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PET Recommendation Report 1 Version 2

PET Imaging in Colorectal Cancer

K. Chan, S. Welch, 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

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

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PET Recommendation Report 1 Version 2: Section 1

PET Imaging in Colorectal Cancer: Recommendations

K. Chan, S. Welch, C. Walker-Dilks, and A.O. Raifu

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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 colorectal cancer?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for colorectal cancer?
- What benefit to clinical management does PET or PET/CT contribute when the recurrence of colorectal cancer is suspected but not proven?
- What benefit to clinical management does PET or PET/CT contribute to restaging at the time of the documented recurrence for colorectal cancer?
- 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 colorectal 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 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 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 systematic review undertaken to retrieve the same level of evidence for the period from August 2005 to May 2010.

Diagnosis/Staging

The routine use of PET is not recommended for the diagnosis or staging of clinical Stage I-III colorectal cancers.

PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease.

Diagnosis

PET: One systematic review of two primary studies and one additional primary study in the 2007 Health Technology Assessment (HTA) review (1) summarized the fact that PET has good sensitivity to detect primary tumours > 2 cm, but not smaller tumours, with variable specificity. No additional studies were identified in the update searches.

PET/CT: No studies of PET/CT for diagnosis were identified.

Staging

PET: Two primary studies in the HTA review (1), and four studies from the update searches (Furukawa et al [2], Llamas-Elvira et al [3], Nahas et al [4], and Kosugi et al [5]) were identified. These studies had different patient case mixes and proportions of patients with stage IV disease. While some studies showed changes in patient management because of changes in M-staging, such findings were in studies with a relatively large proportion of stage IV disease. Furukawa et al (2) and Nahas et al (4) did not show any significant changes in M-staging. Kosugi et al (5) included 53 patients with lymph node metastases on CT. PET detected 24 para-aortic and 29 epicolic/paracolic/or intermediate lymph nodes. The results of Kosugi et al (5) showed that PET has lower sensitivity, higher specificity, higher accuracy and higher positive value (PPV) than CT for N1 and N2-3 lymph nodes. For N4 lymph node, PET has high sensitivity and high specificity, while CT has only high sensitivity but low specificity and low PPV. Thus, it is reasonable to consider using PET when N4 nodes are suspected.

PET/CT: The HTA review did not identify any studies that involved the use of PET/CT exclusively for staging prior to any therapy. The 2005-2008 update search identified five studies (Veit-Haibach et al [6], Park et al [7], Kinner et al [8], Tsunoda et al [9], and Orlacchio et al [10]). Park et al (8) included only patients with equivocal CT findings or elevated carcinoembryonic enzyme (CEA), which resulted in 49% stage IV patients. PET/CT changed the management in 24% of those patients. Tsunoda et al (10) evaluated the detection rate of PET/CT with respect to nodal metastasis (proximal and distal). PET/CT had better performance than CT overall. Given the small proportion of patients with distant nodal metastasis plus the fact that the study did not separately compare PET/CT and CT with respect to distant nodal metastasis only, it is difficult to know whether distant nodal M-staging is changed significantly with the use of PET/CT. Veit-Haibach et al (7) and Kinner et al (9) did not show a significant change in M-staging. In Orlacchio et al (10), which included 467 patients, there was concordance among PET, CT, and PET/CT in 91.2% of the cases. Seventy-two percent (72%) of the cases were true positive for liver metastases, suggesting the patients in the study had a higher index of suspicion for liver metastases than might be expected in the routine clinical setting. The study provided formal statistical Z test comparison which showed that PET/CT is better than PET alone or CT alone with p-values < 0.05. The sensitivity and specificity were all greater than 90% in CT, PET, and PET/CT.

Qualifying Statements

- Some studies evaluated the diagnostic performance of PET or PET/CT with respect to each metastatic site/organ/lesion, while some evaluated it with respect to the M-staging of each patient. It would appear that studies that analyzed results based on each

site/organ/lesion showed a better performance of PET or PET/CT, while studies that analyzed results based on the overall M-staging of patients did not show an obvious improvement in performance of PET or PET/CT. As solitary or oligo-metastasis is not a very common presentation in the initial diagnosis of colorectal cancer, it would be unlikely that PET or PET/CT would detect such a situation when CT missed it, if the objective was to change the M-staging and management of these patients. However, in patients who already have suspicious or confirmed metastasis based on CT, it is quite possible that PET or PET/CT could detect further metastases in other sites/organs that were not conclusively detected by CT alone. This would inflate the diagnostic performance of PET or PET/CT, if an analysis was based on sites/organs/lesions instead of the overall M-staging of each patient. This factor might be important when making recommendations for early-stage disease versus metastatic disease.

- On the other hand, for patients who already have what appears to be solitary or oligo-metastases on CT only, and who are potential candidates for resection, and given that the possibility of further metastasis in other sites/organs is not low, PET or PET/CT might assist in the decision making of resection with curative intent by helping to assess the extent of metastasis. Studies that analyzed the diagnostic performance of PET or PET/CT, with respect to sites/organs/lesions, provided evidence to support this approach. Therefore, there may be a role for the use of PET or PET/CT when conventional imaging raises suspicion of the presence of potentially resectable metastatic disease, and patients are potential candidates to undergo such surgery. The incremental benefit of PET or PET/CT over magnetic resonance imaging (MRI) of the liver is unclear in such populations as none of the studies included the routine use of MRI as part of conventional imaging.
- Most studies that showed that PET or PET/CT changed the management of a significant proportion of patients included a relatively large number with stage IV disease (up to 46% of patients). Studies that included a relatively small proportion of stage IV patients did not appear to show a significant benefit or change in the patient management plan with PET or PET/CT. Some of those changes in management involved the detection of a larger than expected volume of disease in the liver or extrahepatic metastasis by PET or PET/CT in patients originally diagnosed with low-volume resectable liver metastasis by conventional imaging.
- Most studies that compared PET or PET/CT with conventional imaging were done in the time period when multidetector CT (MDCT) was not yet widely available. The only study (Furukawa et al [3]) that clearly stated that MDCT was used did not show clinically relevant superiority of PET in addition to MDCT. As MDCT is being used routinely in most of the cancer centres and hospitals in Ontario, the incremental benefit of PET or PET/CT for the routine staging of colorectal cancers remains to be established.
- While some studies reported the numerical comparisons of diagnostic performance between PET, or PET/CT, and conventional imaging, few studies tested whether the numerical differences observed were statistically significant or not.
- It is unclear whether PET or PET/CT leads to an improvement in survival or simply results in stage migration. Nonetheless, many practitioners may accept that more accurate staging will lead to a better choice of treatment plan, thereby avoiding overtreatment and sparing patients the unnecessary risks or side effects of therapy or avoiding undertreatment when patients might otherwise benefit from aggressive curative-intent therapy.
- There are very few studies that evaluated rectal cancer and colon cancer separately. The current limited evidence did not obviously suggest or refute that PET or PET/CT significantly changed management in patients with non-metastatic rectal cancer. However, some studies seemed to suggest that PET or PET/CT has better N-stage accuracy

than CT. It is unclear how PET or PET/CT compares with MRI or trans-rectal ultrasound (TRUS) with respect to N-staging. There may be a role for PET/CT with respect to N-staging in the decision making for patients with non-metastatic rectal cancer who might be candidates for preoperative chemoradiotherapy.

- When conventional imaging with CT suggests equivocal para-aortic lymph node involvement as the only potential site of concern and that the patient is otherwise a potential candidate for curative intent surgery of the primary colorectal cancer, PET can be considered in order to rule in or out para-aortic region metastatic disease.

Assessment of Treatment Response

The routine use of PET is not recommended for the measurement of treatment response in locally advanced rectal cancer before and after preoperative chemotherapy.
PET: The update searches identified a randomized control trial (RCT), Bystrom et al (11), that evaluated PET before and after 2 cycles of chemotherapy and also evaluated CT before and after 4 cycles of chemotherapy. The results showed that PET correlated with CT and had a relatively low sensitivity and specificity. PET also failed to predict the time to progression or overall survival in patients with metastatic colorectal cancer. The study suggested that PET should not be used as a substitute for CT for short-term response and should not be used as a surrogate for long-term clinical endpoints. The HTA review identified six non-randomized studies showing that changes in standardized uptake values (SUV) between pretherapy and posttherapy scans may predict response. The update searches identified four additional primary studies evaluating treatment response. Cascini et al, 2006 (12) included patients receiving PET before and 12 days after the initiation of preoperative therapy and supported the finding of the HTA review that changes in SUV may predict response. However, one-time PET after preoperative therapy poorly predicted complete pathologic response after preoperative therapy in Capirci et al (13) and Kalff et al (14) and poorly predicted posttherapy staging in Capirci et al (12). Glazer et al (15) conducted a prospective cohort study of 138 patients, each with presumptive diagnosis of liver metastasis, who had at least one PET scan after chemotherapy and before liver resection. The study showed that ultrasonography also guides surgical decision during intraoperative assessment and suggested PET after chemotherapy should not be used in decision making for liver resection. **PET/CT**: The HTA review did not have any studies of PET/CT in predicting treatment response. The update searches identified 2 studies (Capirci et al, 2007 [16], Kristiansen et al, 2008 [17]). Capirci et al (16) suggested that a change in SUV before and after preoperative chemoradiotherapy predicted a tumour regression grade (TRG) in rectal cancer, while Kristiansen et al (17) suggested a single PET/CT after preoperative therapy poorly predicted complete pathologic response.

Qualifying Statements

None.

Recurrence/Restaging

PET is not recommended for routine surveillance in patients with colorectal cancer treated with curative surgery at high risk for recurrence.
PET is recommended to determine the site of recurrence in the setting of rising carcinoembryonic antigen **(CEA) when a conventional workup fails to unequivocally identify metastatic disease.**

HTA review (1) : One systematic review with 13 primary studies and two additional primary studies showed that PET had a sensitivity for detecting recurrence of ≥ 85% and specificities varying from 43% to 90%. Accuracy and sensitivity were superior to CT and similar to MRI. Two studies noted that PET's ability to detect lesions < 1 cm was poor.

The update searches identified one RCT (Sobhani et al, 2008 [18]), which evaluated the role of PET in surveillance of colorectal cancer in patients who underwent curative surgery and were at high risk for recurrence. Overall, there was no difference in recurrence rate with the addition of PET to conventional workup, but there was a significant improvement in the time to detection of recurrence and in the numbers of patients treated with potentially curative surgery. The small sample size (n=130) precludes definitive conclusions on the role of PET as part of surveillance in colorectal cancer.

Qualifying Statements

None.

Liver Metastasis

PET is recommended in the preoperative assessment of colorectal cancer liver metastasis prior to surgical resection.

HTA review (1): One systematic review with nine primary studies and five additional studies in primary and recurrent populations showed PET to be more accurate than comparators for the detection of liver metastases. Furthermore, in 15 studies of mixed populations, including patients with suspected recurrence, PET sensitivity was about 90% compared with 73% sensitivity for CT. PET specificity was ≥ 85%. The change in management attributed to PET (compared with conventional imaging) varied from 9% to 39% in reported trials. Two studies noted that 6% and 15%, respectively, had the staging incorrectly changed.

The update searches identified one prospective randomized study (Ruers et al, 2009 [19]) that considered 150 patients with colorectal cancer liver metastasis eligible for potentially curative surgery suggested a significant decrease in futile laparotomy (45% versus [vs.] 28%) when 18-fluoro-deoxyglucose (FDG) PET was added to the preoperative imaging strategy and seven studies (Rappeport et al, 2007 [20], Huguet et al, 2007 [21], Lubezky et al, 2007 [22], Adie et al [23], Liu et al [24], Kitajima et al [25], and Potter et al [26]) that supported the recommendation. Rappeport et al (20) showed that CT and MRI were more sensitive but less specific than PET/CT in the detection of liver metastases. However, PET/CT was more sensitive and specific for the detection of extrahepatic metastasis than CT alone. In Huguet et al (21), PET had a higher sensitivity than did CT for hepatic, pulmonary, and extrahepatic/extrapulmonary sites. Clinical management was changed in nine of 31 patients (29%), and the change was attributed to the results of PET. Adie et al (23) suggested preoperative assessment with PET/CT is not useful for hepatic colorectal metastases, particularly when preoperative chemotherapy is used, with a trend towards the underestimation of lesions. Liu et al (24) supported the superiority of PET/CT over contrast-enhanced CT for the detection of metastatic lesions of colorectal cancer. Kitajima et al (25) showed that integrated PET/contrasted-enhanced CT is an accurate modality for assessing colorectal cancer recurrence, with results that led to changes in the subsequent therapy. Potter et al (26) recommended serial imaging review, with a careful correlation of suspicious findings with previous studies in any suspected recurrence. Therefore, PET/CT was suggested as useful tool when findings remain equivocal after a serial imaging review for colorectal cancer.

Qualifying Statements

- Despite the change in management reported in these nonrandomized studies, the possibility cannot be ruled out that factors other than PET results were involved in that change (Facey et al [1]).
- In the evaluation of patients potentially eligible for the curative resection of colorectal cancer liver metastasis, a diagnostic CT is necessary in addition to PET/CT to provide information on hepatic vasculature and anatomy (Facey et al [1]).
- The sensitivity of PET for detecting metastases decreases following neoadjuvant chemotherapy in patients with colorectal cancer liver metastasis (Lubezky et al [22]). PET is less sensitive than CT for detecting metastases following neoadjuvant chemotherapy. If PET is to be used for staging purposes, it should be performed before and after neoadjuvant chemotherapy.

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QUESTIONS

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- 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 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 September 19, 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 November 25, 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 two clinical lead authors,

nominated by the PEBC 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 PEBC GI DSG. The draft recommendations were refined during a DSG teleconference. The GI DSG is comprised of medical and radiation oncologists and surgeons and is 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 (HTA) 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 such a review. The United Kingdom (U.K.) HTA systematic review (1) (referred to as the HTA review from this point forward) evaluated the effectiveness of FDG PET imaging in several selected cancers, including colorectal. 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 the 2005 to 2008 search and Appendices 3 and 4 for the 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 the 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 were that the review:

- was 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 that the study:

- was a prospective clinical study of dedicated FDG PET in a single cancer of interest;

- was published after the search date of a robust systematic review covering that cancer management decision;
- was published as a full article in a peer-reviewed journal;
- reported evidence related to diagnostic accuracy, change in patient management, or clinical outcomes;
- included ≥ 12 patients with the cancer of interest;
- 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, marked as relevant or not relevant, according to the inclusion criteria from the HTA review, and 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 a final decision on their 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 for update searches from August 2005 to May 2010. Full text and data extractions of the studies from the update searches were provided to the clinical lead authors to aid in the formulation of the recommendations. Telephone conferences and email correspondence between the clinical leads and the PEBC methodologist took place to clarify details and answer questions.

CONSENSUS

DSG Consensus Process

The clinical lead authors 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. Due to the special interest of the GI DSG, a recommendation was also drafted pertaining to the use of PET in colorectal cancer liver metastasis. 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 September 19, 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 colorectal table held the two clinical leads 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 leads and refined and confirmed by the GI DSG were presented by the clinical leads to the group at the colorectal table.
- During small-group discussion at the colorectal 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 colorectal cancer included three systematic reviews and 24 primary studies. The 2005 to 2008 update included six systematic reviews and 19 primary studies. The more recent 2008 to 2010 update included three systematic reviews and nine primary studies.

Data extracted from the systematic reviews and primary studies in the HTA review (1) are available on the HTA website (pages 108-130). Data extracted from the primary studies from the updated search are in Appendices 5 and 6. None of the systematic reviews from the updated search provided any additional evidence to those from the primary studies. Only the key evidence identified from the primary studies is described below, in an abbreviated fashion. References to the nine systematic reviews can be found towards the end of the reference list.

Key Evidence

Diagnosis/Staging

Diagnosis

PET: One systematic review of two primary studies and one additional primary study in the HTA review 2007 (1) summarized that PET has good sensitivity to detect primary tumours > 2 cm, but not smaller tumours, with variable specificity. No additional studies were identified in the 2005-2008 update search.

PET/CT: No studies of PET/CT for diagnosis were identified.

Staging

PET: Two primary studies in the HTA review (1), and four studies from the update searches (Furukawa et al [2], Llamas-Elvira et al [3], Nahas et al [4], and Kosugi et al [5]) were identified. These studies had different patient case-mixes and proportions of patients with stage IV disease. While some studies showed changes in patient management because of changes in M-staging, such findings were in studies with a relatively large proportion of stage IV disease. Furukawa et al (2) and Nahas et al (4) did not show any significant changes in M-staging. Kosugi et al (5) included 53 patients with lymph node metastases on CT. PET detected 24 para-aortic and 29 epicolic, paracolic, or intermediate lymph nodes. The results of Kosugi et al (5) showed that PET has a lower sensitivity, higher specificity, higher accuracy and higher PPV than CT for N1 and N2-3 lymph nodes. For N4 lymph node, PET has a high sensitivity and high specificity, while CT has only a high sensitivity, with low specificity and PPV. Thus, it is reasonable to consider using PET when N4 nodes are suspected.

PET/CT: The HTA review did not identify any studies that involved the use of PET/CT exclusively for staging prior to any therapy. The 2005-2008 update search identified five studies (Veit-Haibach 2006 [6], Park 2006 [7], Kinner 2007 [8], Tsunoda 2008 [9], and

Orlacchio et al [10]). Park et al, 2006 (8) included only patients with equivocal CT findings or elevated CEA, which resulted in 49% stage IV patients. PET/CT changed management in 24% of those. Tsunoda et al, 2008 (10) evaluated the detection rate of PET/CT with respect to nodal metastasis (proximal and distal). PET/CT had better performance than CT overall. Given the small proportion of patients with distant nodal metastasis plus the fact that the study did not separately compare PET/CT and CT with respect to distant nodal metastasis only, it is difficult to know whether distant nodal M-staging is changed significantly with the use of PET/CT. Veit-Haibach et al, 2006 (7) and Kinner et al, 2007 (9) did not show a significant change in M-staging. In Orlacchio et al (10), which included 467 patients, there was concordance among PET, CT, and PET/CT in 91.2% of the cases. Seventy-two percent (72%) of the cases were true positive for liver metastases, suggesting the patients in the study had a higher index of suspicion for liver metastases than might be expected in the routine clinical setting. The study provided formal statistical Z test comparison which showed that PET/CT is better than PET alone or CT alone with p-values < 0.05. The sensitivity and specificity were all greater than 90% in CT, PET, and PET/CT.

Assessment of Treatment Response

PET: The update searches identified a randomized control trial (Bystrom et al [11]) that evaluated PET before and after 2 cycles of chemotherapy and also evaluated CT before and after 4 cycles of chemotherapy. The results showed that PET correlated with CT and has a relatively low sensitivity and specificity. PET also failed to predict the time to progression or overall survival in patients with metastatic colorectal cancer. The study suggested that PET should not be used to substitute CT for short-term response and should not be used as a surrogate for long-term clinical endpoints. The HTA review identified six non-randomized studies showing that changes in standardized uptake values (SUV) between pretherapy and posttherapy scans may predict response. The update searches identified four additional primary studies evaluating treatment response. Cascini et al, 2006 (12) included patients receiving PET before and 12 days after the initiation of preoperative therapy and supported the finding of the HTA review that changes in SUV may predict response. However, one-time PET after preoperative therapy poorly predicted complete pathologic response after preoperative therapy in Capirci et al [13] and Kalff et al [14] and poorly predicted posttherapy staging in Capirci et al [12]). Glazer et al [15] conducted a prospective cohort study of 138 patients with a presumptive diagnosis of liver metastasis that had at least one PET scan after chemotherapy and before liver resection. The study showed that ultrasonography also guides surgical decision during intraoperative assessment and suggested PET after chemotherapy should not be used in decision making for liver resection.

PET/CT: The HTA review did not have any studies of PET/CT in predicting treatment response. The update searches identified two studies (Capirci et al, [16], Kristiansen et al, [17]). Capirci et al, (16) suggested that the change in SUV before and after preoperative chemoradiotherapy predicted the tumour regression grade (TRG) in rectal cancer, while Kristiansen et al (17) suggested a single PET/CT after preoperative therapy poorly predicted for complete pathologic response.

Recurrence/Restaging

HTA review (1): One systematic review with 13 primary studies and two additional primary studies showed that PET had sensitivity for detecting recurrence of ≥ 85% and specificities varying from 43% to 90%. Accuracy and sensitivity were superior to CT and similar to MRI. Two studies noted that PET's ability to detect lesions < 1 cm was poor.

The update searches identified one RCT (Sobhani et al, 2008 [18]) that evaluated the role of PET in the surveillance of colorectal cancer in patients who underwent curative surgery and were at a high risk for recurrence. Overall, there was no difference in recurrence

rate with the addition of PET to the conventional workup, but there was a significant improvement in the time to detection of recurrence and in the numbers of patients treated with potentially curative surgery. The small sample size (n=130) precludes definitive conclusions on the role of PET as a part of surveillance in colorectal cancer.

Liver Metastasis

HTA review (1): One systematic review with nine primary studies and five additional studies in primary and recurrent populations showed PET to be more accurate than comparators for the detection of liver metastases. Furthermore, in 15 studies of mixed populations, including patients with suspected recurrence, PET sensitivity was about 90% compared with 73% sensitivity for CT. PET specificity was ≥ 85%. The change in management attributed to PET (compared with conventional imaging) varied from 9% to 39% in reported trials. Two studies noted that 6% and 15%, respectively, had staging incorrectly changed.

The update searches identified one prospective randomized study (Ruers et al [19]) that considered 150 patients with colorectal cancer liver metastasis eligible for potentially curative surgery. That study suggested a significant decrease in futile laparotomy (45% vs. 28%) when FDG PET was added to the preoperative imaging strategy and eight studies (Rappeport et al, 2007 [20], Huguet et al, 2007 [21], Lubezky et al, 2007 [22], Adie et al [23], Liu et al [24], Kitajima et al [25], and Potter et al [26]) that supported the recommendation. Rappeport et al (20) showed that CT and MRI were more sensitive but less specific than PET/CT in the detection of liver metastases. However, PET/CT was more sensitive and specific for the detection of extrahepatic metastasis than was CT alone. In Huguet et al (21), PET had a higher sensitivity than did CT for hepatic, pulmonary, and extrahepatic/extrapulmonary sites. Clinical management was changed in nine of 31 patients (29%), a change that was attributed to the results of PET. Adie et al (23) suggested that preoperative assessment with PET/CT is not useful for hepatic colorectal metastases, particularly when preoperative chemotherapy is used, with a trend towards the underestimation of lesions. Liu et al (24) supported the superiority of PET/CT over contrast-enhanced CT for the detection of colorectal cancer metastatic lesions. Kitajima et al (25) showed that integrated PET/contrasted-enhanced CT is an accurate modality for assessing colorectal cancer recurrence, which led to changes in the subsequent therapy. Potter et al (26) recommended serial imaging review with the careful correlation of suspicious findings with previous studies in suspected recurrence, which suggested PET/CT as a useful tool when findings remain equivocal after a serial imaging review for colorectal cancer.

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

DRAFT DSG Recommendation

The routine use of PET or PET/CT is not indicated for the diagnosis or staging of clinical stage I-III colorectal cancers.

Provincial Consensus Meeting Deliberations

While there was agreement in principle with this recommendation, there was debate in the small-group discussion and again in the large-group discussion around putting forward a recommendation for PET in the initial assessment of rectal cancer to determine N stage for consideration of neoadjuvant locoregional chemoradiation. However, it was agreed instead to include this as an area for future research. In the small group, and confirmed in the large group discussion, the suggestion was to include a second recommendation regarding a role for PET in determining management and prognosis of patients if conventional imaging is equivocal for the presence of metastatic disease.

Recommendations Put to Vote

a) The routine use of PET is not indicated for the diagnosis or staging of clinical stage I-III colorectal cancers.

	1 – Strongly Agree			5 – Neither Agree nor Disagree				9 – Strongly Disagree		N/A
	1	2	3	4	5	6	7	8	9	
Total	10	6	1		1					

Votes = 18 (1 participant did not vote)

b) If conventional imaging is equivocal for the presence of metastatic disease, PET is recommended for determining management and prognosis.

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

Votes = 19
Issues raised on voting questionnaires:
-Need to clarify "presence of metastatic disease."

FINAL RECOMMENDATION

a. The routine use of PET is not recommended for the diagnosis or staging of clinical stage I-III colorectal cancers.
b. PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease.

Qualifying Statements

- Some studies evaluated the diagnostic performance of PET or PET/CT with respect to each metastatic site/organ/lesion, while some evaluated it with respect to the M-staging of each patient. It would appear that studies that analyzed results based on each

site/organ/lesion showed a better performance of PET or PET/CT, while studies that analyzed results based on the overall M-staging of patients did not show an obvious improvement in the performance of PET or PET/CT. As solitary or oligo-metastasis is not a very common presentation in the initial diagnosis of colorectal cancer, it would be unlikely that PET or PET/CT would detect such a situation, when CT missed it, if the objective was to change M-staging and management of these patients. However, in patients who already have suspicious or confirmed metastasis based on CT, it is quite possible that PET or PET/CT could detect further metastases in other sites/organs that were not conclusively detected by CT alone. This will inflate the diagnostic performance of PET or PET/CT if analysis was based on sites/organs/lesions instead of overall M-staging of each patient. This factor may be important when making recommendations for early-stage disease versus metastatic disease.

- On the other hand, for patients who already have what appears to be solitary or oligo-metastases on CT only and are potential candidates for resection, and given that the possibility of further metastasis in other sites/organs is not low, PET or PET/CT may assist in the decision making of resection with curative intent by helping to assess the extent of metastasis. Studies that analyzed the diagnostic performance of PET or PET/CT with respect to sites/organs/lesions provided evidence to support this approach. Therefore, there may be a role for the use of PET or PET/CT when conventional imaging raises suspicion of the presence of potentially resectable metastatic disease, and patients are potential candidates to undergo such surgery. The incremental benefit of PET or PET/CT over MRI of the liver is unclear in such populations as none of the studies included the routine use of MRI as part of conventional imaging.
- Most studies that showed PET or PET/CT changed the management of a significant proportion of patients included a relatively large number with stage IV disease (up to 46% of patients). Studies that included a relatively small proportion of stage IV patients did not appear to show a significant benefit or change in the patient management plan with PET or PET/CT. Some of those changes in management involved the detection of a larger than expected volume of disease in the liver or extrahepatic metastasis by PET or PET/CT in patients originally diagnosed with low-volume resectable liver metastasis by conventional imaging.
- Most studies that compared PET or PET/CT with conventional imaging were done in the time period when multidetector CT (MDCT) was not yet widely available. The only study (Furukawa et al, 2006 [3]) that clearly stated that MDCT was used did not show clinically relevant superiority of PET in addition to MDCT. As MDCT is being used routinely in most of the cancer centres and hospitals in Ontario, the incremental benefit of PET or PET/CT for the routine staging of colorectal cancers remains to be established.
- While some studies reported the numerical comparisons of diagnostic performance between PET, or PET/CT, and conventional imaging, few studies tested whether the numerical differences observed were statistically significant or not.
- It is unclear whether PET or PET/CT leads to improvement in survival or simply results in stage migration. Nonetheless, many practitioners may accept that more accurate staging will lead to a better choice of treatment plan, thereby avoiding overtreatment and sparing patients the unnecessary risk or side effects of therapy or avoiding undertreatment when patients might otherwise.
- There are very few studies that evaluated rectal cancer and colon cancer separately. The current limited evidence did not obviously suggest or refute that PET or PET/CT significantly changed management in patients with non-metastatic rectal cancer. However, some studies seemed to suggest that PET or PET/CT has better N-stage accuracy than CT. It is unclear how PET or PET/CT compares with MRI or TRUS with respect to N-

staging. There may be a role of PET/CT with respect to N-staging in the decision making for patients with non-metastatic rectal cancer who may be candidates for preoperative chemoradiotherapy.

- When conventional imaging with CT suggests equivocal para-aortic lymph node involvement as the only potential site of concern and that the patient is otherwise a potential candidate for curative intent surgery of the primary colorectal cancer, PET can be considered to rule in or out metastatic disease in the para-aortic region.

ASSESSMENT OF TREATMENT RESPONSE

Clinical Question

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

DRAFT DSG Recommendation

The routine use of PET or PET/CT in locally advanced rectal cancer before and after preoperative chemoradiotherapy is not indicated.

Provincial Consensus Meeting Deliberations

The extent of agreement with this recommendation was fairly strong, and no major issues were raised during the small or large group discussion.

Recommendation Put to Vote

The routine use of PET/CT in locally advanced rectal cancer before and after preoperative chemoradiotherapy to measure treatment response is not indicated.

	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	3							

Votes = 19

Issues raised on voting questionnaires:

-May need a trial.

FINAL RECOMMENDATION

The routine use of PET is not recommended to measure treatment response in locally advanced rectal cancer before and after preoperative chemoradiotherapy.

Qualifying statements

None.

RECURRENCE/RESTAGING

Clinical Question

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

DRAFT DSG Recommendations

a. PET is not indicated for routine surveillance in patients with colorectal cancer treated with curative surgery at high risk for recurrence.

b. PET is recommended to determine the site of recurrence in the setting of rising CEA or suspicious symptoms when conventional workup fails to unequivocally identify metastatic disease.

Provincial Consensus Meeting Deliberations

The extent of agreement with these recommendations was fairly strong. The suggestion was made to remove "suspicious symptoms" from b.

Recommendations Put to Vote

a. PET is not indicated for routine surveillance in patients with colorectal cancer treated with curative surgery at high risk for recurrence.

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

Votes = 18 (1 participant did not vote)

a. PET is recommended to determine site of recurrence in the setting of rising CEA when conventional workup fails to unequivocally identify metastatic disease.

	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	1	2						

Votes = 19

Issues raised on voting questionnaires:

-I am concerned with the nonspecificity of this statement.

FINAL RECOMMENDATION

a. PET is not recommended for routine surveillance in patients with colorectal cancer treated with curative surgery at high risk for recurrence.
b. PET is recommended to determine site of recurrence in the setting of rising CEA when conventional workup fails to unequivocally identify metastatic disease.

Qualifying Statements

None.

LIVER METASTASIS

DRAFT DSG Recommendation

PET is indicated in the preoperative assessment prior to surgical resection of colorectal cancer liver metastasis.

Provincial Consensus Meeting Deliberations

There was discussion about an ongoing RCT (PETCAM) on this topic, because this recommendation could affect accrual. The possibility of evidence to support the use of PET for this indication might be an ethical reason to end the trial. The suggestion was made that the safety monitoring board of the trial should be consulted.

Recommendation Put to Vote

PET is indicated in the preoperative assessment prior to surgical resection of colorectal cancer liver metastasis.

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

Votes = 18 (1 participant did not vote)

Issues raised on voting questionnaires:

-Get PETCAM results. Recommend by the disease management committee.

-We should not jeopardize the RCT. Recommend referring this to trial DSMB.

-Ask Data and Safety Monitoring Board (DSMB) to review.

FINAL RECOMMENDATION

PET is recommended in the preoperative assessment of colorectal cancer liver metastasis prior to surgical resection.

Qualifying Statement

- Despite the change in management reported in these nonrandomized studies, the possibility cannot be ruled out that factors other than PET results were involved in the change in management (HTA 2007 [1]).
- In the evaluation of patients potentially eligible for curative resection of colorectal cancer liver metastasis, a diagnostic CT is necessary in addition to PET/CT to provide information on hepatic vasculature and anatomy (HTA 2007 [1]).
- The sensitivity of PET for detecting metastases decreases following neoadjuvant chemotherapy in patients with colorectal cancer liver metastasis (Lubezky 2007 [22]). PET is less sensitive than CT for detecting metastases following neoadjuvant chemotherapy. If PET is to be used for staging purposes, it should be performed before and after neoadjuvant chemotherapy.

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.

RECENT UPDATE SEARCH

The same approach applied for the 2005 to 2008 search was used for data extraction for the evidence from the recent update search conducted June 2008 to May 2010. Full-text and data extractions of the studies from the update search were sent to the clinical lead authors to review the new evidence. The clinical lead authors concluded that the new evidence did not necessitate any alteration to the previous recommendations and that the only change needed was an additional qualifying statement regarding diagnosis and staging.

FUTURE RESEARCH

An initial draft recommendation regarding the use of PET in the diagnosis and staging of colorectal cancer stated that there may be a role for PET in the initial assessment of rectal cancer to determine N stage in the setting of clinical decision making that included

consideration of neoadjuvant locoregional chemoradiation. Due to a lack of evidence on this topic, the consensus was to refrain from making a recommendation and to consider it for future research.

JOURNAL REFERENCE

The following guideline recommendations article has been published by *Clinical Oncology* (© 2011 The Royal College of Radiologists. Published by Elsevier Ltd.):

- Chan K, Welch S, Walker-Dilks C, Raifu A. Evidence-based guideline recommendations on the use of positron emission tomography imaging in colorectal cancer. Clin Oncol (R Coll Radiol). doi:10.1016/j.clon.2011.11.008. Epub 2011 Dec 20.

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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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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 colorectal cancer: summary of the primary study evidence from 2005 to 2008.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Key Results (see full data extractions for additional details)	Conclusions
Diagnosis/Staging								
Veit-Haibach, 2006 (6)	To evaluate the diagnostic accuracy of PET/CT in staging CRC compared with CT alone and CT followed by PET	47	PET/CT from skull to upper thigh	Histopathology or clinical follow-up (M1 pts)	CT alone CT followed by PET	All participating physicians blinded to other imaging results, colonoscopy, and histopathology	PET/CT (see data extraction forms for CT and CT+PET results): Tumour detection: Sens=98%, Spec=75%, PPV=98%, NPV=75% N stage: Sens=80%, Spec=97%, PPV=94%, NPV=88% M stage: Sens=100%, Spec=100%, PPV=100%, NPV=100%	PET/CT is at least equivalent to CT followed by PET for tumour staging.
Park, 2006 (7)	To assess the use of PET/CT in evaluation of primary CRC and evaluate impact on changes to treatment plan	100	PET/CT from head to abdomen	Histopathology and clinical follow-up	CT	NR	Identification of metastatic disease: 13 true negative, 10 false positive or false negative PET/CT results changed treatment modality in 9 pts: 8 true positive, 1 false negative. PET/CT changed extent of surgery in 18 pts. In 10 pts with increased operative intent: 8 true positive, 2 false positive. In 8 pts in whom unnecessary procedure prevented: all 8 true positive.	PET appears to accurately change tumour stage in one-third of patients and alter therapy in about one-fifth.
Furukawa, 2006 (2	To evaluate the additional value of PET as a staging modality complementary to routine CT	44	FDG PET from skull base to groin	Histopathology	CT and macroscopic diagnosis	PET interpretation blinded to pts' medical history and CT. Pathologists blinded to preoperative PET and CT.	Tumour detection rate: 100% for PET, 95% for CT, 100% for macroscopic diagnosis. N stage (PET): Sens=37%, Spec=83%, PPV=70%, NPV=43%, Accuracy=59% N stage (CT): Sens=58%, Spec=67%, PPV=65%, NPV=60%, Accuracy=62%	PET is not superior to routine CT in the initial staging of primary CRC.
Llamas-Elvira, 2007 (3)	To evaluate PET in initial staging compared with conventional staging methods	104	FDG PET	Histopathology or clinical follow-up	CT	PET and CT interpretation blinded to other imaging results	N stage: Sens=21%, Spec=95%, PPV=83%, NPV=51%, Accuracy=56% M stage: Sens=89%, Spec=93%, PPV=73%, NPV=98%, Accuracy=92% PET changed tumour staging in 13.46% of pts, modified scope of surgery in 11.54%, and led to change in therapeutic approach in 17.85%.	PET appears to be useful in pre-surgical staging compared with conventional techniques.
Kinner, 2007 (8)	To assess PET/CT for staging CRC	55	PET/CT from skull base to upper thighs	Histopathology	CT	NR	PET/CT: TNM staging accuracy=74%, T stage accuracy=84%, N-stage accuracy=82% CT: TNM staging accuracy=44%, T stage accuracy=70%, N-stage accuracy=68% PET/CT significantly more accurate than CT.	Staging patients with PET/CT is feasible, has accurate tumour detection rates and shows promising staging results.
Tsunoda, 2008 (9)	To assess the diagnostic value of PET/CT for lymph node metastases of CRC	88	FDG PET/CT from skull base to pelvic floor	Histopathology	None	PET interpretation blinded to clinical information	Visual diagnosis: Sens=28.6%, Spec=92.9%, Accuracy=75.0% Size diagnosis (cutpoint 10mm): Sens=30.6%, Spec=95.3%, Accuracy=74.4% SUV diagnosis (cutpoint 1.5): Sens=53.1%, Spec=90.6%, Accuracy 80.1%	PET is useful for detection of distant lymph node metastases. SUV is a better diagnostic criterion than abnormal FDG uptake or nodal diameter.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Key Results (see full data extractions for additional details)	Conclusions
Nahas, 2008 (4)	To determine the accuracy of PET in detecting distant disease in pts otherwise eligible for neoadjuvant CRT	93	FDG PET	Surgical exploration, clinical follow-up, imaging, or histopathology	CT for pre-CRT stage IV pts	PET interpretation blinded to clinical information but not CT images	Pre-CRT PET: Distant metastases: Sens=78%, Spec=99%, PPV=56%, NPV=100%, Accuracy=94% Liver: Sens=100%, Spec=99%, PPV=88%, NPV=100%, Accuracy=100% Lung: Sens=80%, Spec=100%, PPV=100%, NPV=99%, Accuracy=100% Post-CRT PET: Distant metastases: Sens=39%, Spec=100%, PPV=88%, NPV=99%, Accuracy=77% Liver: Sens=71%, Spec=100%, PPV=100%, NPV=98%, Accuracy=85% Lung: Sens=40%, Spec=99%, PPV=67%, NPV=97%, Accuracy=89%	Baseline PET can reliably detect metastatic disease in liver and lung.
Treatment Response								
Cascini, 2006 (12)	To monitor PET findings during neoadjuvant CRT and correlate SUV changes and pathologic response	33	FDG PET before and 12 days after initiation of CRT	Histopathology	None	Pathologist blinded to clinical and PET findings	The cutpoint value of mean decrease in SUV ≥52% yielded Sens. And Spec. of 100%. Significant correlation between pathologic tumour regression grade and early SUV changes ($p<0.0001$).	Early PET can predict pathologic response to neoadjuvant CRT.
Capirci, 2006 (13)	To assess prognostic value of PET performed at restaging following neoadjuvant CRT	88	FDG PET 6-7wks after neoadjuvant CRT	Histopathology	None	NR	Prediction of downstaging after CRT: Sens=61%, Spec=74%, Accuracy=70%	Prediction of downstaging by post-CRT PET was not absolute but PET in combination with pathologic evaluation can identify a subgroup of pts with more favourable prognosis.
Kalff, 2006 (14)	To determine the prognostic value of degree of change in tumour on PET induced by neoadjuvant CRT	34	FDG PET before and after neoadjuvant CRT	Histopathology	None	NR	PET indicated complete response in 17 of 30 pts but only 5 of these pts had pathological absence of tumour. PET response was significantly associated with OS and PFS ($p<0.0001$).	Complete response with PET does not indicate complete pathologic response in most cases. Qualitative analysis of PET can provide prognostic information.
Capirci, 2007 (16)	To evaluate sequential PET/CT compared with conventional imaging to predict response to neoadjuvant CRT	48	FDG PET/CT from skull to upper legs	Histopathology	None	PET/CT interpretation blinded to histopathologic analysis	Using SUV max decrease cutpoint of 66.2%: Sens=81%, Spec=79%, PPV=77%, NPV=89%, Accuracy=80%	PET is potentially useful as complementary diagnostic and prognostic procedure to assess treatment response. Suggest reserving for prospective controlled studies at this stage of clinical research.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Key Results (see full data extractions for additional details)	Conclusions
Kristiansen 2008 (17)	To investigate the ability of PET/CT to predict pathologic response to neoadjuvant CRT	30	FDG PET/CT from skull base to proximal thigh	Histopathology	None	Pathologist blinded to PET/CT results	Sens=45%, Spec=75%, PPV=83%, NPV=33%, Accuracy=53%	PET/CT performed 7 wks after completion of CRT cannot predict complete pathologic response or extent of residual disease.
Recurrence								
Sarikaya, 2007 (27)	To evaluate PET and intraoperative gamma probe for detection of suspected recurrent CRC	21	FDG PET/CT, scull base to proximal femoral region	Histopathology	Intra-operative gamma probe	NR	PET: Sens=84%, Spec=31% Intraoperative gamma probe: Sens=95%, Spec 38%	PET and intraoperative gamma probe potentially helpful to locate and determine extent of tumour recurrence. Intraoperative gamma probe more sensitive in detecting extent of abdominal and pelvic recurrence but PET more sensitive in detecting liver metastases.
Sobhani, 2008 (18)	To assess the contribution of systematic PET to the detection and treatment of CRC recurrence following curative surgery in pts at high risk of recurrence	130	FDG PET 9 and 15 mos after surgery, plus conventional workup	Histopathology, clinical follow-up	Conventional workup	PET interpretation blinded to CT, but not patient history or other conventional workup findings	Time from baseline until detection of recurrence shorter with PET than conventional work-up alone (12.1 vs. 15.4 mos; p=0.01) PET: Sens=96%, Spec=92%, PPV=89%, NPV=97% Conventional work-up alone: Sens=91%, Spec=93%, PPV=88.6%, NPV=95%	Regular PET monitoring may lead to earlier detection of recurrence and influence treatment strategies.
Liver metastases								
Denecke, 2007 (28)	To evaluate PET for the assessment of local control and systemic disease in pts with suspected tumour progression after laser-induced thermotherapy of CRC liver metastases	21	FDG PET from skull to upper legs	Histopathology Imaging Clinical follow-up	None	PET interpretation blinded to other imaging methods and clinical information	PET detection of residual tumour: Visual diagnosis (overall, including immediate, short-term, and long-term follow-up): Sens=97%, Spec=96%, PPV=97%, NPV=96%, Accuracy=96% T/N, SUVmax: Sens=97%, Spec=92%, PPV=93%, NPV=96%, Accuracy=94%	PET is a reliable tool for the evaluation of local control and detection of unexpected extrahepatic disease in pts with suspected recurrence after laser-induced thermotherapy of CRC liver metastases.

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Key Results (see full data extractions for additional details)	Conclusions
Rappeport, 2007 (20)	To compare PET/CT, MRI, PET, and CT in the detection of liver metastases and extrahepatic tumour	35	PET/CT	Ultrasound morphology or histopathology	MRI CT PET alone	Interpretation blinded to results of other imaging studies	Detection of liver metastases (analysis by lesion): PET/CT: Sens=66%, Spec=99%, PPV=98%, NPV=76%, Accuracy=83% CT: Sens=89%, Spec=67%, PPV=72%, NPV=86%, Accuracy=77% PET: Sens=54%, Spec=99%, PPV=97%, NPV=69%, Accuracy=77% MRI: Sens=82%, Spec=81%, PPV=81%, NPV=82%, Accuracy=82% Detection of extrahepatic tumour (analysis by patient): PET/CT: Sens=84%, Spec=96% CT: Sens=59%, Spec=87%	CT and MRI are more sensitive but less specific than PET in detection of liver metastases. PET/CT detected more patients with extrahepatic tumour than CT alone.
Lubezky, 2007 (22)	To examine the effect of neoadjuvant chemotherapy for CRC liver metastases on CT and PET/CT findings and to determine the role of these imaging modalities	75	PET/CT from head to pelvic floor	Histopathology	CT	NR	Identification of liver metastases in pts without neoadjuvant chemotherapy (n=27): PET: Sens=93.3% CT: Sens=87.5% Identification of liver metastases in pts with neoadjuvant chemotherapy (n=48): PET: Sens=49%, Spec=83,3% CT: Sens=65.3%, Spec=75%	Sensitivity of PET in detecting liver metastases decreases following neoadjuvant chemotherapy. Pts should be staged with PET/CT before and after neoadjuvant therapy. CT is more sensitive than PET in detecting metastases following neoadjuvant therapy.
Wiering, 2007 (29)	To evaluate the accuracy of preoperative and intraoperative PET and CT imaging of pts with CRC liver metastases	131	FDG PET	Histopathology Intraoperative ultrasound as backup	CT	NR	PET and CT missed most lesions smaller than 10 mm and 25% of lesions between 10 and 20 mm. PET: Sens=98%, Spec=100% CT: Sens=99%, Spec=0% (0/3) Extrahepatic intra-abdominal disease was found in 10 pts. PET missed 4 pts and CT missed 8 pts.	CT and PET have a similar diagnostic yield for identification of liver metastases but both are inadequate to detect small lesions. Frequency of unexpected findings at laparotomy is relatively low when using CT and PET in the preoperative work-up.
Huguet, 2007 (21)	To evaluate FDG PET in patients being considered for resection of colorectal liver metastases and whether PET alters treatment management	31	FDG PET	Surgical exploration, histopathology Clinical radiological follow-up	CT	NR	PET Sens: liver mets=96%, pulmonary mets=100% extrapulmonary/extrahepatic=100% CT Sens: liver mets=70% pulmonary=83% extrapulmonary/extrahepatic=20% PET results altered clinical management in 9 patients (29%)	FDG PET offers higher sensitivity than CT in the detection of colorectal cancer secondary deposits and has a major influence on the selection of patients for resection of colorectal liver metastases.

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

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

Author, year	Objective	# of pts	PET	Reference Test	Comparison Test	Blinding	Key Results (see full data extractions for additional details)	Conclusions
Diagnosis/Staging								
Kosugi et al, 2008 (5)	To evaluate the impact of FDG PET for the preoperative detection of lymph node (LN) metastasis and associated locations, in patients with diagnosed locally advanced and/or para-aortic LN metastatic colorectal adenocarcinoma, as determined by CT findings, compared with pathologic and CT findings.	53	FDG PET from upper portion of the abdomen to pelvis	Histopathology	CT	Radiologists were blinded of the clinical findings	PET primary tumours and lymph node metastasis: N1: Sens=52.2%, Spec=87.5%, Accuracy=70.2%, PPV=80.0%, NPV=65.6% N2-3: Sens=75.0%%, Spec=94.4%, Accuracy=89.6%, PPV=81.1%, NPV=91.9% N4: Sens=100.0%, Spec=100.0%, Accuracy=100.0%, PPV=100.0%, NPV=100.0% CT primary tumours and lymph node metastasis: N1: Sens=91.3%, Spec=41.6%, Accuracy=65.9%, PPV=60.0%, NPV=83.3% N2-3: Sens=91.7%%, Spec=72.2%, Accuracy=77.1%, PPV=52.3%, NPV=96.3% N4: Sens=100.0%, Spec=17.6%, Accuracy=41.7%, PPV=33.3%, NPV=100.0%	While FDG PET is markedly more sensitive than CT for detection of N4 LN involvement, the number of metastatic LNs is difficult to determine.
Orlacchio et al, 2009 (10)	The aim of this study was to compare the diagnostic accuracy of 2-[fluorine-18] fluoro-2-deoxy-Dglucose positron emission tomography (18F-FDG PET) and computed tomography (CT) with PET/CT in the detection of liver metastases during tumour staging in patients suffering from colorectal carcinoma for the purposes of correct surgical planning and follow-up.	467	FDG PET	Histopathology or clinical follow-up	CT and FDG PET	Radiologist and nuclear physician were double blinded	PET: Sens=94.05% (95% CI: 91.52-96.58%), Spec=91.60% (95% CI: 86.85-96.35%), Accuracy=93.36% (95% CI: 91.10-95.62%), PPV=96.64% (95% CI: 94.69-98.59%), NPV= 85.71% (95% CI: 79.92-91.51%) CT: Sens=91.07% (95% CI: 88.90-94.12%), Spec=95.42% (95% CI: 91.84-99.00%), Accuracy=92.29% (95% CI: 89.87-94.71%), PPV= 98.08% (95% CI: 96.55-99.60%), NPV= 80.65% (95% CI: 74.43-86.86%) PET/CT: Sens=97.92% (95% CI: 96.39-99.44%), Spec=97.71% (95% CI: 95.15-100.00%), Accuracy=97.86% (95% CI: 96.55-99.17%), PPV= 99.10% (95% CI: 98.08-100.00%), NPV= 94.81% (95% CI: 91.07-98.56%)	This study indicates that PET/CT is very useful in staging and restaging patients suffering from colorectal cancer. It was particularly useful when recurrences could not be visualized either clinically or by imaging despite increasing tumour markers, as it guaranteed an earlier diagnosis. PET/CT not only provides high diagnostic performance in terms of sensitivity and specificity, enabling modification of patient treatment, but it is also a unique, high-profile procedure that can produce cost savings.
Ruers et al, 2009 (19)	To investigate the value of the addition of FDG PET to conventional CT-based diagnostic imaging in patients considered eligible for hepatic surgery of colorectal liver metastases.	150	Whole body FDG PET scanning	Histopathology or clinical follow-up	CT	NR	Significant proportion (45%) of patients in control group underwent futile laparotomy compared to 28% in the experimental group (p=0.042). Relative risk reduction was 38% (95% CI: 4-60%) with absolute difference of 17% means that 6 pts need to undergo FDG PET to avoid 1 futile laparotomy.	Preoperative FDG PET in patients with CRCLM considered respectable based on CT reduces the number of futile laparotomies due to unexpected unresectable disease. The finding of extrahepatic disease on PET and PET negative liver lesions should not be disregarded.

Treatment Response								
Bystrom et al, 2009 (11)	To evaluate FDG PET for early evaluation of response to palliative chemotherapy and for prediction of long-term outcome in patients with metastatic colorectal cancer (mCRC).	51	FDG PET including trunk and the neck	Histopathology or clinical follow-up	None	Pathologist blinded to clinical and PET findings	Radiological group: Mean baseline SUV for responders was 5.6 (95% CI: 4.4-6.8) compared with non-responders 7.4 (95% CI: 6.3-8.5) with p=0.02 PET group: Mean baseline SUV for responders was 6.1 (95% CI: 4.9-7.1) compared with 7.3 (95% CI: 6.1-8.5) with p=0.11 Follow-up and survival: Median follow-up time was 19 months. 1-year survival rates for PET responders were 78% and non-responders were 57%.	Although metabolic response assessed by FDG–PET reflects radiological tumour volume changes, the sensitivity and specificity are too low to support the routine use of PET in mCRC. Furthermore, PET failed to reflect long-term outcome and can, thus, not be used as surrogate end point for hard endpoint benefit.
Glazer et al, 2010 (15)	To determine the accuracy of PET scans to detect residual viable colorectal cancer liver after a significant response to systemic chemotherapy	138	FDG PET	Histopathology	None	NR	PET within 4 weeks of chemotherapy: Sens=89.9% (95% CI: 83.3-94.5%), Spec=22.2% (95% CI: 2.8-60.0%), PPV=94.3% (95% CI: 88.6-97.7%), NPV=13.3% (95% CI: 1.7-40.5%), Accuracy=85.5% (95% CI: 78.5-90.9)	Positron emission tomography within 4 weeks of chemotherapy is not a useful test for evaluation of colorectal hepatic metastases. The high rate of false-negative results is likely due to metabolic inhibition caused by chemotherapeutic drugs. We recommend that physicians not use PET in patients recently completing chemotherapy; they should undergo the appropriate oncologic hepatic operation based on the high probability of viable malignant disease.
Recurrence								
Kitajima et al, 2009 (25)	To evaluate the accuracy of integrated PET/CT using FDG with IV contrast for depiction of suspected recurrent colorectal cancer and to assess the impact of PET/contrast-enhanced CT findings on clinical management compared with PET/non-contrast-enhanced CT and CT component	170	Whole body FDG PET/CT scanning from meatus of the ear to the mid-thigh	Histopathology, radiological imaging, and clinical follow-up	CT	Radiologist were blinded of imaging results and other clinical data	Patient-based diagnostic results: CT alone: Sens=79.7% (95% CI: 70.5-88.9%), Spec=93.8% (95% CI: 89.0-98.6%), PPV=90.8% (95% CI: 83.8-97.8%), NPV=85.7% (95% CI: 78.8-92.7%), Accuracy=87.6% (82.7-92.6%) PET/non-contrast-enhanced CT: Sens=89.2% (95% CI: 82.1-96.3%), Spec=94.8% (95% CI: 90.4-99.2%), PPV=93.0% (95% CI: 87.1-98.9%), NPV=91.9% (95% CI: 86.5-97.3%), Accuracy=92.4% (88.4-96.4%) PET/contrast-enhanced CT: Sens=93.2% (95% CI: 87.5-98.9%), Spec=95.8% (95% CI: 91.8-99.8%), PPV=94.5% (95% CI: 89.3-99.7%), NPV=94.8% (95% CI: 90.4-99.2%), Accuracy=94.7% (91.3-98.1%) Change in Management: CT alone: 12/170 (7%) PET/contrast-enhanced CT: 64/170 (38%) PET/non-contrast-enhanced CT: 4/170 (2%)	Integrated PET/contrast-enhanced CT is an accurate modality for assessing colorectal cancer recurrence and led to changes in the subsequent therapy.

Potter et al, 2009 (26)	To examine the sensitivity and specificity of CT/magnetic imaging serial review compared to 18FDG PET/CT scanning to optimize colorectal cancer follow-up	50	FDG PET/CT	Histopathology, and clinical follow-up	CT/MRI	Radiologist were blinded to all imaging report	PET: Sens=83% to 87%, Spec=93% to 96%, Accuracy=88% to 92% CT/MRI: Sens=83%, Spec=89% to 100%, Accuracy=86% to 92%	With suspected recurrence, we recommend undertaking serial imaging review with careful correlation of suspicious findings with previous studies. 18FDG PET-CT imaging was useful when findings remain equivocal after serial imaging review for CRC recurrence.
Liver metastases								
Adie et al , 2009 (23)	To investigate FDG PET/CT as a preoperative planning tool for dissecting liver lesions in patients with and without preoperative chemotherapy.	74	FDG PET/CT	Histopathology	None	Nuclear medicine physicians were no blinded to prior patient imaging results	21 Pts with preoperative chemotherapy: Accurate scans in 6 pts (28.6%), False-negative scans in 11 pts (52.4%), False positive in 4 pts (19.0%) 53 Pts without preoperative chemotherapy: Accurate scans in 28 pts (52.8%), False-negative scans in 18 pts (34.0%), False positive in 7 pts (13.2%) 27 Pts with Necrosis: Accurate scans in 11 pts (40.7%), False-negative scans in 10 pts (37.0%), False-positive scans in 6 pts(22.2%) 47 Pts without Necrosis: Accurate scans in 22 pts (46.8%), False-negative scans in 20 pts (42.6), False positives in 5 pts (10.6%)	Preoperative assessment with FDG PET/CT is not useful for hepatic colorectal metastases, particularly when preoperative chemotherapy is used, with a trend towards underestimation of lesions.
Liu et al, 2009 (24)	To assess the impact of PET/CT on the therapeutic strategy of the patience with colorectal cancer metastasis	15	Whole body FDG PET/CT scanning	Histopathology or clinical follow-up	CT	NR	Liver metastasis: PET/CT: Sens=100%, Spec=100% CT: Sens=80%, Spec=100% Statistical significant difference with p=0.0009	PET/CT is superior to contrast-enhanced CT (ceCT) for the detection of the metastatic lesions of the colorectal cancer, and is a valuable tool to help select the correct therapeutic strategies

Abbreviations: CI, confidence interval; CRCLM , colorectal cancer liver metastases; CT, Computed Tomography; FDG PET, Fluoro-2-deoxy-D-glucose Positron Emission Tomography; iv, intravenous; LN, lymph node; 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;