VRAAG 3: IS PET-CT SENSITIEVER EN/OF SPECIFIEKER VOOR DE DETECTIE VAN OVERIGE METASTASEN WELKE TOT MOGELIJKE WIJZIGING IN BELEID LEIDEN BIJ PATIËNTEN MET POTENTIEEL LOKAAL TE BEHANDELEN METASTASEN?

Systematic reviews

<table>
<tr><th>Study ID</th><th>Method</th><th>Patient characteristics</th><th>Intervention(s)</th><th>Results primary outcome</th><th>Results secondary and other outcomes</th><th>Critical appraisal of review quality</th></tr>
<tr>
<td>(Chan, Welch, Walker-Dilks, Raifu, & Ontario provincial Gastrointestinal Disease Site Group, 2012)</td>
<td>

Design: SR.
Source of funding: Ontario Ministry of Health
Search date: May 2010
Searched databases: MEDLINE, EMBASE (Aug 2005- May 2010)
Included study designs:

8 SR
28 primary studies (randomised study, non-randomised studies)

Only 6 studies were of interest to the research question.

</td>
<td>

Eligibility criteria (see also Facey et al.):

SR:

FDG-PET in CRC in humans
evidence related to diagnostic accuracy, change in patient management, clinical outcomes or treatment response

Primary studies:

Prospective
Full article available
evidence related to diagnostic accuracy, change in patient management, clinical outcomes or treatment response
12 patients ore more included
Suitable Comparison test

</td>
<td>

Index test(s): (Whole body) (FDG)-PET-CT
Comparison test: CT, MRI, CT and FDG-PET, intraoperative gamma probe, none
Reference test: histopathology or clinical (radiological) follow-up, (intraoperative) ultrasound morphology, surgical exploration, none

</td>
<td>

Detection of hepatic metastases:

<table>
<tr><th>FDG-PET/CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Adie, 2009</td><td>28</td><td>7</td><td>18</td><td>0</td><td>61%</td><td>0%</td><td>80%</td><td>0%</td></tr>
<tr><td>Lubezky, 2007</td><td></td><td></td><td></td><td></td><td>93%</td><td></td><td></td><td></td></tr>
<tr><td>Rappeport, 2007</td><td></td><td></td><td></td><td></td><td>66%</td><td>99%</td><td>98%</td><td>76%</td></tr>
<tr><td>Orlacchio, 2009</td><td></td><td></td><td></td><td></td><td>97%</td><td>98%</td><td>99%</td><td>95%</td></tr>
<tr><th>CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Adie, 2009</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lubezky, 2007</td><td></td><td></td><td></td><td></td><td>88%</td><td></td><td></td><td></td></tr>
<tr><td>Rappeport, 2007</td><td></td><td></td><td></td><td></td><td>89%</td><td>67%</td><td>72%</td><td>86%</td></tr>
<tr><td>Orlacchio, 2009</td><td></td><td></td><td></td><td></td><td>91%</td><td>95%</td><td>98%</td><td>81%</td></tr>
</table>

Detection of extra hepatic metastases:

<table>
<tr><th>Rappeport, 2007</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>PET-CT</td><td></td><td></td><td></td><td></td><td>84%</td><td>96%</td><td></td><td></td></tr>
<tr><td>CT</td><td></td><td></td><td></td><td></td><td>95%</td><td>87%</td><td></td><td></td></tr>
</table>

Other outcomes:

Staging primary tumor
Treatment response
RT planning
Recurrence
Cost effectiveness
Patient management

</td>
<td>
One randomized study showed a change in treatment plan: decrease in futile surgery from 48% to 28%(p=0,042). (Ruers T.J.M. et al., 2009)

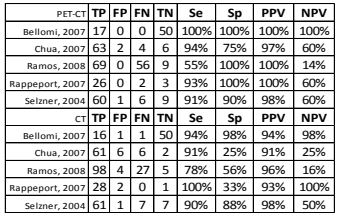
Sensitivity of PET in detecting liver metastases decreases following neoadjuvant chemo-therapy.
PET is less sensitive but more specific than MRI for detection of hepatic metastases.

</td>
<td>

Level of evidence: B
Adequate search
Quality appraisal performed, but level of evidence not shown
Heterogeneity not clearly reported
Probably (high) risk of bias due to:

Partial verification
Differential verification
Blinding not always reported
Analysis by lesion (one study)

</td>
</tr>
</table>

<table>
<tr><th>Study ID</th><th>Method</th><th>Patient characteristics</th><th>Intervention(s)</th><th>Results primary outcome</th><th>Results secondary and other outcomes</th><th>Critical appraisal of review quality</th></tr>
<tr><td></td><td></td><td>• Patient characteristics:
○ CRC</td><td></td><td></td><td></td><td></td></tr>
<tr><td>(Patel, McCall, Ohinmaa, Bigam, & Dryden, 2011)</td><td>• Design: SR
• Source of funding: University of Alberta, Canada.
• Search date: March 30, 2009.
○ MEDLINE (1950–2009),
○ EMBASE (1980–2009),
○ Scopus (February 2009),
○ Web of Science (February 2009),
○ Cochrane Library (Issue 1, 2009), PubMed (limited to the last 6 months),
○ DARE,
○ grey literature including Conference Papers Index (2003–2009),
○ American College of Radiology (2001–2009),
○ American College of Surgeons (2002–2009),
○ Royal College of Radiologists (2003–2009),
○ Canadian Association of</td><td>• Included if:
○ Index test 2-18-F-fluoro-2-deoxyglucose PET/CT scan
○ Comparison test CT scan
○ histological gold standard,
○ sufficient data to populate a 2 × 2 table.
• Excluded if:
○ clearly irrelevant,
○ intact primary tumors,
○ previous hepatic therapy for cancer,
○ pregnant patients,
○ alternate radio-compound,
○ separate PET and CT scans.
• Patient characteristics:
○ adults (≥18 years)
○ colorectal liver metastases
○ being assessed for liver resection</td><td>• Index test(s): 2-18-F-fluoro-2-deoxyglucose PET/CT
• Comparison test: CT, MRI</td><td>• PET-CT has a higher accuracy for detection of extra-hepatic and hepatic colorectal metastatic disease than CT alone.
• For hepatic lesions (5 studies; 316 patients), PET/CT had higher SN and SP than CT (PET/CT SN = 91%–100% and SP = 75%–100%; CT SN = 78%–94% and SP = 25%–98%).
• For extra-hepatic lesions (3 studies; 178 patients), PET/CT was more sensitive than CT, but specificities were similar (PET/CT sensitivity [SN] =75%–89% and specificity [SP] = 95%–96% vs. CT SN = 58%–64% and SP = 87%–97%).
• Detection of hepatic metastases:
 
<table>
<tr><th>PET-CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Bellomi, 2007</td><td>17</td><td>0</td><td>0</td><td>50</td><td>100%</td><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td>Chua, 2007</td><td>63</td><td>2</td><td>4</td><td>6</td><td>94%</td><td>75%</td><td>97%</td><td>60%</td></tr>
<tr><td>Ramos, 2008</td><td>69</td><td>0</td><td>56</td><td>9</td><td>55%</td><td>100%</td><td>100%</td><td>14%</td></tr>
<tr><td>Rappeport, 2007</td><td>26</td><td>0</td><td>2</td><td>3</td><td>93%</td><td>100%</td><td>100%</td><td>60%</td></tr>
<tr><td>Selzner, 2004</td><td>60</td><td>1</td><td>6</td><td>9</td><td>91%</td><td>90%</td><td>98%</td><td>60%</td></tr>
<tr><th>CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Bellomi, 2007</td><td>16</td><td>1</td><td>1</td><td>50</td><td>94%</td><td>98%</td><td>94%</td><td>98%</td></tr>
<tr><td>Chua, 2007</td><td>61</td><td>6</td><td>6</td><td>2</td><td>91%</td><td>25%</td><td>91%</td><td>25%</td></tr>
<tr><td>Ramos, 2008</td><td>98</td><td>4</td><td>27</td><td>5</td><td>78%</td><td>56%</td><td>96%</td><td>16%</td></tr>
<tr><td>Rappeport, 2007</td><td>28</td><td>2</td><td>0</td><td>1</td><td>100%</td><td>33%</td><td>93%</td><td>100%</td></tr>
<tr><td>Selzner, 2004</td><td>61</td><td>1</td><td>7</td><td>7</td><td>90%</td><td>88%</td><td>98%</td><td>50%</td></tr>
</table>
• Detection of extrahepatic metastases:</td><td>• Change in treatment plan
○ change in surgery: 13%
○ avoided surgery based on the PET/CT: 20%
○ change in treatment plan: 9%- 20%
○ Overall: PET/CT affected clinical practice in 8% to 20% of patients.
• Chemotherapy effect
○ PET-CT:
With chemo: Se: 98%, Sp: 100%
Without chemo: Se: 95%, Sp: 60%
○ Chemo did not confound PET-CT
○ No FDG uptake in extrahepatic meta's :
With chemo: 66%
Without chemo: 8%</td><td>• Level of evidence: B
• Adequate search
• One study did not describe their population.
• Differential verification in one study.
• Assessments of heterogeneity and reporting bias were planned but not executed because of the small number of studies.
• Planned pooled analyses were not calculated given the heterogeneity in the studies.</td></tr>
</table>

<table>
<tr><th>Study ID</th><th>Method</th><th>Patient characteristics</th><th>Intervention(s)</th><th>Results primary outcome</th><th>Results secondary and other outcomes</th><th>Critical appraisal of review quality</th></tr>
<tr>
<td></td>
<td>

General Surgeons (2003–2009),
American Society of Clinical Oncology (2003–2009),
Google Scholar,
Clinical Trials Registry,
health technology websites,
reference lists of all included studies.

Prospective, retrospective, cross sectional.
6 studies.
Sample sizes ranged from 35 to 131.

</td>
<td></td>
<td></td>
<td>
<table>
<tr><th>PET-CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Bellomi, 2007</td><td>6</td><td>0</td><td>2</td><td>0</td><td>75%</td><td>NA</td><td>100%</td><td>0%</td></tr>
<tr><td>Rappeport, 2007</td><td>10</td><td>1</td><td>2</td><td>22</td><td>83%</td><td>96%</td><td>91%</td><td>92%</td></tr>
<tr><td>Selzner, 2004</td><td>32</td><td>2</td><td>4</td><td>38</td><td>89%</td><td>95%</td><td>94%</td><td>90%</td></tr>
<tr><th>CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Bellomi, 2007</td><td>8</td><td>0</td><td>0</td><td>59</td><td>100%</td><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td>Rappeport, 2007</td><td>7</td><td>3</td><td>5</td><td>20</td><td>58%</td><td>87%</td><td>70%</td><td>80%</td></tr>
<tr><td>Selzner, 2004</td><td>23</td><td>1</td><td>13</td><td>39</td><td>64%</td><td>98%</td><td>96%</td><td>75%</td></tr>
</table>
</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Brush J. et al., 2011)</td>
<td>

Design: SR
Source of funding: National Institute for Health Research Health Technology Assessment programme (HTA).
Search date: May 2009.
Searched databases:

BIOSIS Previews;
Cumulative Index to Nursing and Allied Health Literature
(CINAHL) Plus;
The Cochrane Library;
Compendex;
ProQuest Dissertations and Theses;
EMBASE;

</td>
<td>

Eligibility criteria:

Inclusion:

Adults with known or suspected primary cancer of the colon or rectum;
Undergoing pre-operative staging prior to curative surgery;
in a secondary care setting
Studies that combined patients with colorectal and anal cancer, only if < 20% of patients had anal cancer.

Exclusion:

Studies solely in

</td>
<td>

Index tests: integrated FDG PET/CT with both contrast-enhanced and non contrast-enhanced CT.
Comparator tests: standard imaging tests including ultrasound, diagnostic CT, MRI and PET, alone or in combination.
Reference standards: histopathology of surgical resected specimens (gold standard), histopathology based on biopsy, or follow-up (clinical

</td>
<td>

Target condition: known or suspected primary, recurrent or metastatic CRC.
FDG PET-CT sensitivity, range: 87%–100%, specificity, range: 75%–100%
CT sensitivity, range: 75%–98%, specificity, range: 25%–100%
Detection of hepatic metastases, patient level:

<table>
<tr><th>PET-CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>D'Souza, 2009</td><td>7</td><td>0</td><td>1</td><td>0</td><td>88%</td><td>NA</td><td>100%</td><td>0%</td></tr>
<tr><td>Chua, 2007</td><td>63</td><td>2</td><td>4</td><td>6</td><td>94%</td><td>75%</td><td>97%</td><td>60%</td></tr>
<tr><td>Kong, 2008</td><td>60</td><td>0</td><td>1</td><td>4</td><td>98%</td><td>100%</td><td>100%</td><td>80%</td></tr>
<tr><td>Rappeport, 2007</td><td>26</td><td>0</td><td>2</td><td>3</td><td>93%</td><td>100%</td><td>100%</td><td>60%</td></tr>
<tr><td>Coenegrachts, 2009</td><td>23</td><td>0</td><td>1</td><td>0</td><td>96%</td><td>NA</td><td>100%</td><td>0%</td></tr>
<tr><td>Wildi, 2008</td><td>10</td><td>3</td><td>3</td><td>0</td><td>77%</td><td>0%</td><td>77%</td><td>0%</td></tr>
<tr><td>CT</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>D'Souza, 2009</td><td>6</td><td>0</td><td>2</td><td>0</td><td>75%</td><td>NA</td><td>100%</td><td>0%</td></tr>
<tr><td>Chua, 2007</td><td>61</td><td>6</td><td>6</td><td>2</td><td>91%</td><td>25%</td><td>91%</td><td>25%</td></tr>
<tr><td>Kong, 2008</td><td>60</td><td>0</td><td>1</td><td>4</td><td>98%</td><td>100%</td><td>100%</td><td>80%</td></tr>
<tr><td>Rappeport, 2007</td><td>28</td><td>2</td><td>0</td><td>1</td><td>100%</td><td>33%</td><td>93%</td><td>100%</td></tr>
<tr><td>Coenegrachts, 2009</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>Wildi, 2008</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
</table>
</td>
<td>

Changes in patient management.
Adverse effects
Economic evaluation

</td>
<td>

Level of evidence: B
Adequate search
The poor quality of the studies means that the validity of these estimates is threatened by several biases, and the lack of paired data prevented statistical tests from eliminating chance findings.

</td>
</tr>
</table>

<table>
<tr><th>Study ID</th><th>Method</th><th>Patient characteristics</th><th>Intervention(s)</th><th>Results primary outcome</th><th>Results secondary and other outcomes</th><th>Critical appraisal of review quality</th></tr>
<tr>
<td></td>
<td>

Global Health;
Global Health Library regional indexes (comprising LILACS, AFRO, EMRO, PAHO, WHOLIS);
Index to Theses;
Inspec;
MEDLINE;
Meta Register of Current Controlled Trials;
National Technical Information Services;
OpenSIGLE (System for Information on Grey Literature in Europe);
UK Clinical Research Network;
Web of Science, including Conference Proceedings Citation Index;
EMBASE.

Included study designs: prospective and retrospective patient series (diagnostic cohort), cross-sectional, before and after studies and RCTs.
Number of included studies: 16 prospective (5) and retrospective patient series (10), unclear design (1).
In total 890 patients.

</td>
<td>
patients with anal cancer.

Patient characteristics:

age 58-65 years
CRC

</td>
<td>examination or imaging tests).</td>
<td>

Detection of hepatic metastases, lesion level:

<table>
<tr><th>PET-CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Lubezky, 2007</td><td>29</td><td>2</td><td>2</td><td>0</td><td>94%</td><td>0%</td><td>94%</td><td>0%</td></tr>
<tr><td>Cantwell, 2008</td><td>67</td><td>4</td><td>33</td><td>6</td><td>67%</td><td>60%</td><td>94%</td><td>15%</td></tr>
<tr><td>Rappeport, 2007</td><td>47</td><td>1</td><td>24</td><td>74</td><td>66%</td><td>99%</td><td>98%</td><td>76%</td></tr>
<tr><td>CT</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lubezky, 2007</td><td>28</td><td>1</td><td>4</td><td>0</td><td>88%</td><td>0%</td><td>97%</td><td>0%</td></tr>
<tr><td>Cantwell, 2008</td><td>85</td><td>0</td><td>15</td><td>10</td><td>85%</td><td>100%</td><td>100%</td><td>40%</td></tr>
<tr><td>Rappeport, 2007</td><td>63</td><td>25</td><td>8</td><td>50</td><td>89%</td><td>67%</td><td>72%</td><td>86%</td></tr>
</table>

Detection of hepatic metastases, lesion level, after neo adjuvant chemotherapy:

<table>
<tr><th>Lubezky, 2007</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>PET-CT</td><td>48</td><td>4</td><td>50</td><td>20</td><td>49%</td><td>83%</td><td>92%</td><td>29%</td></tr>
<tr><td>CT</td><td>64</td><td>6</td><td>34</td><td>18</td><td>65%</td><td>75%</td><td>91%</td><td>35%</td></tr>
</table>

Detection of extra hepatic metastases, patient level:

<table>
<tr><th>PET-CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Selzner, 2004</td><td>32</td><td>2</td><td>38</td><td>4</td><td>46%</td><td>67%</td><td>94%</td><td>10%</td></tr>
<tr><td>Rappeport, 2007</td><td>10</td><td>1</td><td>2</td><td>22</td><td>83%</td><td>96%</td><td>91%</td><td>92%</td></tr>
<tr><td>CT</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Selzner, 2004</td><td>23</td><td>1</td><td>39</td><td>13</td><td>37%</td><td>93%</td><td>96%</td><td>25%</td></tr>
<tr><td>Rappeport, 2007</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
</table>

Per patient basis (pooled estimate), hepatic metastases:

The pooled accuracy data showed FDG PET/CT to have a sensitivity of 91% (95% CI 87% to 94%) and a specificity of 76% (95% CI 58% to 88%).

</td>
<td></td>
<td></td>
</tr>
</table>

<table>
<tr><th>Study ID</th><th>Method</th><th>Patient characteristics</th><th>Intervention(s)</th><th>Results primary outcome</th><th>Results secondary and other outcomes</th><th>Critical appraisal of review quality</th></tr>
<tr>
<td>(Niekel M.C., Bipat S., & Stoker J., 2010)</td>
<td>

Design: SR and Meta analysis
Source of funding: unknown, but authors stated no financial relationship to disclose.
Search date: Jan 2010.
Searched databases: MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Review, and Web of Science (articles published from Jan 1990 – Jan 2010).
Included study designs: prospective.
Number of included studies: 39 (3391 patients).
Pooled data were calculated with 3 studies for FDG PET/CT and with 9 studies for CT.

</td>
<td>

Eligibility criteria:

Inclusion:

Prospective study design
Study population > 10 patients
Imaging techniques: CT, MR imaging, FDG PET, or FDG PET-CT.
reference standard: intraoperative findings (palpation and/or US) or histo-pathologic examination or follow-up.
retrievable data were present for calculating sensitivity and specificity.

Exclusion:

Combination of imaging modalities presented
data about a single modality could not be extracted.
Studies including patients who had previously undergone treatment (surgery, radiation therapy, and/or chemotherapy).

Patient characteristics:

Mean age: 61 years (range: 20-93 years), 1863 males, 1317 females.

</td>
<td>

Index test(s): CT, MR imaging, FDG PET, or FDG PET-CT
Comparison test: intraoperative findings (palpation and/or US) or histo-pathologic examination or follow-up.

</td>
<td>

Detection of hepatic liver metastases, per patient basis (pooled estimate):

FDG PET-CT (n=3):

Se: 96.5 (94.2, 97.9)
Sp: 97.2 (92.8, 99.0)

CT (n=9):

Se: 83.6 (66.9, 92.8)
Sp: 94.9 (92.9, 96.3)

<table>
<tr><th>FDG PET-CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Zelzner et al (28)</td><td>60</td><td>1</td><td>6</td><td>9</td><td>91%</td><td>90%</td><td>98%</td><td>60%</td></tr>
<tr><td>Rappeport et al (38)*</td><td>26</td><td>0</td><td>2</td><td>3</td><td>93%</td><td>100%</td><td>100%</td><td>60%</td></tr>
<tr><td>Orlacchio et al (47)*</td><td>329</td><td>3</td><td>7</td><td>128</td><td>98%</td><td>98%</td><td>99%</td><td>95%</td></tr>
</table>
</td>
<td>

Data about FDG PET/CT were limited, with a per-lesion sensitivity of 66.2% and a per-patient sensitivity of 96.5%.
On a per-patient basis, the sensitivity of CT was significantly lower than that of FDG PET (P = .025); specificity estimates were comparable.
Per-lesion basis (pooled estimate):

FDG PET-CT (n=1): Se: 66.2 (54.5, 76.2)
CT (n=38): Se: 74.4 (68.7, 79.3)
<table>
<tr><th>FDG PET/CT</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Se</th><th>Sp</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Rappeport et al (38)*</td><td>47</td><td></td><td>24</td><td></td><td>66%</td><td>NA</td><td>100%</td><td>0%</td></tr>
</table>
</td>
<td>

Level of evidence: B
Adequate search
Prospective studies only.
Quality appraisal performed: level 4 of evidence (according to Oxford Centre for Evidence Based Medicine)
Because of the limited number of FDG PET/CT studies, no check for heterogeneity was performed.
Probably (high) risk of bias due to:

Partial verification
Differential verification
Blinding not always reported.

</td>
</tr>
</table>

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		○ Histopathologically proved primary CRC ○ Imaging modalities were evaluated for both patients suspected of having colorectal metastases and those known to have colorectal liver metastases.				
(Facey F., Bradbury I., Laking G., & Payne E., 2007)	• Design: SR • Source of funding: National Institute for Health Research Health Technology Assessment programme (HTA). • Search date: August 2005 ○ English systematic reviews published since the search for the ultra rapid review (May 2004) ○ Systematic reviews published in a Western European, non-English language since 1966 (with those prior to 2000 deselected by hand) ○ English and non-English primary studies since 2000. • Searched databases:	• Eligibility criteria: SR inclusion criteria: ○ dedicated FDG-PET in the stated cancers in humans ○ evidence related to diagnostic accuracy, change in patient management, clinical outcomes, treatment response or RT planning ○ robust qualitative or quantitative systematic reviews ○ studies in English, French, German, Spanish or Italian. SR exclusion criteria: ○ gamma PET (dual-headed camera) ○ coincidence detection emission	• Index test(s): PET-(CT) • Comparison test: PET, CT, MRI, US • Reference test: histopathology, core biopsy, or clinical follow-up, (min. 6 months).	• Detection of hepatic metastases: Zelsner, 2004: PET-CT TP 60, FP 1, FN 6, TN 9, Se 91%, Sp 90%, PPV 98%, NPV 60%; CT TP 61, FP 3, FN 5, TN 7, Se 92%, Sp 70%, PPV 95%, NPV 58% • Other outcomes: ○ Staging primary tumor ○ Treatment response ○ RT planning ○ Recurrence ○ Cost effectiveness ○ Patient management	• Staging/restaging: FDG-PET more sensitive than CT to detect hepatic and extrahepatic metastases. • 13 studies report some form of patient management changes affecting 9–59% of patients. • PET correctly upstaged 12/58 patients (21%), so liver resection was not undertaken and chemo or no further therapy was given (Rosa, 2004). • Change in surgery: 8% • Avoided surgery based on the PET/CT: 13%. • PET-CT 10–15% more sensitive or specific than FDG-PET. • PET sensitivity much better than CT, particularly for multiple CLM and extrahepatic disease 23% patients avoided surgery and associated surgical morbidity (lots of bias in this study: Arulampalam, 2004) PET: Kinkel, 2002 TP – FP – FN – TN – Se >84% Sp – PPV – NPV –; Arulampalam, 2004 TP 17 FP 1 FN 0 TN 10 Se 100% Sp 91% PPV 94% NPV 100%; Truant, 2005 TP 78 FP 1 FN 21 TN 4 Se 79% Sp 80% PPV 99% NPV 16% CT: Kinkel, 2002 Se 72% Sp 91% PPV 89% NPV 53%; Arulampalam, 2004 TP 8 FP 1 FN 9 TN 10 Se 47%; Truant, 2005 TP 78 FP 3 FN 21 TN 1 Se 79% Sp 25% PPV 96% NPV 5%	• Level of evidence: B • Adequate search • Quality appraisal performed, but level of evidence not shown • Heterogeneity not clearly reported • Probably (high) risk of bias due to: ○ Partial verification ○ Differential verification ○ Blinding not always reported ○ Analysis by lesion (one study)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	○ MEDLINE,MEDLINE in process and other non-indexed citations and EMBASE, The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE) and the HTA database international database of HTA reports. ○ Members of the International Network of Agencies for Health Technology Assessment (INAHTA) were contacted in August 2005 for details of systematic reviews not yet listed on the HTA database, or to clarify incomplete HTA database entries. • Sources searched for primary studies. ○ The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE in-process and	tomography (CDET) ○ tracers other than FDG ○ systematic reviews that have been superseded ○ reports that cost more than £50 to obtain ○ no English abstract available published as (conference) abstract only. Primary studies inclusion criteria: ○ prospective study of dedicated FDG-PET in a single cancer of interest ○ published after the search date of a robust systematic review covering that management decision ○ clinical study published as a full article in a peer-reviewed journal ○ evidence related to diagnostic accuracy, change in patient management or clinical outcomes ○ at least 12				

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	other non-indexed citations, and EMBASE. • Included study designs: :prospective comparative and retrospective • 1 SR and 1(Selzner, 2004) primary studies were of interest to the research question.	human patients with the cancer of interest ○ patient pathway similar to that used in the UK ○ suitable reference standard used in diagnostic studies ○ studies in English, French, German, Spanish or Italian. Primary studies exclusion criteria: ○ evaluations of gamma PET or CDET ○ abstracts from conferences, etc. ○ preliminary or interim analyses or case series that were later augmented ○ retrospective studies ○ tracers other than FDG ○ cancers other than the eight specified ○ mixed cancers that were not reported separately with at least 12 patients in one cancer ○ review/editorial PET technical papers (e.g. SUVs, FDG uptake,				

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		phantom studies, quantitation papers) ○ abstract does not allow study characteristics to be determined ○ reports that cost more than £50 to obtain ○ no English abstract available ○ studies in non-English languages that were duplicated in English papers. • Patient characteristics: ○ CRC				

Diagnostische studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Mainenti P.P. et al., 2010)	• Design: prospective • Source of funding: unknown • Setting: hospital • Sample size: 34 patients. • Duration: July 2005 – March 2007.	• Eligibility criteria: Inclusion: ○ Histologically proven diagnosis of colorectal adenocarcinoma. ○ Scheduled for surgery. Exclusion: ○ Refusal to participate ○ Known contraindications to one of the examinations • Patient characteristics: ○ Mean Age: 63 years (range 29-81years) ○ Male/female ratio: 20:14.	• Index test(s): PET-CT. • Reference standard: CE-US, MDCT and SPIO enhanced MRI (all patients). • Gold standard: Surgical palpation, IOUS, histopathology and follow-up MDCT (all patients).	• Detection of hepatic metastases, patient based analysis PET-CT • Se: 100% • Sp: 96% • PPV: 86% • NPV: 100% • Accuracy: 97%. CT • Se: 83% • Sp: 96% • PPV: 83% • NPV: 96% • Accuracy: 94%.		• Level of evidence: B • Dropouts: none • All modalities were randomly performed, but radiologist was not blinded with the results of preoperative imaging modalities.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		• Prevalence of disease: ○ Six out of 34 (17.6%) patients presented at least one hepatic metastasis. ○ Multiple liver metastases were present in four out of the six patients; ○ The maximum number of lesions in a patient was six. ○ A total of 6/34 were classified as patients with metastasis ○ 28/34 patients were free from metastases. ○ A diffuse fatty infiltration involving the right hepatic lobe was observed in a patient. ○ No malignant lesions different from colo-rectal Metastasis.				

Randomised Controlled Trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
(Ruers T.J.M. et al., 2009)	• Design: RCT for diagnostic accuracy of two detection modalities • Source of funding: this study was supported by a grant from The Netherlands Organization for Health Research and Development. • Setting: hospital • Sample size: 150 • Duration: follow-up of at least 3 years	• Eligibility criteria: ○ tumor free resection margins of CRC, ○ without evidence of extrahepatic metastatic disease ○ no recurrent or second CRC ○ age: 18-75 years. • Exclusion: ○ previous malignancies other than in situ carcinoma of the cervix or nonmelanoma skin cancer, unless there ○ had been a disease-free interval of at least	• Intervention(s): FDG-PET + CT • Comparator(s):CT	• Risk reduction futile laparotomy: 38% • Primary outcome: the number of futile laparotomies was 34 (45%) in the control arm without 18F-FDG PET and 21 (28%) in the experimental arm with 18F-FDG PET; Conclusion: • The number of futile laparotomies was reduced from 45% to 28%; thus, the addition of 18F-FDG PET to the work-up for	Survival: All patients were followed up for at least 3 y after randomization. • experimental group ○ OS: 61.3% ○ DFS: 35.5% • control group ○ OS: 65.8% ○ DFS: 29.8% (P(OS) = 0.378 and P(DFS) = 0.194).	• Level of evidence: A2 • Dropouts: none • Results critical appraisal: high validity, applicable to the patient group targeted in the search question. • Futile laparotomies defined as:

		10 y ○ signs of liver dysfunction (bilirubin, alkaline phosphatase 3 times the upper limit of normal); active infection ○ poorly regulated diabetes mellitus. • A priori patient characteristics: patients with colorectal liver metastases selected for surgical treatment by imaging with CT. • Group comparability: comparable on 5% level.		surgical resection of colorectal liver metastases prevented unnecessary surgery in 1 of 6 patients.		

Abbreviations: CDET: coincidence detection emission tomography; CRC: colorectal cancer; CE-US: Contrast Enhanced Ultrasound Staging; CLM: colorectal liver metastases; FDG PET-CT: 2-[18F]-fluoro-2-deoxy-D-glucose Positron emission tomography - computed tomography; HTA: National Institute for Health Research Health Technology Assessment programme; IOUS: intra operative Ultrasound Staging; MDCT: multi detector row computed tomography; MRI: magnetic resonance imaging; NPV: negative predictive value; PPV: positive predictive value; PS: primary study; Se: sensitivity; Sp: specificity; SPIO: super paramagnetic iron oxide; SR: systematic review; SUV: standardized uptake value; UK: United Kingdom; US: Ultrasound Staging.

References

Brush J., Boyd K., Chappell F., Crawford F., Dozier M., Fenwick E., et al. (2011). The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: A systematic review and economic evaluation. *Health Technology Assessment, 15*(35), i-142.

Chan, K., Welch, S., Walker-Dilks, C., Raifu, A., & Ontario provincial Gastrointestinal Disease Site Group. (2012). Evidence-based guideline recommendations on the use of positron emission tomography imaging in colorectal cancer. *Clinical Oncology (Royal College of Radiologists (Great Britain)), 24*(4), 232-249.

Facey F., Bradbury I., Laking G., & Payne E. (2007). Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. *Health Technology Assessment, 11*(44), iii-85.

Mainenti P.P., Mancini M., Mainolfi C., Camera L., Maurea S., Manchia A., et al. (2010). Detection of colo-rectal liver metastases: Prospective comparison of contrast enhanced US, multidetector CT, PET/CT, and 1.5 tesla MR with extracellular and reticulo-endothelial cell specific contrast agents. *Abdominal Imaging, 35*(5), 511-521.

Niekel M.C., Bipat S., & Stoker J. (2010). Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: A meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology, 257*(3), 674-684.

Patel, S., McCall, M., Ohinmaa, A., Bigam, D., & Dryden, D. M. (2011). Positron emission tomography/computed tomographic scans compared to computed tomographic scans for detecting colorectal liver metastases: A systematic review. *Annals of Surgery, 253*(4), 666-671.

Ruers T.J.M., Wiering B., Van Der, S. J., Roumen R.M., De, J. K., Comans E.F.I., et al. (2009). Improved selection of patients for hepatic surgery of colorectal liver metastases with 18F-FDG PET: A randomized study. *Journal of Nuclear Medicine, 50*(7), 1036-1041.