 24	2390
27	(conference or conference proceeding or conference proceeding$ or conference paper or conference paper$ or discussion or discussion$ or in brief or invited comment or invited comment$).ti,ab.	104653
28	25 not 27	816
29	26 not 27	2363
30	(200806: or 200807: or 200808: or 200809: or 20081: or 2009: or "201005").ed.	1098653
31	28 and 30	483
32	29 and 30	1485

Appendix 4. EMBASE search strategy update U.K. Health Technology Assessment systematic review on PET imaging in selected cancers.

Search run 26 May 2010

Combines basic FDG PE strategy with Mijnhout FDG PET strategy and includes primary studies (n=6362) and systematic reviews (n=1925)
Retrieval period from June 2008 to May 2010

#	Searches	Results
1	Tomography, Emission-Computed/ or (positron adj emission adj tomography).ti,ab. or PET.ti,ab. or PET-FDG.ti,ab. or Fluorodeoxyglucose F18/ or 18f fluorodeoxyglucose.ti,ab. or 18f fluorodeoxyglucose.ti,ab. or 18fdg.ti,ab. or 2-fluoro-2-deoxy-d-glucose.ti,ab. or 2-fluoro-2-deoxyglucose.ti,ab. or 18f-fdg.ti,ab. or fluorine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluorodeoxyglucose.ti,ab. or flourine-18-fluorodeoxyglucose.ti,ab. or flourine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluordeoxyglucose.ti,ab. or positron emission tomography/ or PET-CT.ti,ab. or PET$CT.ti,ab.	66941
2	deoxyglucose/ or deoxyglucose.ti,ab. or desoxyglucose.ti,ab. or desoxy-glucose.ti,ab. or desoxy-d-glucose.ti,ab. or deoxy-d-glucose.ti,ab. or 2deoxyglucose.ti,ab. or 2deoxy-d-glucose.ti,ab. or fluorodeoxyglucose.ti,ab. or fluorodesoxyglucose.ti,ab. or fludeoxyglucose.ti,ab. or fluordeoxyglucose.ti,ab. or fluodeoxyglucose.ti,ab. or fluordesoxyglucose.ti,ab. or 18fluorodeoxyglucose.ti,ab. or 18fluorodesoxyglucose.ti,ab. or fdg$.ti,ab. or 18fdg$.ti,ab. or 18f-dg$.ti,ab.	21132
3	(fluor or 2fluor$ or fluoro or flouro or fluorodeoxy or fludeoxy or flourodeoxy or fluorine or 18f or 18flu$ or 18fluo$).ti,ab.	24705
4	glucose.ti,ab.	172136
5	(pet or petscan$ or pet ct).ti,ab.	40566
6	Tomography, Emission-Computed/	6449
7	emission.ti,ab.	69323
8	(tomograph or tomographs or tomographic$ or tomogrpahy or tomographies).ti,ab.	18575
9	7 and 8	1918
10	5 or 6 or 9	44340
11	3 and 4	4680
12	2 or 11	21518
13	10 and 12	14763
14	exp neoplasm/ or neoplasm staging/ or cancer$.ti,ab. or tumor$.ti,ab. or tumour$.ti,ab. or carcinoma$.ti,ab. or neoplasm$.ti,ab. or lymphoma.ti,ab. or thymoma.ti,ab. or melanoma.ti,ab. or staging.ti,ab. or metastas$.ti,ab. or metastatic.ti,ab. or exp neoplasm metastasis/ or exp neoplastic processes/ or neoplastic process$.ti,ab. or non small cell.ti,ab. or adenocarcinoma$.ti,ab. or squamous cell.ti,ab. or nsclc.ti,ab. or osteosarcoma$.ti,ab. or phyllodes.ti,ab. or cytosarcoma$.ti,ab. or fibroadenoma$.ti,ab. or (non adj2 small adj2 cell).ti,ab. or (nonsmall adj2 cell).ti,ab. or plasmacytoma$.ti,ab. or myeloma.ti,ab. or multiple	1633962

	myeloma.ti,ab. or lymphoblastoma$.ti,ab. or lymphocytoma$.ti,ab. or lymphosarcoma$.ti,ab. or immunocytoma.ti,ab. or sarcoma$.ti,ab. or hodgkin$.ti,ab. or (nonhodgkin$ or non hodgkin$).ti,ab.	
15	1 and 14	28581
16	13 and 14	10492
17	15 or 16	28583
18	limit 17 to (human and english language and yr="2008 - 2010")	8742
19	(comment or comment$ or discussion or discussion$ or editorial comment$ or in brief or letter or case reports or invited commentary).pt.	409209
20	18 not 19	8287
21	(integrative research review$ or research integration or (methodologic$ adj10 review$) or (methodologic$ adj10 overview$) or (quantitativ$ adj10 review$) or (quantitativ$ adj10 overview$) or (quantitativ$ adj10 synthes$) or (systematic adj10 review$) or (systematic adj10 overview$) or (metaanal or meta anal$)).ti,ab. or meta-analysis/	88318
22	(review-tutorial or review-academic or review).pt. or (pooling or pooled analys$ or mantel heanszel$).ti,ab.	1169765
23	(peto$ or der simonian or dersimonian or fixed effect$).ti,ab.	4627
24	21 or 22	1214417
25	20 and 24	1925
26	20 not 24	6362

Appendix 5: PET for esophageal cancer: summary of the primary study evidence from 2005 to 2008.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
Diagnosis/Staging								
Kato, 2005 (4)	To compare PET with bone scintigraphy in the evaluation of bony metastases in esophageal carcinoma	44	FDG PET from head to thigh	Histopathology or clinical/ radiological follow-up	Bone scintigraphy	NR	PET: Sens=92%, Spec=94%, PPV=86%, NPV=97%, Accuracy=93% Bone scintigraphy: Sens=77%, Spec=84%, PPV=67%, NPV=90%, Accuracy=82%	PET was superior to bone scintigraphy in detecting bony metastases of esophageal cancer. PET is useful for detection and follow-up of bone tumours when bone scintigraphy findings are negative.
Lowe, 2005 (29)	To compare the accuracy of PET, CT, and endoscopic ultrasound in staging of esophageal cancer	75	FDG PET of neck, chest, abdomen, pelvis	Histopathology	CT Endoscopic ultrasound	PET interpretation blinded to results of other imaging tests	PET: T stage: Correct=43%, Understaged=29%, Overstaged=29% N stage: Sens=82%, Spec=60% M stage: Sens=81%, Spec=91% Treatment assignment was correct by PET in 70%, by CT in 65%, and by 75% in EUS. See full data extractions for CT and ultrasound results	EUS had better T staging ability over PET and CT. EUS, CT, and PET had similar performance in N staging. There was a trend toward improved M staging with CT or PET over EUS.
Duong, 2006 (30)	To assess whether incremental PET findings affect management plan of pts undergoing primary staging	68	FDG PET of lower neck, thorax, abdomen to iliac crests	Histopathology or serial imaging and clinical follow-up	Conventional staging	Not blinded	Discordance between post-PET stage and conventionally determined stage in 30 of 68 pts Stage I-IIA pts: 26% upstaged, 0% downstaged Stage IIB-III pts: 39% upstaged, 30% downstaged Stage IV: 0% upstaged, 45% downstaged Total: 26% upstaged, 18% downstaged PET changed treatment intent in 15/68 patients (palliative vs. curative) and changed treatment modality in 7/68 patients. Post-PET stage could be verified in 20 of these 22 cases and was correct in 19/20 cases.	PET changed clinical management of more than one-third of pts.
Yuan, 2006 (6)	To assess the value of PET/CT in the diagnosis of locoregional lymph node metastases	45	FDG PET/CT from head to thigh	Histopathology	PET alone	Interpretation of PET/CT blinded to clinical history and previous conventional imaging tests	Analysis by nodal group: PET/CT: Sens=94%, Spec=92%, PPV=75%, NPV=98%, Accuracy=92% PET alone: Sens=82%, Spec=87%, PPV=63%, NPV=95%, Accuracy=86%	Combined PET/CT has additional value over review of side-by-side PET and CT in assessing locoregional lymph nodes. PET/CT improves sensitivity, accuracy, and NPV.
Buchmann, 2006 (31)	To evaluate the use of PET in imaging the primary tumour and N and M staging and the effect of PET on changes in clinical management	20	FDG PET from skull base to proximal thigh	Histopathology and clinical-radiological follow-up for N and M staging	None	NR	Primary tumour: Sens=96% N stage: Sens=20%, Spec=100%, Accuracy=58% M stage: Sens=60%, Spec=93%, Accuracy=86% PET finding caused change of treatment due to upstaging in 1 pt (5%)	PET is excellent at detecting primary tumour and efficient in M-staging. PET is of limited value in detecting locoregional lymph node metastases.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
van Westreenen, 2007 (32)	To assess the additional value of PET in staging pts with esophageal cancer	199	FDG PET from mid-skull to mid-femur	Histopathology or clinical or imaging follow-up	None	PET interpreters aware of tumour presence and location but blinded to other data	Metastases: Sens=63%, PPV=27% PET led to upstaging in 8 patients and synchronous neoplasms were detected in 7 patients. False-positive rate: 7.5% False-negative rate: 4.5%	PET improves selection of pts for potentially curative surgery but high false-positive and false-negative rates make broad implementation in daily clinical practice questionable
Katsoulis, 2007 (5)	To evaluate PET as a staging tool for thoracic esophageal and gastro-esophageal junction cancer	22	FDG PET from skull base to pubic symphysis	Histopathology	CT	NR	Regional lymph nodes: PET: Sens=71%, Spec=67%, PPV=83%, NPV=50% CT: Sens=29%, Spec=67%, PPV=67%, NPV=29% Distant metastases: PET: Sens=50%, Spec=100%, PPV=100%, NPV=83% CT: Sens=33%, Spec=88%, PPV=67%, NPV=64% PET led to change in treatment plan in 5 patients. PET led to unnecessary laparotomy in 2 patients.	PET is more accurate than CT in defining N and M status.
Chung, 2008 (33)	To compare ^{201} T1 SPECT and PET in primary esophageal cancer	100	FDG PET or PET/CT	Histopathology or clinical follow-up	^{201}T1 SPECT	NR	Primary tumour: PET: Sens=91% SPECT: Sens=85%	SPECT imaging can detect primary tumours at a rate comparable to that of PET
McDonough, 2008 (34)	To determine if PET offers additional information following CT and EUS in deciding treatment stratification	50	FDG PET	Histopathology	CT and EUS	PET interpretation blinded to pt identifying information and demographics	Clinical management decisions were identical with and without PET in 49 of 50 pts. Of 21 pts with surgical pathology data, PET had 3 false positives, CT had 1 and EUS had none. Each imaging test had 5 false negatives.	The addition of PET to EUS and CT offers little information to the initial treatment stratification of pts with esophageal cancer. PET may have some clinical utility in pts with incomplete EUS.
Treatment Response								
Song, 2005 (14)	To determine the usefulness of PET in predicting pathologic response to neoadjuvant CRT	32	FDG PET pre- and post-CRT	Histopathology	Conventional diagnostic modalities	NR	Treatment response in esophagus: PET: Sens=27%, Spec=95%, PPV=75%, NPV=71% Conventional: Sens=73%, Spec=48%, PPV=42%, NPV=77% Treatment response in lymph nodes: PET: Sens=16%, Spec=98%, PPV=36%, NPV=93% Conventional: Sens=16%, Spec=92%, PPV=15%, NPV=93%	Pathologic response might be correlated with metabolic response on PET after neoadjuvant CRT.
Levine, 2006 (15)	To determine the utility of PET in detecting response to CRT	64	FDG PET from chin to pelvis, pre-CRT and 4 to 6 wks post-CRT	Histopathology	None	NR	Mean $SUV_{max1\ hour}$ after CRT was higher in pts with pathologic complete response or microscopic residual disease than in pts with macroscopic disease (13.4 vs. 7.1; p=0.02). See full data extractions for details regarding detection of primary disease and disease outside the primary tumour.	Pre-treatment and post-treatment PET can be useful to predict significant response to CRT.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
Westerterp, 2006 (13)	To assess the accuracy of PET to monitor early treatment response by correlating metabolic activity reduction with histologic response	26	FDG PET at baseline and 2-3 wks after start of hyperthermia and CRT	Histopathology	None	Pathologist blinded to clinical and PET data	Cutpoint of 31% decrease from baseline SUV Prediction of response: Sens=75%, Spec=75%, PPV=75%, NPV=75%. Median decrease in SUV -44% in responders vs. -15% in non-responders (p=0.05).	Changes in FDG uptake correlated well with pathologic response and a promising tool in early response monitoring.
Duong, 2006 (16)	To determine whether a single post-treatment PET scan can predict tumour response	53	FDG PET 4 to 5 wks after CRT	Histopathology or clinical follow-up	CT	NR	PET results were verified in 48 pts and confirmed to be correct in 38 (79%). A change in treatment intent (curative, palliative) occurred in 5 pts. A change in treatment modality occurred in 14 pts.	Post-treatment PET for assessment of tumour response changed clinical management of more than one-third of pts. Response status by PET powerfully stratified prognosis.
Ott, 2006 (35)	To validate an a priori defined metabolic response in PET as a predictor for treatment response	65	FDG PET at baseline and 2 wks after chemotherapy started	Histopathology	None	Pathologists, radiologists and endoscopists blinded to PET response and patient outcomes	SUV decrease from baseline >35% in predicting histopathologic response: Sens=80%, Spec=78%, PPV=44%, NPV=95%, Accuracy=79%	Changes in tumour metabolic activity during chemotherapy predict response, prognosis and recurrence.
Gillham, 2006 (23)	To determine whether PET can predict pathologic response after the first week of neoadjuvant CRT	32	FDG PET from skull base to mid- thigh, at diagnosis and 1 wk after start of CRT	Histopathology	None	Pathologist blinded to clinical and PET data	Change in SUV and volume of metabolically active tissue (MTV) not significantly different between responders and non-responders. SUV reduction >20%: PPV=27%, NPV=71% MTV reduction >20%: PPV=35%, NPV=80%	Early repeat PET scanning was not proven to predict pathologic response. Early inflammatory response to radiation may be a confounding variable.
Kim, 2007 (17)	To evaluate the accuracy of PET in assessing complete metabolic response and predicting pathologic complete response and survival	62	FDG PET from skull base to upper thigh, at baseline and at least 2 to 3 wks after end of CRT	Histopathology	Endoscopic biopsy, CT scan, clinical response	NR	Detection of residual disease: PET: Sens=52%, Spec=67%, PPV=79%, NPV=64%, Accuracy=71% CT: Sens=85%, Spec=17%, PPV=58%, NPV=44%, Accuracy=58% Endoscopic biopsy: Sens=30%, Spec=100%, PPV=100%, NPV=67%, Accuracy=71% Clinical response: Sens=76%, Spec=82%, PPV=84%, NPV=74%, Accuracy=79%	Complete metabolic response by PET has a significant correlation with pathologic complete response and can predict long-term outcome
Lordick, 2007 (26)	To evaluate the feasibility and effect of administering PET response-guided chemotherapy	111	FDG PET at baseline and 2 wks after start of chemotherapy	Histopathology	None	NR	29 of 50 metabolic responders had pathologic response. SUV decrease not significantly different between complete pathologic responders compared with subtotal pathologic responders (median decrease 56% vs. 47%). No pathologic response seen in metabolic nonresponders.	Early metabolic response evaluation is useful and a PET-guided treatment algorithm is feasible.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
Wieder, 2007 (18)	To determine the appropriate time for monitoring tumour response by PET and to determine whether it is better to measure absolute FDG uptake or relative changes (SUV)	24	FDG PET at baseline, 2 wks after start of chemotherapy and 3 to 4 wks after end of chemotherapy	Histopathology	None	Pathologist blinded to PET results and patient outcome data	No difference in absolute tumour SUV between responders and non-responders at baseline, after 2 wks of chemotherapy, or 3 to 4 wks after end of chemotherapy. Relative changes in SUV were related to pathologic response. Baseline to 2 wks after chemotherapy started: -33% SUV: Sens=100%, Spec=63%, Accuracy=75% -35% SUV: Sens=88%, Spec=69%, Accuracy=75% Baseline to 3 to 4 wks after end of chemotherapy: -63% SUV: Sens=75%, Spec=87%, Accuracy=83%	Relative changes in FDG uptake are better predictors of response than absolute SUV. Metabolic changes in the first 2 wks of therapy are at least as efficient for prediction of response and survival as later changes.
Smithers et al, 2008 (19)	To determine if FDG PET could be correlated with a pathological response in patients with esophageal adenocarcinoma receiving neoadjuvant chemotherapy and/or chemoradiation therapy.	45	Whole body FDG PET scanning	Histopathology	None	NR	No significant difference in SUV reduction between the responders and the non-responders when a response greater than 50% reduction in the uptake of FDG PET. Prediction of response (reduction in FDG uptake >50%): Mean change in SUV for responders vs. non-responders was -56.8% vs. -27.9% (p=0.03). Mean change in tumour/liver ratios (TLR) was -49.8% vs. -27.3% (p=0.128). Chemotherapy group: Sens=100% and Spec=79% for both SUV and tumour to liver ratio (TLR) Chemoradiation group: Sens=66.7%, Spec=71% for SUV and Sens=66.7%, Spec=57% for TLR Chemoradiation- SUV: Sens=67%, Spec=71% TLR: Sens=67%, Spec=57% Chemotherapy- SUV: Sens=100%, Spec=79% TLR: Sens=100%, Spec=79%	There was no difference between the two methods of assessment, however there was less variation with SUV. There was no correlation between the FDG PET response and the histopathological response. Presently an FDG PET scan performed 3-6 weeks after neoadjuvant therapy for adenocarcinoma of the esophagus should not be used as a marker of the potential result of the treatment. The optimal timing of a second FDG PET remains unclear.
Recurrence								
Guo, 2007 (27)	To evaluate the diagnostic and prognostic value of PET/CT for pts with suspected recurrence after definitive treatment	56	FDG PET/CT from middle skull to proximal thigh	Histopathology or clinical follow-up	None	Not blinded	Local: Sens=97%, Spec=50%, Accuracy=84% Regional: Sens=90%, Spec=82%, Accuracy=87% Distant: Sens=91%, Spec=93%, Accuracy=91% Overall: Sens=93%, Spec=76%, Accuracy=87% Patient-based analysis: Sens=96%, Spec=55%, Accuracy=88%	PET has a high sensitivity, specificity, and accuracy in detection of regional and distant recurrence. Specificity at local sites is relatively low due to a high rate of false positives.

Abbreviations: CT, Computed Tomography; FDG PET, Fluoro-2-deoxy-D-glucose Positron Emission Tomography; mets, metastasis; MRI, Magnetic Resonance Imaging; NPV, Negative Predictive Value; NR, not reported; PPV, Positive Predictive Value; pts, patients; Sens, sensitivity; Spec, specificity; SUV, Standard Uptake Value; pts, patients

Appendix 6: PET for esophageal cancer: summary of the primary study evidence from 2008 to 2010.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
Diagnosis/Staging								
Chatterton et al., 2009 (7)	1. To determine the incremental information provided by 18F-FDG PET in staging patients with esophageal cancer 2. To determine the impact of PET staging on post-PET clinical management of esophageal cancer, and on prognosis	129	FDG PET from the base skull to the upper thighs	Clinical follow-up	CT	NR	PET: Detected 315 lesions (129 primary tumours, 114 regional lymph nodes and 72 distant metastases). CT: Detected 210 lesions (131 all primary tumours, 79 regional lymph nodes, and 35 distant metastases). T status: 94% unchanged, 3% upstaged, and 3% downstaged N status: 73% unchanged, 16% upstaged, 10% downstaged, 0% changed to NX or MX, 2% changed from NX or MX. M status: 73% unchanged, 22% upstaged, 0% downstaged, 0% changed to NX or MX, 5% changed from NX or MX Significant management change (high or medium impact) in 38% of patients. There was significant shorter progression-free survival in patients who have additional lesions on PET with P-value < 0.05 without any relation to SUVmax.	The study clearly demonstrated the significant impact of PET on the management of patients with newly diagnosed esophageal cancer, and the ability to stratify patients prognosis based on the PET findings. The information gained suggests that PET should be routine in the staging of esophageal cancer patients.
Cheze-Le Rest, et al., 2008 (8)	To assess prognosis on the basis of the initial fluorodeoxyglucose (FDG)-PET scan, focusing on the correlation between overall survival and FDG uptake in the primary, as well as the presence of FDG positive lymph nodes or distant metastases	52	Whole body FDG PET imaging	Histopathology and clinical follow-up	PET alone	NR	PET: 24 patients had early-stage disease and others (57%) had stage III or IV tumours. 33 patients had T3 or T4 primary lesion, 26 had N1 (56%) lymph node metastases and 8 had distant metastases. Median follow-up time: 32 months Overall survival time for all 47 patients was 17.3 months with 1-year and 2-year survival rate of 67% and 44% respectively. All primary lesions detected correspond to 100% sensitivity Intensity of FDG uptake in the primary and presence of a minimum of two nodes on PET images were independent significant prognostic for overall survival	FDG PET was found to provide prognostic information supporting a new indication for initial FDG PET examination in esophageal cancer.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
Higuchi, et al., 2008 (20)	To investigate the usefulness of PET with FDG F18 in assessment of response of advanced esophageal squamous cell carcinoma to neoadjuvant treatment to establish new criteria to predict postoperative long-term survival.	50	Whole body FDG PET imaging	Histopathology	PET alone	Not blinded	Initial clinical staging was stage III or more: Stage III in 24 pts, Stage IVA in 11 pts and Stage IVB in 15 pts. Histologic response and residual tumour size: 8 pts with grade 0, 22 pts with grade 1, 14 pts with grade 2 and 6 pts with grade 3. Posttreatment PET diagnosis for prediction: Sens=85.7%, Spec=93.1%, and accuracy=90.0% Posttreatment PET diagnosis and survival after surgery: The median follow-up was 26.5 months (range 5.4-84.2 months) Negative PET: cause-specific median survival > 84.2 months with 1-year survival = 95.0%, 3-year survival =73.9%, and 5-year survival = 67.7% Positive PET: cause-specific median survival =18.2 months with 1-year survival = 75.9%, 3-year survival = 41.1%, and 5-year survival = 36.5%. Comparison between Negative PET and Positive PET survival rate was significant (p=0.0042)	Posttreatment PET with FDG F18 reliably predicted histologic response and postoperative survival in advanced esophageal squamous cell carcinoma. This tool could potentially be used to tailor optimal treatment according to individual responses.
Hsu et al., 2009 (9)	To investigate the role of PET/CT in thoracic esophageal squamous cell carcinoma in predicting locoregional invasion	45	Whole body FDG PET/CT scanning	Histopathology	PET alone	Not blinded	Tumour invasion depth: Mean SUVmax for primary tumour was 11.64 ± 5.00 (range 0 to 23.00). T1 stage: mean SUVmax was 5.09 ± 4.00 T2 stage: mean SUVmax was 14.17 ± 2.46 T3 stage: mean SUVmax was 13.32 ± 3.96 T4 stage: mean SUVmax was 10.37 ± 1.94 T1 stage SUVmax was significantly lower than T2 and T3. (T1 vs. T2, P-vale = 0.001; T1 vs. T3, p<0.001) ROC cut-off point for SUVmax was 6.5 for predicting T1 and non-T1 status (AUC = 0.901, p<0.001) Regional lymph node in 21 patients (46.7%): PET/CT:Sens=57.1%, Spec=83.3%, Accuracy=71.1% Non-regional lymph node in 11 patients (24.4%): PET/CT:Sens=36.4%, Spec=82.4%, Accuracy=71.1%	Locoregional invasion in esophageal cancer can be predicted by PET/CT. The SUVmax of the primary tumour helped identify T1 tumour, and the SUVmax of the regional lymph nodes correlated with the severity of nodal involvement.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
Hu et al., 2009 (10)	To compare dual-time-point and single-time-point 18F-FDG PET in the evaluation of locoregional lymph node metastasis in patients with esophageal squamous cancer.	34	FDG PET from proximal thigh to the cranium	Histopathology	CT or MRI	Physicians were blinded to clinical history except for CT or MRI	Lymph node metastasis: PET: Sens=76.06% to 88.73%, Spec=85.16% to91.87%, Accuracy=83.33% to 91.24%, NPV=93.41% to 97.01%, PPV=56.25% to 73.25%	The results of this study indicate the clinical potential of dual-time-point FDG PET for the evaluation of locoregional LNs in thoracic esophageal squamous cell cancer, it appears that there is an increase in the uptake of 18F-FDG over time in locoregional malignant lymph nodes in thoracic esophageal squamous cell cancer detected by dual-time-point PET. In contrast, the SUV in normal and inflammatory lymph nodes decreases over time. More studies are needed to further the understanding of this technique and confirm these preliminary results.
Noble et al, 2009 (11)	To document the impact of integrated positron-emission tomography and computed tomography (PET/CT) on the management of a cohort of UK patients undergoing PET/CT as part of their staging investigations for potentially curable esophageal cancer.	191	FDG PET at variety of sites	Histopathology	CT and EUS	NR	PET/CT: Helpful in planning management in 174 cases (91%), changed in staging in 65 cases (34%), and management un 50 cases (26%) Detection of distant metastases: Positive: 31 patients (16%), Negative: 160 patients (84%), True positive: 21 patients (11%), Upstaged: 18 patients (9.4%), Unexpected synchronous pathology: 3 (1.6%), False positive: 10 patients (5%), True negative: 158 patients (83%), Downstaged: 8 patients (4%), Negative also on combined CT/EUS: 150 patients (79%), False negative: 2 patients (1%) Overall detection rate: Sens=91%, Spec=94%	This study confirms the role of PET/CT in a multicentre UK setting in the management of patients with potentially curable carcinoma of the esophagus, improving the accuracy of pre-treatment staging compared with CT and EUS alone. Early tumours infrequently show evidence of metastasis on PET/CT, although further data are required to confidently determine the stage of tumours where PET/CT has no additional value.
Okada et al, 2009 (12)	To assess whether integrated FDG PET/CT can improve the diagnostic accuracy of metastatic regional lymph nodes (LNs) in esophageal cancer compared with contrast enhanced CT (CECT)	18	Whole body FDG PET scanning	Histopathology	CT	Two CECT evaluators were blinded	PET LN metastasis detection: Sens=60.0%, Spec=99.5%, Accuracy=94.8% PPV=93.8%, NPV=94.8%	Integrated PET/CT improves the PPV of regional LNs when compared with CECT.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
Shimizu et al, 2009 (13)	To determine the appropriateness of adding FDG PET to CT and other pre-existing diagnostic imaging modalities for detecting subclinical lymph node metastasis of esophageal cancer, by comparing images from these modalities with the results of histopathological analysis.	20	Whole-body FDG PET from the top of the skull to the proximal thighs	Histopathology	Thin-slice CT	Independent review without access to other images	PET/CT detection rate for lymph node metastasis: Cervical supraclavicular: Sens=50%, Spec=94% Mediastinal: Sens=14%, Spec=85% Abdominal: Sens=11%, Spec=100% Thin-slice CT detection rate for lymph node metastasis: Cervical supraclavicular: Sens=100%, Spec=94% Mediastinal: Sens=86%, Spec=69% Abdominal: Sens=22%, Spec=100%	The detection rate of subclinical lymph node metastasis did not improve with the use of PET-CT, for either the cervical and supraclavicular, mediastinal, or abdominal regions. It is not recommended to use FDG PET or PET-CT alone as a diagnostic tool to determine CTV if pathologically involved lymphatic regions are to be included in the CTV in the treatment protocol. The accuracy of PET-CT must be further improved in order to better detect positive nodes and improve the definition of the CTV.
Treatment Response								
Klaeser et al, 2009 (21)	To predict histopathological non-response, correlate metabolic response with event-free survival (EFS) and overall survival (OS) and determine whether metabolic response may be a useful prognostic parameter.	45	FDG PET pre- and post-CRT	Histopathology	Conventional diagnostic modalities	NR	Prediction of histopathological non-response after CRT: Overall: Sens=68%, Spec=52%, PPV=58% and NPV=63% Adenocarcinoma: Sens=60%, Spec=50%, PPV=64% and NPV=45%	Metabolic response correlated with histopathology after preoperative therapy. However, FDG PET did not predict non-response after induction chemotherapy with sufficient clinical accuracy to justify withdrawal of subsequent CRT and selection of patients to proceed directly to surgery.
Shenfine et al, 2009 (22)	To assess if the quantitative values obtained by preoperative FDG PET are independent prognostic indicators for survival in patients with resectable esophageal adenocarcinoma undergoing surgical treatment without neoadjuvant therapy.	45	Whole-body FDG PET scan	Histopathology	None	NR	Median follow-up time for all patients was 44 months (range 18-61 months) and the median overall survival time of 24 months. Median SUVmax was 5.7 (range 2.3-19.6) Clinically advanced disease: 17 of 45 patients (38%) Pathologically advanced disease: 31 of 45 patients (69%) (p=0.003) with SUVmax cutoff point of 5, PPV= 84.6% and NPV=52.6%, Sens=71%, Spec=71.4% Dichotomized SUVmax was predictive of both overall survival (log rank 7.20, p=0.007) and disease-free survival (p=0.017)	Preoperative FDG PET SUVmax is associated with outcome after esophageal adenocarcinoma resection but remains less accurate than postoperative variables. A high FDG PET SUVmax could be used to identify a high-risk population who would benefit most from neoadjuvant therapies.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Results	Authors' Conclusions
Vallbohmer et al, 2009 (25)	To evaluate the potential of FDG PET after the completion of neoadjuvant chemoradiation for the assessment of histopathologic response and prognosis in the multimodality treatment of patients with esophageal cancer.	119	FDG PET scanning from skull to proximal thighs	Histopathology or clinical follow-up	None	Nuclear Physician were blinded to all findings	Intratumoural SUVmax before radiochemotherapy: SUV1 was 8.4 (range: 1.8-34.0). No significant differences for the SUV1 were found between men and women (median:8.6 vs. 7.8; p=0.471) It was significantly lower in adenocarcinoma compared with squamous cell cancer (median: 6.7 vs. 9.1; p=0.003) 4 weeks after completion of neoadjuvant therapy: SUV2 decrease significantly to median value of 3.0 (range: 1.0-9.3; p<0.0001). No significant differences for SUV2 were found between men and women (median: 2.7 vs. 3.0; p=0.864) or between squamous cell cancer and adenocarcinoma (median: 2.8 vs. 3.0; p=0.108)	FDG PET seems not to be an imaging system that effectively characterizes the groups of major and minor response as well as survival in patients with esophageal cancer after multimodality treatment.
Recurrence								
Jingu et al., 2010 (28)	To reveal the utility of 18F-fluorodeoxyglucose positron emission tomography (FDG PET) within 7days after chemoradiotherapy to predict prognosis in patients with postoperative recurrent esophageal cancer.	24	Whole body FDG PET/CT bed position scanning	Histopathology or clinical follow-up	None	Not blinded	The 1-year and 3-year cause-specific survival rate were 80.0% with 95% CI (62.5-97.5%) and 48.0% with 95% CI (25.6-70.4%) respectively. The 1-year and 3-year local control rates in the 20 patients were 69% with 95% CI (48.4-89.7%) and 51.8% with 95% CI (28.9-74.7%) respectively. Before chemoradiotherapy (CRT): Median SUVmax in the 20 patients after chemoradiotherapy was 8.4 (range 3.0 – 20.0) There tended to be significant difference between cause-specific survival rates in patients with SUVmax < 8.4 and those with SUVmax ≥ 8.4 before CRT (3 years, 67.5% vs. 30.0%; p=0.076) There was no significant difference between local control rates in patients with SUVmax < 8.4 and those with SUVmax ≥ 8.4 after CRT (3 years, 46.7% vs. 58.3%; p=0.98) After CRT: Median SUVmax in the 20 patients after chemoradiotherapy was 2.4 (range 1.2-5.2) There was significant difference between cause-specific survival rates in patients with SUVmax > 2.4 and those with SUVmax ≤ 2.4 after CRT (3 years, 20% vs. 77.8%; p=0.033) There was significant difference between local control rates in patients with SUVmax > 2.4 and those with SUVmax ≤ 2.4 after CRT (3 years, 23.3% vs. 78.8%; p=0.01)	FDG PET performed even < 7 days after CRT predicts prognosis in patients with postoperative recurrent esophageal cancer.

Abbreviations: CT, Computed Tomography; FDG PET, Fluoro-2-deoxy-D-glucose Positron Emission Tomography; LN(s), lymph nodes; mets, metastasis; MRI, Magnetic Resonance Imaging; NPV, Negative Predictive Value; NR, not reported; PPV, Positive Predictive Value; Sens, sensitivity; Spec, specificity; SUV, Standard Uptake Value