A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence

M Pennant, Y Takwoingi, L Pennant, C Davenport, A Fry-Smith, A Eisinga, L Andronis, T Arvanitis, J Deeks and C Hyde
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Abstract

A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence

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*Corresponding author

Background: Breast cancer (BC) accounts for one-third of all cases of cancer in women in the UK. Current strategies for the detection of BC recurrence include computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. Positron emission tomography (PET) and, more recently, positron emission tomography/computed tomography (PET/CT) are technologies that have been shown to have increasing relevance in the detection and management of BC recurrence.

Objective: To review the accuracy of PET and PET/CT for the diagnosis of BC recurrence by assessing their value compared with current practice and compared with each other.

Data sources: MEDLINE and EMBASE were searched from inception to May 2009.

Study selection: Studies were included if investigations used PET or PET/CT to diagnose BC recurrence in patients with a history of BC and if the reference standard used to define the true disease status was histological diagnosis and/or long-term clinical follow-up. Studies were excluded if a non-standard PET or PET/CT technology was used, investigations were conducted for screening or staging of primary breast cancer, there was an inadequate or undefined reference standard, or raw data for calculation of diagnostic accuracy were not available.

Study appraisal: Quality assessment and data extraction were performed independently by two reviewers. Direct and indirect comparisons were made between PET and PET/CT and between these technologies and methods of conventional imaging, and meta-analyses were carried out. Analysis was conducted separately on patient- and lesion-based data. Subgroup analysis was conducted to investigate variation in the accuracy of PET in certain populations or contexts and sensitivity analysis was conducted to examine the reliability of the primary outcome measures.

Results: Of the 28 studies included in the review, 25 presented patient-based data and 7 presented lesion-based data for PET and 5 presented patient-based data and 1 presented patient- and lesion-based data for PET/CT; 16 studies conducted direct comparisons with 12 comparing the accuracy of PET or PET/CT with conventional diagnostic tests and 4 with MRI.

For patient-based data (direct comparison) PET had significantly higher sensitivity [89%, 95% confidence interval (CI) 83% to 93% vs 79%, 95% CI 72% to 85%, relative sensitivity 1.12, 95% CI 1.04 to 1.21, p = 0.005] and significantly higher specificity [93%, 95% CI 83% to 97% vs 83%, 95% CI 67% to 92%, relative specificity 1.12, 95% CI 1.01 to 1.24, p = 0.036] compared with conventional imaging tests (CITs) — test performance...
did not appear to vary according to the type of CIT tested. For patient-based data (direct comparison) PET/CT had significantly higher sensitivity compared with CT (95%, 95% CI 88% to 98% vs 80%, 95% CI 65% to 90%, relative sensitivity 1.19, 95% CI 1.03 to 1.37, p = 0.015), but the increase in specificity was not significant (89%, 95% CI 69% to 97% vs 77%, 95% CI 50% to 92%, relative specificity 1.15, 95% CI 0.95 to 1.41, p = 0.157). For patient-based data (direct comparison) PET/CT had significantly higher sensitivity compared with PET (96%, 95% CI 90% to 98% vs 85%, 95% CI 77% to 91%, relative sensitivity 1.11, 95% CI 1.03 to 1.18, p = 0.006), but the increase in specificity was not significant (89%, 95% CI 74% to 96% vs 82%, 95% CI 64% to 92%, relative specificity 1.08, 95% CI 0.94 to 1.20, p = 0.267). For patient-based data there were no significant differences in the sensitivity or specificity of PET when compared with MRI, and, in the one lesion based study, there was no significant differences in the sensitivity or specificity of PET/CT when compared with MRI.

Limitations: Studies reviewed were generally small and retrospective and this may have limited the generalisability of findings. Subgroup analysis was conducted on the whole set of studies investigating PET and was not restricted to comparative studies.

Conventional imaging studies that were not compared with PET or PET/CT were excluded from the review. Conclusions: Available evidence suggests that for the detection of BC recurrence PET, in addition to conventional imaging techniques, may generally offer improved diagnostic accuracy compared with current standard practice. However, uncertainty remains around its use as a replacement for, rather than an add-on to, existing imaging technologies. In addition, PET/CT appeared to show clear advantage over CT and PET alone for the diagnosis of BC recurrence.

Future work: Future research should include: prospective studies with patient populations clearly defined with regard to their clinical presentation; a study of diagnostic accuracy of PET/CT compared with conventional imaging techniques; a study of PET/CT compared with whole-body MRI; studies investigating the possibility of using PET/CT as a replacement for rather than an addition to CITs; and using modelling of the impact of PET/CT on patient outcomes to inform the possibility of conducting large-scale intervention trials.

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<th>Abbreviation</th>
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<tbody>
<tr>
<td>BC</td>
<td>breast cancer</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CITs</td>
<td>conventional imaging tests</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CW</td>
<td>conventional workup</td>
</tr>
<tr>
<td>FDG</td>
<td>¹⁸F-fluorodeoxyglucose</td>
</tr>
<tr>
<td>FN</td>
<td>false-negative</td>
</tr>
<tr>
<td>FP</td>
<td>false-positive</td>
</tr>
<tr>
<td>HSROC</td>
<td>hierarchical summary receiver operating characteristic</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PET/CT</td>
<td>positron emission tomography/computed tomography</td>
</tr>
<tr>
<td>SROC</td>
<td>summary receiver operating characteristic</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>TN</td>
<td>true-negative</td>
</tr>
<tr>
<td>TP</td>
<td>true-positive</td>
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All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.
Executive summary

Background

Breast cancer (BC) affects 1 in 13 women in their lifetime. Treatment options have developed significantly over the past decade and have had an impact on survival. The diagnosis of BC recurrence is important to allow appropriate treatment. Positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) are technologies that have application in the detection and management of cancer. The adoption of PET or PET/CT depends not only on their diagnostic accuracy but also on their comparative advantage over existing diagnostic approaches.

Objectives

This report covers the question of the effectiveness of PET and PET/CT for diagnosing BC recurrence and a second report (to follow) will provide economic modelling to address the question of their cost-effectiveness in this context. The aim of this review was to assess the value of PET and PET/CT, in addition to current practice, for the diagnosis of BC recurrence. The objectives were: (1) to assess the diagnostic accuracy of PET compared with conventional diagnostic strategies; (2) to assess the diagnostic accuracy of PET/CT compared with conventional diagnostic strategies; (3) to assess the diagnostic accuracy of PET and PET/CT compared with magnetic resonance imaging (MRI); (4) to compare the accuracy of PET with PET/CT; (5) to assess the overall diagnostic accuracy of PET and PET/CT; (6) to investigate the impact of PET and PET/CT on patient management; and (7) to explore possible mediators of the accuracy of PET and PET/CT.

Methods

A systematic review was conducted. A search for primary studies in MEDLINE (Ovid) and EMBASE (Ovid) was conducted with no language restrictions. Studies of PET or PET/CT in patients with history of BC and suspicion of recurrence were selected for inclusion. Studies were excluded if investigations were conducted for screening or staging of primary BC, if a non-standard PET or PET/CT technology was used, if there was an inadequate or undefined reference standard, or if raw data for calculation of diagnostic accuracy were not available. Both comparative and non-comparative studies were included.

Data extraction and quality assessment were conducted independently by two reviewers with any disagreements resolved by consensus. Direct and indirect comparisons were made between PET and PET/CT and between these technologies and methods of conventional imaging, and a meta-analysis was performed using a bivariate random effects model. Analysis was conducted separately on patient- and lesion-based data. Subgroup analysis was conducted to investigate variation in the accuracy of PET in certain populations or contexts and sensitivity analysis was conducted to examine the reliability of the primary outcome measures.

Results

Twenty-eight studies were included in the current review and, of these, 26 investigated the diagnostic accuracy of PET. Twenty-five presented patient-based data and seven presented lesion-based data for PET. Six studies investigated the accuracy of PET/CT, five presenting patient-based data and one presenting lesion-based data. Sixteen studies conducted direct comparisons and, of these, 12 compared the accuracy of PET or PET/CT with conventional diagnostic tests and four compared PET or PET/CT with an MRI technology. Quality varied between studies, and the major quality issue identified was the time delay between conventional tests and PET or PET/CT in comparative studies. The PET or PET/CT technology used was similar across the studies.

1. For patient-based data, in studies where direct comparisons were made, PET had significantly higher sensitivity [89%, 95% confidence interval (CI) 83% to 93% vs 79%, 95% CI 72% to 85%, relative sensitivity 1.12, 95% CI 1.04 to 1.21, \( p = 0.005 \)] and significantly higher
specifcity (93%, 95% CI 83% to 97% vs 83%, 95% CI 67% to 92%, relative specificity 1.12, 95% CI 1.01 to 1.24, \( p = 0.036 \)), compared with conventional imaging tests (CITs) (\( n = 10 \)). Test performance did not appear to vary according to the type of CIT that was compared with PET (\( p = 0.500 \)). Indirect comparisons, where all CIT (\( n = 11 \)) and PET (\( n = 25 \)) studies were included, gave the same findings. For lesion-based data, no significant differences in sensitivity or specificity between PET and CIT were observed for studies making direct comparisons (\( n = 3 \)) or for indirect comparisons for all PET (\( n = 7 \)) and CIT (\( n = 3 \)) studies. In the sensitivity analysis of patient data, for studies in which the time period between PET and comparator tests was clearly less than 1 month (\( n = 6 \)), differences between PET and CIT tended to be smaller and the difference in sensitivity became non-significant.

2. For patient-based data, in all studies where direct comparisons were made (\( n = 4 \)), the CIT used was CT. In these studies, compared with CT, PET/CT had significantly higher sensitivity (95%, 95% CI 88% to 98% vs 80%, 95% CI 63% to 90%, relative sensitivity 1.19, 95% CI 1.03 to 1.37, \( p = 0.015 \)) but the increase in specificity was not significant (89%, 95% CI 69% to 97% vs 77%, 95% CI 50% to 92%, relative specificity 1.15, 95% CI 0.95 to 1.41, \( p = 0.157 \)). Indirect comparisons, where all CIT (\( n = 11 \)) and PET/CT (\( n = 5 \)) studies were included, gave the same findings. No lesion-based data compared PET/CT with CIT. In the sensitivity analysis of patient data, for studies in which the time period between PET/CT and comparator tests was clearly less than 1 month (\( n = 3 \)) differences between PET/CT and CT became non-significant.

3. For patient-based data, three studies compared PET with different types of MRI technology. In each of these studies, there were no significant differences in the sensitivity or specificity of PET compared with MRI. One study compared PET/CT and MRI on a lesion basis and there were no significant differences in sensitivity or specificity for PET/CT compared with MRI.

4. For patient-based data, in the analysis of studies directly comparing PET/CT and PET (\( n = 4 \)), PET/CT had significantly higher sensitivity (96%, 95% CI 90% to 98% vs 85%, 95% CI 77% to 91%, relative sensitivity 1.11, 95% CI 1.03 to 1.18, \( p = 0.006 \)), but the increase in specificity was not significant compared with PET (89%, 95% CI 74% to 96% vs 82%, 95% CI 64% to 92%, relative specificity 1.08, 95% CI 0.94 to 1.20, \( p = 0.267 \)). The same pattern of results was observed for the indirect comparison of all PET/CT (\( n = 5 \)) and PET (\( n = 25 \)) studies. In the lesion-based analysis, indirect comparison of PET/CT (\( n = 2 \)) and PET (\( n = 7 \)) showed no significant differences in sensitivity or specificity between PET/CT and PET.

5. For overall diagnostic accuracy, on a patient basis, PET/CT (\( n = 5 \)) and PET (\( n = 25 \)) had sensitivities of 96% (95% CI 89% to 99%) and 91% (95% CI 86% to 94%) and specificities of 89% (95% CI 75% to 95%) and 86% (95% CI 79% to 91%) respectively. On a lesion basis, PET/CT (\( n = 2 \)) and PET (\( n = 7 \)) had sensitivities of 96% (95% CI 80% to 99%) and 89% (95% CI 78% to 95%) and specificities of 83% (95% CI 61% to 94%) and 91% (95% CI 83% to 96%), respectively. There was considerable heterogeneity in the spread of results for PET.

6. Changes in patient management in study participants ranged from 11% to 74% (median 27%). These changes included initiation and avoidance of medical treatment such as hormone therapy and chemotherapy. In the three studies where only changes in management directly due to PET or PET/CT were considered (patients were not correctly diagnosed by conventional imaging techniques), estimates ranged from 11% to 25%.

7. In subgroup analysis, the accuracy of PET did not appear to be related to the location of disease or to whether PET was conducted with or without knowledge of previous clinical history and imaging studies. Characteristics of patient populations varied in many respects and it was not possible to draw definite conclusions about patient characteristics that may have an impact on test accuracy.

Conclusions

- For detection of BC recurrence, in addition to conventional imaging techniques, PET may generally offer improved diagnostic accuracy compared with current standard practice. Uncertainty remains around its use as a replacement, rather than an add-on, to existing imaging technologies.
- PET/CT appears to show a clear advantage over CT for the diagnosis of BC recurrence. Although PET/CT may give an advantage over other CITs, its incremental value over
other tests has yet to be directly assessed in studies. Concurrent use with, rather than replacement of, other conventional tests may be appropriate.

- PET/CT appears to show a clear advantage over PET and it is likely to be preferred to PET for use in this context.
- PET and PET/CT appear to have some impact on patient management but there is currently no evidence of the effect of their use on patient outcomes.

**Recommendations for future research**

- Prospective studies with patient populations clearly defined with regard to their clinical presentation.
- Study of the diagnostic accuracy of PET/CT compared with conventional imaging techniques.
- Study of PET/CT compared with whole-body MRI.
- Studies investigating the possibility of using PET/CT as a replacement for, rather than an addition to, CITs.

- Using modelling of the impact of PET/CT on patient outcomes (to be published in another report) to inform the possibility of conducting large-scale intervention trials to assess impacts on long-term patient outcomes.

**Implications for policy**

PET/CT has largely superseded PET in current practice, and the apparent advantage of PET/CT over PET found in this review supports that move. On the basis of some of the uncertainties observed, it may be premature to make recommendations about the precise diagnostic role of PET/CT in practice. However, current recommendations for its use for diagnosing metastatic BC following equivocal findings on conventional imaging techniques appear to be justified. It appears that PET/CT may be useful as an addition to current practice for the diagnosis of BC recurrence but this should be reassessed in light of the analysis of its cost-effectiveness.
Chapter 1
Introduction

Breast cancer

One in thirteen women in the UK will develop breast cancer (BC) in their lifetime. In women, BC accounts for one-third of all cases of cancer. In the UK, from 2004–6, the incidence rate of new BC was 122 per 10,000 women. Most women fortunately present with early-stage breast cancer (ESBC) and the UK NHS Breast Screening Programme currently offers screening at 50 years of age. ESBC is treated with surgery and adjuvant therapy often involving combinations of hormone therapy, chemotherapy and radiation therapy. Treatment options have developed significantly over the past decade and, with early diagnosis, rates of 5-year survival are currently > 80% and have increased steadily over the past 10–20 years. However, a number of women will develop metastatic disease and die of their BC.

Follow-up and treatment in the setting of recurrence

In most BC units, after treatment for the initial disease, patients are routinely followed up with clinical examination and mammography for at least 5 years, specifically looking for treatable local recurrence and symptoms to suggest metastatic disease. Investigational screening for metastatic disease is not performed routinely. If symptoms suggest relapse with metastatic disease, further investigations may be conducted where there is suspicion of disease. Rates of BC recurrence have been shown to be around 20% and recurrence may be local (in the breast), regional (lymph nodes in the ipsilateral axilla) or distant metastases (in tissues such as bone, liver, lungs and brain). Of patients with BC recurrence, one study showed that 27% had bone metastases, 27% had local recurrence, 16% had lung metastases and 13% had liver metastases. If metastatic disease is established, patients are generally not curable and treatment is aimed at palliating symptoms and improving survival if possible. Useful and sometimes lengthy clinical responses can be obtained by using hormone therapy in hormone-responsive disease and with chemotherapy, particularly with the newer agents. Taxane-based chemotherapy is considered likely to increase overall survival, time to progression and overall response in the second-line setting and Herceptin® (trastuzumab, Roche) is showing promising results in HER (human epidermal growth factor receptor)-2-positive disease. Radiotherapy, combined with appropriate analgesia, may be effective in reducing persistent localised bone pain.

Existing diagnostic strategies

Women with a past history of BC may present with symptoms that may be innocent or indicate disease. There is a range of strategies that may be involved in patient diagnosis and the choice of tests used depends on the presenting symptoms. Conventional workup (CW) often includes conventional X-rays, computed tomography (CT), ultrasound, bone scintigraphy and measurement of serum tumour markers and, in a limited number of settings, magnetic resonance imaging (MRI) may be available for use.

Conventional X-rays are widely available and are routinely used for cases of suspected BC recurrence. X-rays may be particularly useful for the diagnosis of metastases in the lung and bones (chest or individual bone X-ray). CT scans can be used to detect cancer in a range of tissue types (lung, bone, soft tissue, etc.). Ultrasound can be used to detect liver metastases. Bone scintigraphy uses radionuclides of technetium-99m-labelled disphosphonates and is used for the identification of bone metastases. Several biochemical compounds in the serum/plasma may act as indicators of the presence, risk or prognosis of cancer. In patients with history of BC, elevated tumour marker levels may represent cases of tumour relapse. It has been shown that increasing levels of these markers is associated with disease recurrence and may indicate the need for further investigation. MRI may be used for the detection of local BC recurrence or, with imaging of the whole body, for the additional detection of
bone metastases and other distant metastases. However, access to MRI is limited and it is not routinely used for diagnosing suspected BC recurrence.

In the setting of diagnosis of BC recurrence, CW is likely to comprise a combination of these technologies (in most cases, CW will not include MRI). Patients may undergo a variety of tests depending on their presenting symptoms and on the basis of the results of other imaging tests.

**PET and PET/CT**

Positron emission tomography (PET) and, more recently, positron emission tomography/computed tomography (PET/CT) are technologies that have been increasingly shown to have application in the detection and management of cancer, with the introduction of whole-body PET and PET/CT in the late 1990s. These technologies involve administration of a radioactive isotope and detection of photons produced in the process of radioactive decay and interaction with surrounding tissues. In oncology, the most commonly used radionuclide is 18F-fluorodeoxyglucose (FDG) which is taken up into cells in the same way as glucose. FDG accumulates in tumour tissue owing to increased glucose requirements and therefore increased glucose uptake. Also, in most tissues, FDG accumulates following uptake and phosphorylation, as, unlike glucose, it cannot enter the normal glycolytic pathway. FDG is administered intravenously to patients and, following an interval of time (usually 60–90 minutes) to allow uptake, PET scans are conducted. The whole body may be imaged during a single session and these technologies may be used to detect both local and metastatic tumours.

PET/CT combines information obtained from PET with data from CT scanning. As these technologies provide different types of data (PET gives metabolic and CT anatomical data), their combination provides greater diagnostic information. CT data are also used for attenuation correction of PET images. An attenuation map of CT can be used to estimate attenuation factors for PET and this correction can be applied to increase the accuracy of the images produced.

In 2005, the Royal College of Radiologists published a strategy document detailing the provision of PET/CT instruments across the UK. At that time, there were 11 fixed scanning PET/CT units installed in the UK predominantly for clinical use. Recommendations included a hub and satellite system, where central hub staff and resources would be used to maintain PET/CT scanners in more numerous satellite settings. Initially, provision was to be made for one PET/CT system per 1.5 million of the population, equating to ~40 machines for the current UK population.

**Measurement of diagnostic accuracy**

Diagnostic accuracy is usually defined as the sensitivity and specificity of a test, where sensitivity describes the ability of a test to correctly identify individuals with the disease and specificity describes the ability of a test to correctly identify individuals without the disease. The test under study is referred to as the index test and the results of this test are compared with the ‘reference standard’. The reference standard is a test that is considered to show the true disease status of each individual and determines which individuals are classed as having or not having the disease. The comparison of the index test with the reference standard allows findings for each patient to be classed into one of four categories:

- **True-positive (TP)**: The index test detects disease and is in agreement with the reference standard that also detected disease.
- **True-negative (TN)**: The index test does not detect disease and is in agreement with the reference standard that also did not detect disease.
- **False-positive (FP)**: The index test detects disease but disagrees with the reference standard that did not detect disease.
- **False-negative (FN)**: The index test does not detect disease but disagrees with the reference standard that did detect disease.

Findings for TP, TN, FP and FN can be used to calculate the sensitivity and specificity of the index test, where sensitivity is the ratio of the number of people correctly identified with the disease compared with the total number of people classed with the disease [sensitivity = TP/(TP + FN)], and specificity is the ratio of the number of people correctly identified as not having the disease compared to the total number of people classed as not having the disease [specificity = TN/(TN + FP)]. As in the current review, where additional comparator tests are also being considered, these
are assessed as if they were another index test, i.e.,
findings for the comparator test are compared with
those of the reference standard to class them as TP,
TN, FP or FN.

Results from test accuracy studies may be
presented on summary receiver operating planes,
where each point on the graph represents the
diagnostic accuracy of a test found in each
particular study. Specificity is plotted on the x-axis
and sensitivity on the y-axis and the results from
meta-analysis of the studies are shown as summary
points.

**Potential modifiers of the
diagnostic accuracy of PET and
PET/CT**

The diagnostic accuracy of PET and PET/CT are
likely to vary depending on features of the patient
population, technology used and design of the
investigative study.

Features of the patient population, such as the
nature of disease, may affect the accuracy of PET
or PET/CT. For example, if lesions are small or
particularly difficult to detect, sensitivity may
tend to be lower. Accuracy may also depend on
the location of disease, and PET and PET/CT may
vary in their ability to diagnose local, regional and
metastatic disease.

The methods used for PET or PET/CT
investigations may be important modifiers of
diagnostic accuracy. As these techniques use
radioactive isotopes of glucose to indicate sites
of increased metabolic activity, misdiagnosis
may result from elevated blood glucose levels.
It is recommended that all patients fast for at
least 4–6 hours before scanning.14 The presence
of patient fasting, and exclusion of those with
diabetes or impaired glucose tolerance, may be
important mediators of diagnostic accuracy. The
presence of attenuation correction, using CT data
or another correction method, is an important
predictor of diagnostic accuracy and may cause
variation in the accuracy of PET or PET/CT in
studies. Further aspects of technology that may
affect diagnosis are features such as the length of
radioisotope uptake, image acquisition time and
the mode of image interpretation.

The study design may also have an impact on
diagnostic accuracy. A distinction may be made
between studies where assessors have knowledge of
previous clinical and imaging findings and studies
where assessors interpret PET or PET/CT without
knowledge of these results. Where assessors
have knowledge of previous findings, apparent
diagnostic accuracy may be anticipated to be
better than when assessors do not have knowledge
of previous imaging findings. This also has
implications for the applicability of study findings
to clinical use. If PET or PET/CT is to be used
instead of existing diagnostic imaging tests, only
the results of studies in which previous imaging
results are unknown may be relevant, whereas, if
PET and PET/CT are to be used as technologies in
addition to standard imaging procedures, studies
in which assessors have knowledge of previous
findings may be more applicable.

**Current guidelines**

Guidelines have been developed by the National
Institute for Health and Clinical Excellence (NICE)
for the treatment of early/locally advanced3 and
advanced17 BC. In the early BC guidance, key
recommendations for the follow-up of patients
with BC include provision of designated health-
care professionals, dates for review of any adjuvant
therapy, surveillance with mammography and
contact points for specialist care.3 The guidance
suggests that future research should involve
determination of the appropriate length of follow-
up and suitable methods for detecting disease
recurrence.3

The advanced BC guidelines give advice on the
treatment of advanced/metastatic disease that is
generally only amenable to palliative care without
curative intent. These guidelines do not specifically
relate to the diagnosis of BC recurrence. However,
some guidance given may be applicable. The
NICE guidelines state that ‘Positron emission
tomography fused with computed tomography
(PET-CT) should only be used to make a new
diagnosis of metastases for patients with breast
cancer whose imaging is suspicious but not
diagnostic of metastatic disease.’17 In other words,
PET/CT would only be used for diagnosis in cases
where conventional imaging techniques fail to
properly diagnose the presence or absence of
metastases. Although these guidelines relate to
the use of PET/CT, all of the evidence reviewed
to inform them are studies or systematic reviews
of PET and not PET/CT. Additionally, these
guidelines refer only to the diagnosis of metastatic,
and not local, recurrence and the evidence base
relating to the application of PET and PET/CT for
the detection of recurrent BC is not clear.
Chapter 2
Rationale and objectives

This report covers the question of the effectiveness of PET and PET/CT for diagnosing BC recurrence and another report (to follow) will provide economic modelling to address the question of their cost-effectiveness in this context.

We have reviewed existing systematic reviews assessing the effectiveness of PET and PET/CT in the diagnosis of recurrent BC. The two most relevant were the Blue Cross/Blue Shield report 2001 and Isasi et al. 2005. The latter provides the most up-to-date assessment of test accuracy of PET in evaluations up to 2004, but no estimation of accuracy compared with existing diagnostic strategies. However, the key outstanding issue was the amount of improvement that PET and PET/CT offer over existing diagnostic approaches and this was the focus of the current review.

The main aims of this review were to assess the incremental diagnostic accuracy of PET and PET/CT compared with existing diagnostic strategies and to compare the diagnostic accuracy of PET and PET/CT for the diagnosis of BC recurrence. The accuracy of PET and PET/CT were to be considered in addition to standard practice.

Further aims were to assess the overall test accuracy of PET and PET/CT, to assess the impact of PET and PET/CT on patient management and to investigate possible determinants of variation in the diagnostic accuracy of PET. For clarity, objectives were, in the detection of BC recurrence:

1. To assess the incremental diagnostic accuracy of PET in addition to standard practice compared with conventional imaging tests (CITs).
2. To assess the incremental diagnostic accuracy of PET/CT in addition to standard practice compared with CITs.
3. To assess the incremental diagnostic accuracy of PET and PET/CT in addition to standard practice compared with MRI.
4. To compare the diagnostic accuracy of PET and PET/CT.
5. To obtain independent estimates of the diagnostic accuracy for PET and PET/CT in addition to standard practice.
6. To examine changes in patient management owing to the use of PET and PET/CT.
7. To explore possible determinants of variation in the accuracy of PET and PET/CT.
Chapter 3

Methods

The protocol was reviewed by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (see Appendix 10) and there were no major departures from it when conducting the review.

Identifying studies

Search strategy

Searches were conducted in MEDLINE (Ovid) and EMBASE (Ovid) and strategies combined MeSH (Medical Subject Headings) and text words to define the index test (PET and PET/CT) and the population (suspected breast cancer recurrence) (see Appendix 1). No language restrictions were used and searches were carried out from inception of the databases up to May 2009.

Selection of studies

Titles/abstracts obtained from the literature search were scanned for inclusion by one reviewer. Where information given in title/abstracts suggested that the study (1) included patients with past history of breast cancer, (2) conducted PET or PET/CT scans in those patients, and (3) assessed test accuracy, full paper articles were retrieved for further assessment. Additionally, studies potentially containing information on cost-effectiveness or one or more relevant clinical outcome measures were retrieved. If there was doubt regarding inclusion from the title and abstract, the full article was obtained for clarification. Stringent inclusion/exclusion criteria were applied to full paper studies in order to obtain the final set of included studies.

Inclusion/exclusion criteria

Full paper articles were screened in relation to the following inclusion/exclusion criteria by one reviewer with reference to a second reviewer where there was any doubt about their eligibility.

Population

The patient population was to be under investigation for suspicion of BC recurrence.

Patients were to have had a previous diagnosis of BC and to have completed a course of primary treatment. The initial aim of this review was to include only studies in which patients had previously been cleared of BC. However, it soon became evident that, in many studies, the exact patient group was unclear. It was often not fully clear whether patients with history of BC had subsequently been cleared or if they had known BC and were having further imaging investigations in order to diagnose metastatic disease. Exclusion of these types of studies was likely to substantially limit the scope of this review and restrict its application.

A decision was therefore made to include studies investigating the diagnosis of BC recurrence in patient groups that may have been cleared or not cleared of their original disease. All studies were to have been conducted in the context of secondary BC investigations, i.e. they did not form part of the initial BC diagnosis, BC staging or monitoring of response to primary BC treatment. Included studies were required to show evidence that investigations were distinct from primary investigations and were conducted after completion of the primary course of treatment.

Index test

Included studies were to have used PET or PET/CT to diagnose BC recurrence in patients with history of BC. The PET or PET/CT technology was required to be a dedicated machine and use a FDG tracer. Studies were excluded if coincidence gamma camera PET had been used or if other types of radioactive tracers had been used.

Reference standard

Studies were included if the reference standard used to define the true disease status was histological diagnosis (operation/biopsy) and/or long-term clinical follow-up. Studies were excluded if details of the reference standard were not given or if no suitable reference standard was used, e.g. other imaging studies conducted without follow-up.
Comparator

This review included both studies with and without comparator groups. Within-study comparisons are more robust as they effectively eliminate differences in potential modifiers of test accuracy between the two tests being compared. Indirect comparisons (comparison of independently pooled summary estimates across all studies) can also be conducted on the larger set of comparative and non-comparative studies. For studies including comparator groups, those using any diagnostic comparators were included but patients were also to have undergone PET or PET/CT and the reference standard. Studies in which PET or PET/CT and other diagnostic techniques were compared without use of a reference standard were excluded.

Outcomes

Studies giving sufficient information on the diagnosis of BC recurrence to determine the number of TP, TN, FP and FN test results were included. Recurrence could be local, regional or distant but disease was to be considered to be a consequence of the originally diagnosed breast cancer. Additional studies that contained information on the influence of PET or PET/CT on patient management or the reasons for FP and FN results were also included.

Data extraction

The number of TP, TN, FP and FN values were extracted from each study. In all studies, only data for participants who had undergone a satisfactory reference standard were extracted. In studies where there were comparator tests, where possible, only data for participants who had undergone both the index and comparator tests were selected. Information relating to patient management and location sites of FPs and FNs on PET or PET/CT scans was also extracted. Test accuracy data was extracted by two independent reviewers. Where there were differences in the retrieved data, these were discussed and a consensus of the true values was reached. Data related to patient management and sites of FPs and FNs were extracted by one reviewer. Authors of potentially included studies were contacted if relevant study data was incomplete but it appeared likely to have been obtained.

Quality assessment

Quality assessment was conducted independently by two reviewers, using relevant items from the QADAS (Quality Assessment of Diagnostic Accuracy Studies) tool, and differences resolved by consensus. Quality assessment criteria for study methodology related to patient selection, use of the reference standard, blinding and external validity. Additionally, the time delay between the index and comparator tests was assessed as an aspect of study quality as this has potential to bias estimates of relative test accuracy. The technical quality of the PET or PET/CT technology was assessed with reference to procedure guidelines, as used by Isasi et al., with particular reference to pre-scan blood glucose testing, the use of attenuation correction and the duration of FDG uptake. Quality criteria were set with the specifications outlined in Table 1.

Data analysis

Positron emission tomography and PET/CT were considered as independent technologies for analysis. Comparative tests considered to be conventionally used for diagnosis in this setting were grouped together for comparison with PET and PET/CT. CITs were defined as one or more of bone scintigraphy, CT, X-ray and general CW. Single comparators, e.g. CT or bone scintigraphy, were classed as CIT if they were judged to be adequate diagnostic methods in the context of the study. For example, for the diagnosis of bone metastases, bone scintigraphy was considered as CIT because, despite being a single diagnostic test, it would be appropriate in the context of diagnosing bone metastases. MRI was considered as a separate technology from CIT as, in many hospitals, it may not be part of the conventional diagnostic strategy (Professor Patricia Price, Imperial College London, 2010, personal communication). Data from studies in which PET or PET/CT were used in addition to other imaging techniques and studies in which assessors were blinded to previous imaging results were pooled in the analysis. This approach was considered conservative in light of the emphasis of the review (to assess the diagnostic accuracy of PET and PET/CT in addition to standard practice).

REVIEW MANAGER 5.0 was used to produce a methodological quality summary table and
forest plots of sensitivity and specificity for each test from the extracted $2 \times 2$ data and to present meta-analytic results in receiver operating characteristic (ROC) space. In order to make inferences about the relative accuracy of the tests in terms of sensitivity and specificity (instead of the diagnostic odds ratio), a bivariate method, rather than the (7) hierarchical summary receiver operating characteristic (HSROC) method, as specified in the protocol, was used for statistical analysis. A meta-analysis was done for each pairwise comparison of imaging modalities to estimate ratios of sensitivity and specificity. The bivariate random effects approach described by Reitsma et al.\textsuperscript{22} was used to obtain summary estimates of sensitivity, specificity and ratios of values between tests (relative sensitivity and specificity). This approach preserves the two-dimensional nature of the data by incorporating the correlation between sensitivity and specificity. It also takes into account both within-study sampling variability in estimates of sensitivity and specificity and between-study variability in test performance through the inclusion of random effects. All models were fitted using the NLMIXED procedure in SAS based on the formulation proposed by Chu and Cole.\textsuperscript{23}

To investigate differences in test performance according to type of CIT (CT, CW and bone scintigraphy), a second covariate was introduced into the analytical model comparing PET with CIT. To achieve convergence, this model was simplified by setting the correlation parameter equal to zero. This is equivalent to fitting two random effects logistic regression models for sensitivity and specificity separately.

Data presented on a patient and lesion basis were considered separately in the analysis. Patient-based data were used as the basis for the main analysis and for the investigation of heterogeneity. As limited patient data were available on a location-specific basis, lesion data were used to inform investigation of relative test accuracy in different sites. For patient-based data, each patient constituted the unit of analysis and, for lesion-based data, each lesion suspected of disease constituted the unit of analysis.

The primary outcomes of interest were the accuracy of PET and PET/CT compared with conventional technologies and the accuracy of PET compared with PET/CT. Using patient- and lesion-based data (where available), comparisons were made for:

- PET compared with CIT
- PET/CT compared with CIT
- PET compared with PET/CT.

Estimations of the differences in test accuracy were first made using only studies in which PET or PET/CT had been compared directly with other technologies or with each other (referred to as direct comparisons). Indirect comparisons were also made by pooling estimates for each test across all included studies before making between-test comparisons.

<table>
<thead>
<tr>
<th>TABLE I Quality assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality item</td>
</tr>
<tr>
<td>------------------------------------</td>
</tr>
<tr>
<td>Representative spectrum</td>
</tr>
<tr>
<td>Acceptable reference standard</td>
</tr>
<tr>
<td>Acceptable delay between tests</td>
</tr>
<tr>
<td>Partial verification avoided</td>
</tr>
<tr>
<td>Differential verification avoided</td>
</tr>
<tr>
<td>Incorporation avoided</td>
</tr>
<tr>
<td>Index test results blinded</td>
</tr>
<tr>
<td>Relevant clinical information</td>
</tr>
</tbody>
</table>

**Additional technology-specific criteria**

| Measurement of blood glucose      | Exclusion of patients with blood glucose levels ≥ 130 mg/dl? |
| Attenuation correction            | Was attenuation correction used for PET or PET/CT scans? |
| Uptake > 60 minutes               | Were patients given doses of FDG glucose > 60 minutes prior to scanning? |
Methods

Sensitivity analysis
Sensitivity analysis was conducted to examine the reliability of findings for comparisons among PET, PET/CT and CIT. As the emphasis of this review was on studies directly comparing tests, sensitivity analysis was applied only to direct comparisons. Issues of quality related to individual studies, e.g. representativeness of patient spectrum, quality of the reference standard, etc., were unlikely to have affected the comparisons and these factors were therefore not included in the sensitivity analysis. However, aspects that could have differed between tests under investigation were eligible for sensitivity analysis. The area of potential concern, where conditions for different tests may have varied, was the time delay between the index (PET or PET/CT) and comparator tests and the reference standard. In the sensitivity analysis, to remove the bias associated with different time lapses between tests and the reference standard, studies were removed if PET or PET/CT investigations were not conducted within 1 month of comparator tests or if the period of time between tests was unclear.

Subgroup analysis
Subgroup analyses were conducted to investigate factors that may have been sources of heterogeneity. The limited number of direct comparison studies (10 for PET vs CIT and 4 for PET/CT vs CIT) limited subgroup analysis within this set but subgroup analysis was conducted on the larger set of studies in which PET (with or without a comparator group; n = 25) had been performed. Subgroup analysis was not performed for PET/CT owing to the limited amount of data available. Subgroup analysis was conducted to compare studies of:

- PET in patients with negative results for previous imaging studies versus PET in patients with positive or suspicious previous imaging results
- PET in different locations of the body
- PET for investigation of those cleared of BC versus PET for those not cleared/where disease status is unclear
- PET in addition to standard practice versus PET instead of standard practice.
Chapter 4

Results

A total of 2526 citations were retrieved from the search of the databases, of which 522 were duplicates. After title/abstract screening, a total of 185 full papers was ordered for review. Thirty-two studies were included in the final review, 28 provided quantitative data and the reasons for full paper exclusions are given in Figure 1.

Included studies

Twenty-eight studies were identified as containing information on diagnostic accuracy relevant to the current review. Most of these studies investigated PET ($n = 26$) and fewer assessed PET/CT ($n = 6$) (four studies investigated both PET and PET/CT). Sixteen studies were direct comparisons and 12 were non-comparative (Table 2). Direct comparison studies investigated the accuracy of PET or PET/CT compared with MRI ($n = 4$) or with more conventional diagnostic strategies (CW, CT and bone scintigraphy) ($n = 12$). In most studies, data were presented on a patient basis ($n = 26$). In nine studies, lesion data were presented and seven studies presented both patient and lesion data (Table 2). The numbers of patients for the main groups for analysis are shown in Table 2.

Three studies contained information on changes in patient management owing to PET or PET/CT. These were excluded from quantitative synthesis because there was no test accuracy data, a less sophisticated PET technology or an unsatisfactory reference standard, but information from these studies was included in the patient management part of the review (see Chapter 4, Changes in patient management).

FIGURE 1 PRISMA diagram.
Results

Population characteristics

The characteristics of patient populations in the included studies are shown in Table 4 (comparative studies) and Table 5 (non-comparative studies). The size of study samples ranged from 10 to 291 patients (median 45). In most cases the reference standard was a combination of histology and clinical follow-up including conventional imaging techniques.

In all studies, patients were being investigated for BC disease distinct from primary investigations. In 16 of the studies,\textsuperscript{25,30–36,38–40,42,45,46–48} it appeared that all patients had previously been cleared of BC, whereas in the remaining 12 studies,\textsuperscript{24,26–29,37,41,44,45,49–51} investigations were for the diagnosis of metastases in patients with a diagnosis of BC or where the diagnosis of patients was unclear.

Quality of study methodology

In the assessment of study quality (Figure 2), approximately one-third (\(n = 10\)) of the studies,\textsuperscript{25–31,35,43,45–48,50} were considered to have investigated a representative spectrum of patients. In these studies, patients were selected in a consecutive series or all patients examined within a certain period of time were selected for investigation. In other studies, the method for patient selection was unclear or it appeared that the patients being investigated were not representative of those that might typically present for diagnosis of BC recurrence.

The majority of studies used an acceptable reference standard (\(n = 21\)) (histology or follow-up > 6 months) but in three studies in some patients follow-up was < 6 months,\textsuperscript{29,32,41} in two studies the duration of follow-up was unclear,\textsuperscript{24,42} and in one study changes in tumour markers were used to define the reference standard in some patients.\textsuperscript{25}

In the majority of comparative studies, PET or PET/CT were conducted after the comparator. The time delay between PET or PET/CT and the comparator was < 1 month in 11 studies,\textsuperscript{24,27,28,30,32,33,41,44,46,48,51} but, in the rest of the comparative studies, the time delay was either not reported or appeared to be longer than 1 month.

In most studies (\(n = 19\)), it was reported that all patients received a reference standard (avoiding partial verification bias). However, it was often not clear whether this was a criterion for enrolment into the study, i.e. patients without reference standard data (follow-up, histology, etc.) were excluded from the study and not mentioned in the reporting of results. Studies in which exclusions for incomplete follow-up were explicit,\textsuperscript{25–27,29,30,32,33,41,44,46,48,51} but may not have been of poorer study quality but may have simply been more transparent in their reporting of study methods.

The results of PET or PET/CT may have had some influence on the mode or intensity of subsequent patient follow-up (differential verification bias).

### TABLE 2 Numbers of studies and patients/lesions in the main groups for analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of studies*</th>
<th>Number of patients/lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET vs CIT</td>
<td>10</td>
<td>456 patients</td>
</tr>
<tr>
<td>PET/CT vs CIT</td>
<td>4</td>
<td>167 patients</td>
</tr>
<tr>
<td>PET vs PET/CT</td>
<td>4</td>
<td>188 patients</td>
</tr>
<tr>
<td>PET</td>
<td>25</td>
<td>1379 patients</td>
</tr>
<tr>
<td>PET/CT</td>
<td>5</td>
<td>225 patients</td>
</tr>
<tr>
<td><strong>Lesion data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET vs CIT</td>
<td>3</td>
<td>449 lesions (154 patients)</td>
</tr>
<tr>
<td>PET</td>
<td>7</td>
<td>690 lesions (331 patients)</td>
</tr>
<tr>
<td>PET/CT</td>
<td>2</td>
<td>443 lesions (79 patients)</td>
</tr>
</tbody>
</table>

* Numbers do not add up to 28 because some studies contain data for PET and PET/CT or patient and lesion data.
In most studies this was thought to have been likely or uncertain. In one study,\(^5\) follow-up was histology in all patients and therefore differential verification was not considered to have been a source of bias in this study.

Incorporation bias, the inclusion of index test results as part of the reference standard, may have played some role in most studies. Findings from PET or PET/CT may have influenced final diagnosis. However, the relative influence of PET or PET/CT findings compared with subsequent follow-up examinations may have been small and limited the size of this bias.

Blinding of the interpretation of PET or PET/CT to the results of the reference standard (index test blinding) clearly took place in nine studies.\(^{24,25,27,28,30,34,48,49}\) In the remaining studies the presence of blinding was unclear. The interpretation of PET or PET/CT will be naturally blinded in prospective studies as the reference standard diagnosis is assigned after PET or PET/CT during follow-up. In retrospective studies, if results are those of PET or PET/CT reassessed at a later date (after the reference standard), without blinding to final patient diagnosis, there is risk of bias. In the remaining studies, it was often unclear whether (1) studies were prospective or

### TABLE 3

<table>
<thead>
<tr>
<th>Index test</th>
<th>Comparator</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>PET/CT</td>
<td>CIT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient</td>
</tr>
<tr>
<td>Abe 2005(^24)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Aide 2007(^25)</td>
<td>✔</td>
<td>–</td>
</tr>
<tr>
<td>Bender 1997(^26)</td>
<td>✔</td>
<td>–</td>
</tr>
<tr>
<td>Dirisamer 2010(^27)</td>
<td>✔ ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Fueger 2005(^28)</td>
<td>✔ ✔</td>
<td>–</td>
</tr>
<tr>
<td>Gallowitsch 2003(^29)</td>
<td>✔ ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Goerres 2003(^30)</td>
<td>✔</td>
<td>–</td>
</tr>
<tr>
<td>Guillemand 2006(^31)</td>
<td>✔ ✔</td>
<td>–</td>
</tr>
<tr>
<td>Hathaway 1999(^32)</td>
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<td>–</td>
</tr>
<tr>
<td>Haug 2007(^33)</td>
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<td>✔</td>
</tr>
<tr>
<td>Hubner 2000(^34)</td>
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<td>✔</td>
</tr>
<tr>
<td>Kamel 2003(^35)</td>
<td>✔</td>
<td>–</td>
</tr>
<tr>
<td>Kim 2001(^36)</td>
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<td>–</td>
</tr>
<tr>
<td>Lin 2002(^37)</td>
<td>✔ ✔</td>
<td>–</td>
</tr>
<tr>
<td>Liu 2002(^38)</td>
<td>✔ ✔</td>
<td>–</td>
</tr>
<tr>
<td>Lonneux 2000(^39)</td>
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<td>✔</td>
</tr>
<tr>
<td>Moon 1998(^40)</td>
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<td>–</td>
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<tr>
<td>Ohta 2001(^41)</td>
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<td>✔</td>
</tr>
<tr>
<td>Pecking 2004(^42)</td>
<td>✔ ✔</td>
<td>–</td>
</tr>
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<td>Radan 2006(^43)</td>
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<td>✔</td>
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<td>Raileanu 2004(^44)</td>
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<td>✔</td>
</tr>
<tr>
<td>Santiago 2006(^45)</td>
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<td>✔</td>
</tr>
<tr>
<td>Schmidt 2008(^46)</td>
<td>✔ ✔</td>
<td>–</td>
</tr>
<tr>
<td>Suarez 2002(^47)</td>
<td>✔ ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Veit-Haibach 2007(^48)</td>
<td>✔ ✔</td>
<td>✔</td>
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<tr>
<td>Vranjesvic 2002(^49)</td>
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<td>✔</td>
</tr>
<tr>
<td>Wolfert 2006(^50)</td>
<td>✔ ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Yang 2002(^51)</td>
<td>✔ ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Study and date</td>
<td>Age (years)</td>
<td>Data</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td><strong>CIT comparator</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abe 2005</td>
<td>56 (35–81)</td>
<td>44</td>
</tr>
<tr>
<td>Dirisamer 2010</td>
<td>61 (40–84)</td>
<td>52</td>
</tr>
<tr>
<td>Gallowitsch 2003</td>
<td>58 (range NR)</td>
<td>62</td>
</tr>
<tr>
<td>Haug 2007</td>
<td>51 (28–73)</td>
<td>34</td>
</tr>
<tr>
<td>Hubner 2000</td>
<td>59</td>
<td>57</td>
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<tr>
<td>Ohta 2001</td>
<td>49 (29–79)</td>
<td>51</td>
</tr>
<tr>
<td>Radan 2006</td>
<td>60 (32–79)</td>
<td>46</td>
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<tr>
<td>Raileanu 2004</td>
<td>53 (range NR)</td>
<td>20</td>
</tr>
<tr>
<td>Veit-Haibach 2004</td>
<td>56 (36–80)</td>
<td>44</td>
</tr>
<tr>
<td>Vranjesvic 2002</td>
<td>54 (32–91)</td>
<td>61</td>
</tr>
<tr>
<td>Wolfort 2006</td>
<td>NR</td>
<td>23</td>
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<tr>
<td>Yang 2002</td>
<td>38–67</td>
<td>48</td>
</tr>
<tr>
<td>Study and date</td>
<td>Age (years) (range)</td>
<td>n</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>---</td>
</tr>
<tr>
<td><strong>MRI comparator</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bender 1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46 (32–74)</td>
<td>75</td>
</tr>
<tr>
<td>Goerres 2003&lt;sup&gt;b&lt;/sup&gt;</td>
<td>57 (32–76)</td>
<td>49</td>
</tr>
<tr>
<td>Hathaway 1999&lt;sup&gt;d&lt;/sup&gt;</td>
<td>58.4 (45–71)</td>
<td>10</td>
</tr>
<tr>
<td>Schmidt 2008&lt;sup&gt;f&lt;/sup&gt;</td>
<td>55 (24–79)</td>
<td>33</td>
</tr>
</tbody>
</table>

NR, not reported.

a Data that were used for analysis.
b Sixty-four PET scans in 57 patients, only 44 had CT.
c Only 37 of 46 patients had comparative CT data available.
d In this study data for restaging were presented on a patient basis and could therefore be interpreted in terms of diagnostic accuracy: correctly up-staged patients TP, correctly down-staged patients TN, under-staged patients FN, over-staged patients FP. This interpretation gave a conservative assessment of test accuracy as correct patient diagnosis may be achieved without necessarily correct patient staging.
e Only 18 of 23 patients had results for PET, conventional imaging and the reference standard.
f Lesions.
g Only 32 of 49 patients had follow-up data and PET and MRI results.
h Excluding patients being investigated for initial staging in the setting of primary diagnosis.
### TABLE 5  Characteristics of study populations for studies not comparing PET and/or PET/CT with other imaging tests

<table>
<thead>
<tr>
<th>Study and date</th>
<th>Age (years) (range)</th>
<th>n</th>
<th>Data n</th>
<th>Reason for investigation with PET or PET/CT</th>
<th>Prevalence (%)</th>
<th>Location of test</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aide 2007</td>
<td>61 (42–84)</td>
<td>35</td>
<td>35</td>
<td>Suspected recurrence based on increased tumour marker CA 15–3. No abnormality at conventional imaging 3 months before</td>
<td>80</td>
<td>Whole body</td>
<td>Histology or imaging and clinical follow up over &gt; 12 months</td>
</tr>
<tr>
<td>Fueger 2005</td>
<td>53 (29–80)</td>
<td>58</td>
<td>58</td>
<td>Restaging due to elevated tumour markers, symptoms or equivocal/suspicious conventional imaging findings</td>
<td>57</td>
<td>Whole body</td>
<td>Biopsy, other imaging and clinical follow-up</td>
</tr>
<tr>
<td>Guillemand 2006</td>
<td>62 (49–76)</td>
<td>14</td>
<td>14</td>
<td>Suspicion of recurrence based on increased tumour markers. Asymptomatic with inconclusive conventional imaging results</td>
<td>57</td>
<td>Whole body</td>
<td>Histology and follow-up (6–30 months)</td>
</tr>
<tr>
<td>Kamel 2003</td>
<td>55 (30–79)</td>
<td>60</td>
<td>46/57</td>
<td>Clinical suspicion of recurrence based on physical examination (n = 35) and abnormal CIT (n = 25)</td>
<td>52</td>
<td>Whole body</td>
<td>Histopathology or imaging/clinical follow-up for 6–30 months</td>
</tr>
<tr>
<td>Kim 2001</td>
<td>46 (28–62)</td>
<td>27</td>
<td>27</td>
<td>Clinical suspicion of recurrence or systemic disease based on physical examination or imaging studies</td>
<td>63</td>
<td>Whole body</td>
<td>Histology and/or imaging and clinical follow-up for &gt; 6 months</td>
</tr>
<tr>
<td>Lin 2002</td>
<td>48 (35–68)</td>
<td>36</td>
<td>36</td>
<td>Suspected local recurrence or systemic disease</td>
<td>11</td>
<td>Local</td>
<td>Histology and/or biopsy or follow-up &gt; 12 months</td>
</tr>
<tr>
<td>Liu 2002</td>
<td>(mean NR)</td>
<td>30</td>
<td>30</td>
<td>Suspected recurrence based on increased tumour marker levels, all patients negative for conventional imaging</td>
<td>93</td>
<td>Whole body</td>
<td>Histology or clinical imaging and follow-up &gt; 12 months</td>
</tr>
<tr>
<td>Suarez 2002</td>
<td>58 (35–80)</td>
<td>38</td>
<td>38</td>
<td>Suspicion of recurrence based on elevated tumour markers (asymptomatic and negative clinical examinations)</td>
<td>68</td>
<td>Whole body</td>
<td>Histology, other imaging or clinical follow-up for &gt; 12 months</td>
</tr>
<tr>
<td>Moon 1998</td>
<td>55 (30–80)</td>
<td>57</td>
<td>57</td>
<td>Clinical suspicion of recurrence based on symptoms (n = 10), mass lesions (n = 10) and increased tumour markers (n = 13)</td>
<td>51</td>
<td>Whole body</td>
<td>Follow-up imaging studies for &gt; 6 months</td>
</tr>
<tr>
<td>Lonneux 2000</td>
<td>57 (36–78)</td>
<td>39</td>
<td>39</td>
<td>Suspicion of recurrence based on increased tumour markers (n = 34) and clinical symptoms (n = 5)</td>
<td>85</td>
<td>Whole body</td>
<td>Follow-up (12–24 months)</td>
</tr>
<tr>
<td>Pecking 2004</td>
<td>51 (31–79)</td>
<td>291</td>
<td>291</td>
<td>Suspected BC recurrence based on elevated tumour markers (without any evidence of malignancies)</td>
<td>92</td>
<td>Whole body</td>
<td>Conventional imaging and pathology over 2 months or follow-up at 6 and 12 months</td>
</tr>
<tr>
<td>Santiago 2006</td>
<td>55 (34–82)</td>
<td>133</td>
<td>133</td>
<td>Suspicion of recurrence/metastases due to clinical suspicion (n = 31) equivocal conventional imaging (n = 63) or elevated tumour markers (n = 15) or staging/restaging (n = 33)</td>
<td>74</td>
<td>Whole body</td>
<td>Follow-up for &gt; 6 months with conventional imaging</td>
</tr>
</tbody>
</table>

CA, cancer antigen; NR, not reported.

a Data that were used for analysis.
b Forty-six examined for loco-regional recurrence, 57 examined for metastasis.
retrospective, (2) results were for scans assessed at the time of investigation or those of reassessment at a later date, and (3) whether blinding was used if scans were being reassessed. There was therefore some uncertainty around this item of quality.

In 10 studies, PET or PET/CT were interpreted with knowledge of relevant clinical information (knowledge of previous patient history and imaging results). In 10 studies assessors were blinded to previous relevant clinical information. In these studies, the assessment of incremental diagnostic accuracy of PET or PET/CT in addition to standard practice was likely to be underestimated. In eight studies, it was unclear what information was available to assessors.

<table>
<thead>
<tr>
<th>Study</th>
<th>(a)</th>
<th>(b)</th>
<th>(c)</th>
<th>(d)</th>
<th>(e)</th>
<th>(f)</th>
<th>(g)</th>
<th>(h)</th>
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<td>+</td>
<td>+</td>
<td>?</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<td>Aide 2007</td>
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<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bender 1997</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
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<td>?</td>
<td>+</td>
<td>–</td>
<td>?</td>
<td>?</td>
<td>+</td>
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<tr>
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<td>?</td>
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<td>–</td>
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<td>Rada 2006</td>
<td>+</td>
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<td>?</td>
<td>?</td>
<td>–</td>
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</tr>
<tr>
<td>Santiago 2006</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
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</tr>
<tr>
<td>Schmidt 2008</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>Suarez 2002</td>
<td>+</td>
<td>–</td>
<td>?</td>
<td>–</td>
<td>–</td>
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<td>–</td>
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<tr>
<td>Veit-Haibach 2007</td>
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<td>Yang 2002</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**FIGURE 2** Quality assessment of all included studies. (a) Quality item was applied to studies where diagnostic accuracy of tests was compared.
Characteristics and quality of PET or PET/CT technology

The characteristics and quality determinants of the PET and PET/CT technologies used are given in Appendix 2. Quality findings for three specific factors, identified as particularly important aspects of technical quality, are shown in Figure 2. PET and PET/CT machines were considered standard in all of the included studies, but attenuation correction was not used or not reported in the remaining nine studies. Interpretation of scans was predominantly by visual inspection. Standardised uptake values were used for sole classification in one study and, in seven studies, both visual and quantitative methods were used. In almost all studies it was reported that patients were asked to fast at the time of PET, but in only nine studies blood glucose levels were measured before the test and used as criteria for entry into the study. The dose of FDG ranged from 101 MBq to 740 MBq. In 18 studies dose appeared to have been adjusted on the basis of body weight, and in nine studies dose was constant. Dose was not reported in one study. Visual inspection of the three technical aspects of PET and PET/CT quality revealed no relationship between these aspects of quality and the diagnostic accuracy of PET or PET/CT.

Test accuracy results

For each of the objectives, results for patient and then lesion data are presented.

PET compared with CITs

Patient data

Ten studies investigated the diagnostic accuracy of conventional imaging techniques compared with PET on a patient basis. Figure 3 provides individual study data, Table 6 gives pooled summary estimates, Figure 4 gives quality scores and Figure 5 displays the SROC plane for studies directly comparing PET with CITs. In these studies, PET had significantly higher sensitivity [89%, 95% confidence interval (CI) 83% to 93% vs 79%, 95% CI 72% to 85%, relative sensitivity 1.12, 95% CI 1.04 to 1.21, p = 0.005] and significantly higher specificity (93%, 95% CI 83% to 97% vs 83%, 95% CI 67% to 92%, relative specificity 1.12, 95% CI 1.01 to 1.24, p = 0.036) (Table 6). The relative accuracy of PET did not appear to vary according to the type of CIT (bone scintigraphy, CW, CT) with which it was compared (p = 0.50).

For all studies of PET (n = 25) or CIT (n = 11) (indirect comparison), PET had significantly higher sensitivity (91%, 95% CI 87% to 93% vs 81%, 95% CI 73% to 87%, relative sensitivity 1.12, 95%
CI 1.04 to 1.21, \( p = 0.005 \) and significantly higher specificity (86%, 95% CI 79% to 91% vs 73%, 95% CI 59% to 83%, relative specificity 1.18, 95% CI 1.03 to 1.36, \( p = 0.017 \)) compared with CIT (Table 6 and Appendix 3, Figure 13).

**Sensitivity analysis**

When the comparison between PET and CIT was conducted with only studies in which PET and CIT (patient data) were done within a 1-month time period (\( n = 6 \)),24,27,33,41,44,48 PET was no longer significantly more sensitive than CIT (\( p = 0.4797 \)) but the significant increase in specificity remained (\( p = 0.022 \)) (Appendix 7, Table 11a and Figure 27).

**Lesion data**

For lesion-based data, three studies directly compared the diagnostic accuracy of PET with CIT.24,29,51 For these studies, there were no significant differences in sensitivity (relative sensitivity 0.93, 95% CI 0.76 to 1.13, \( p = 0.447 \)) or specificity (relative specificity 1.29, 95% CI 0.57 to 2.90, \( p = 0.540 \)) for PET compared with CIT (Appendix 4, Figures 17 and 18). In the indirect comparison of PET studies presenting lesion data (\( n = 7 \)) with CIT studies presenting lesion data (\( n = 3 \)), there were no significant differences in sensitivity (relative sensitivity 0.98, 95% CI 0.90 to 1.07, \( p = 0.624 \)) or specificity (relative specificity 2.57, 95% CI 0.41 to 16.07, \( p = 0.313 \)) for PET compared with CIT (Appendix 4, Table 9 and Figure 18).

**PET/CT compared with CITs**

**Patient data**

Four studies compared the accuracy of PET/CT with CIT on a patient basis27,33,43,48 and, in each
Results

In these studies, in comparison with CT, PET/CT had significantly higher sensitivity (95%, 95% CI 88% to 98% vs 80%, 95% CI 65% to 90%, relative sensitivity 1.19, 95% CI 1.03 to 1.37, \( n = 4, p = 0.015 \)) but the increase in specificity was not significant (89%, 95% CI 76% to 96% vs 79%, 95% CI 65% to 88%, relative specificity 1.13, 95% CI 0.99 to 1.29, \( p = 0.063 \)) (Table 7).

Sensitivity analysis

One study in which CT was not conducted at the same time as PET/CT was removed in the sensitivity analysis.\(^4\) Despite the continued pattern of advantage of PET/CT over CT in the remaining studies (\( n = 3 \)), PET/CT was no longer significantly more sensitive (\( p = 0.063 \)) or specific (\( p = 0.367 \)) compared with CIT (Appendix 7, Table 11b and Figure 28).

Lesion data

No studies comparing the accuracy of PET/CT with CIT presented lesion-based data.
**TABLE 7** Patient data: direct comparison of the sensitivity and specificity of PET/CT compared with CT and indirect comparison of PET/CT compared with a range of CITs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PET/CT sensitivity % (95% CI)</th>
<th>CIT sensitivity % (95% CI)</th>
<th>Relative sensitivity (95% CI)</th>
<th>PET/CT specificity % (95% CI)</th>
<th>CIT specificity % (95% CI)</th>
<th>Relative specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct PET/CT vs CT</td>
<td>95 (88 to 98), n = 4</td>
<td>80 (65 to 90), n = 4</td>
<td>1.19 (1.03 to 1.37) p = 0.015</td>
<td>89 (69 to 97)</td>
<td>77 (50 to 92)</td>
<td>1.15 (0.95 to 1.41) p = 0.157</td>
</tr>
<tr>
<td>Indirect PET/CT vs CIT</td>
<td>95 (89 to 97), n = 5</td>
<td>78 (72 to 84), n = 11</td>
<td>1.21 (1.11 to 1.31) p &lt; 0.0001</td>
<td>89 (76 to 96)</td>
<td>79 (65 to 88)</td>
<td>1.13 (0.99 to 1.29) p = 0.063</td>
</tr>
</tbody>
</table>

**FIGURE 7** Quality assessment of studies comparing PET/CT and CIT (CT).

**FIGURE 8** Summary receiver operating characteristic curve for studies directly comparing the diagnostic performance of PET/CT (■) and CT (◊) for patients with suspected BC recurrence.
PET and PET/CT compared with MRI

**Patient data**

Three studies investigated the diagnostic accuracy of PET and MRI on a patient basis, but the MRI technologies used in these studies were quite distinct. In one study, auxiliary and supraclavicular MRI was used to diagnose local recurrence. In the second study, whole-body MRI and/or CT was used to detect local recurrence and distant metastases, and in the third study, breast MRI was used for local recurrence. Results for these studies are shown in Figure 9. There were no significant differences in sensitivity or specificity between PET and MRI in any of these studies and, because of the differences in the MRI technologies, results from the studies were not combined.

**Lesion data**

One lesion-based study compared PET/CT with MRI and there was no significant difference in sensitivity and specificity for PET/CT compared with MRI (Appendix 4, Figure 19).

---

**PET/CT compared with PET**

**Patient data**

Four studies compared the accuracy of PET and PET/CT on a patient basis. Figure 10 provides individual study data, Table 8 gives pooled summary estimates, Figure 11 shows quality scores and Figure 12 displays the SROC planes for studies directly comparing PET with PET/CT. In these studies, PET/CT had significantly higher sensitivity (96%, 95% CI 90% to 98% vs 85%, 95% CI 77% to 91%, relative sensitivity 1.11, 95% CI 1.03 to 1.18, \( p = 0.006 \)) but the increase in specificity was not significant (89%, 95% CI 74% to 96% vs 82%, 95% CI 64% to 92%, relative specificity 1.08, 95% CI 0.94 to 1.20, \( p = 0.267 \)) compared with PET (Table 8 and Figure 12). For all patient-based studies of PET/CT (\( n = 5 \)) and PET (\( n = 25 \)), in indirect comparisons PET/CT had significantly higher sensitivity (96%, 95% CI 91% to 98% vs 90%, 95% CI 86% to 93%, relative sensitivity 1.06, 95% CI 1.01 to 1.10, \( p = 0.009 \)) but the increase in specificity was not significant (89%, 95% CI 77% to 95%, vs 86%, 95% CI 79% to 91%, relative specificity 1.04, 95% CI 0.95 to 1.13, \( p = 0.377 \)) compared with PET (Table 8 and Appendix 3, Figure 15).

---

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
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<tr>
<td>Bender 1997</td>
<td>64</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>48</td>
<td>0.71 (0.42 to 0.92)</td>
<td>0.96 (0.86 to 1.00)</td>
</tr>
<tr>
<td>Goerres 2003</td>
<td>74</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>58</td>
<td>0.93 (0.66 to 1.00)</td>
<td>0.97 (0.88 to 1.00)</td>
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<td>Hathaway 1999</td>
<td>32</td>
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<td>5</td>
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<td>13</td>
<td>1.00 (0.77 to 1.00)</td>
<td>0.97 (0.94 to 0.99)</td>
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<tr>
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<td>2</td>
<td>10</td>
<td>0.95 (0.84 to 0.99)</td>
<td>1.00 (0.69 to 1.00)</td>
</tr>
<tr>
<td>Fueger 2005</td>
<td>58</td>
<td>31</td>
<td>4</td>
<td>2</td>
<td>21</td>
<td>0.94 (0.80 to 0.99)</td>
<td>0.84 (0.64 to 0.95)</td>
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<td>1</td>
<td>8</td>
<td>0.96 (0.80 to 1.00)</td>
<td>0.89 (0.52 to 1.00)</td>
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<tr>
<td>Veit-Haibach</td>
<td>44</td>
<td>19</td>
<td>4</td>
<td>0</td>
<td>21</td>
<td>0.89 (0.67 to 0.99)</td>
<td>0.76 (0.55 to 0.91)</td>
</tr>
</tbody>
</table>

**FIGURE 9** Patient data for the diagnostic accuracy of PET and MRI in comparative studies. No studies compared the diagnostic accuracy of PET/CT with MRI on a patient basis.

**FIGURE 10** Patient data for the diagnostic accuracy of PET and PET/CT in comparative studies.
### TABLE 8 Patient data: direct and indirect comparisons of the relative sensitivity and specificity of PET/CT compared with PET

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PET/CT sensitivity % (95% CI)</th>
<th>PET sensitivity % (95% CI)</th>
<th>Relative sensitivity (95% CI)</th>
<th>PET/CT specificity % (95% CI)</th>
<th>PET specificity % (95% CI)</th>
<th>Relative specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct PET/CT vs PET</td>
<td>96 (90 to 98), n = 4</td>
<td>85 (77 to 91), n = 4</td>
<td>1.11 (1.03 to 1.18), p = 0.006</td>
<td>89 (74 to 96)</td>
<td>82 (64 to 92)</td>
<td>1.08 (0.94 to 1.20), p = 0.267</td>
</tr>
<tr>
<td>Indirect PET/CT vs PET</td>
<td>96 (91 to 98), n = 5</td>
<td>90 (86 to 93), n = 25</td>
<td>1.06 (1.01 to 1.10), p = 0.009</td>
<td>89 (77 to 95)</td>
<td>86 (79 to 91)</td>
<td>1.04 (0.95 to 1.13), p = 0.377</td>
</tr>
</tbody>
</table>

### FIGURE 11 Quality assessment of studies comparing the diagnostic accuracy of PET and PET/CT.

### FIGURE 12 Summary receiver operating characteristic plane for studies directly comparing the diagnostic performance of PET (□) and PET/CT (◊) for patients with suspected BC recurrence.
Sensitivity analysis
In all studies in which PET/CT was compared with PET, tests were undertaken simultaneously and no studies were therefore removed in the sensitivity analysis.

Lesion data
No studies comparing the accuracy of PET and PET/CT presented lesion-based data.

Diagnostic accuracy of PET and PET/CT

Patient data
Patient data were presented for PET in 25 studies and for PET/CT in five studies. Sensitivity and specificity for PET were 91% (95% CI 86% to 94%) and 86% (95% CI 79% to 91%) respectively and for PET/CT were 96% (95% CI 89% to 99%) and 89% (95% CI 75% to 95%) respectively. Study data used for the calculation of overall sensitivity and specificity and figures for test accuracy findings are given in Appendix 5 (Figures 20–23).

Lesion data
On a lesion basis, mean sensitivity and specificity for PET (n = 7 studies) were 89% (95% CI 78% to 95%) and 91% (95% CI 83% to 96%). Two studies assessed the accuracy of PET/CT on a lesion basis and pooled sensitivity and specificity were 96% (95% CI 80% to 99%) and 83% (95% CI 61% to 94%) respectively (no model could be fitted to the data). Study data used for the calculation of overall sensitivity and specificity and figures for test accuracy findings are given in Appendix 5 (Figures 24–26).

Changes in patient management
Changes in patient management in individual studies are given in Appendix 6. Overall, the estimated numbers of patients with changes in management in studies ranged from 11% to 74% (median 27%). In the three studies where only changes in management directly owing to PET or PET/CT were considered (patients were not correctly diagnosed by conventional imaging techniques), estimates tended to be lower (11–25%).

Variation in the diagnostic accuracy of PET
Further investigation of the diagnostic accuracy of PET was conducted to investigate factors that may influence test accuracy. Subgroup analysis was not conducted for PET/CT as these data were limited.

PET and location of disease

Table 12 and Figure 29 in Appendix 8 show the relative accuracy of PET in different locations of the body with lesion-based data (limited location-specific patient-based data were available). There were no significant differences in the sensitivity or specificity of PET for the detection of local recurrence, distant metastases or disease in lymph nodes.

PET and previous imaging results
Comparisons were made between studies of PET where all patients had previously had positive or equivocal results on other imaging modalities and studies in which previous imaging had been negative in all patients (Appendix 8, Table 13a and Figure 30). Sensitivity was not significantly different in studies with negative compared with positive/equivocal previous diagnostic imaging (relative sensitivity 0.99, 95% CI 0.899 to 1.093, p = 0.859) but specificity was significantly lower (relative specificity 0.734, 95% CI 0.560 to 0.960, p = 0.024).

PET and disease status at the time of investigation
In 14 studies, PET was exclusively used for the detection of recurrent BC in patients who had been cleared of initial disease. In the remaining 11 studies, PET was used to investigate further metastases in patients with known BC or, in some studies, the disease status of the patient group was a mixture of known and unknown BC diagnosis. There was no difference in sensitivity (relative sensitivity 1.004, 95% CI 0.924 to 1.092, p = 0.920) but specificity was significantly lower for studies in which patients were cleared of initial disease at the time of investigation compared with studies in patients with diagnosed BC or in mixed diagnosis populations (relative specificity 0.844, 95% CI 0.734 to 0.971, p = 0.018) (Appendix 8, Table 13b and Figure 31).

PET and assessors knowledge of previous clinical findings
In nine studies, assessors of PET were blinded to information on previous clinical examination and imaging. In eight
studies\textsuperscript{26,29,36,57,58,39,45,50} assessors had access to previous clinical results, and in eight studies\textsuperscript{28,31,52,53,40,42,44,47} it was unclear whether assessors had knowledge of previous findings. There was no difference in sensitivity (relative sensitivity 0.962, 95\% CI 0.886 to 1.043, \( p = 0.346 \)) or specificity (relative specificity 1.045, 95\% CI 0.910 to 1.201, \( p = 0.533 \)) between studies where assessors did not have information on previous findings compared with studies where assessors had information or where access to previous information was unclear (Appendix 8, Table 13c).

\textbf{FP and FN PET results}

The numbers of FPs and FNs for PET and PET/CT are given for studies where data was available (Appendix 9, Tables 14 and 15). FPs fell largely into three categories: infections and inflammation (41\%), physiological muscle uptake (29\%) and degenerative process/old fracture sites (10\%), while the remaining 20\% were assigned to other artifacts of measurement. FNs were most commonly lesions in the lymph nodes or bone.
Chapter 5
Discussion

Principal findings
PET compared with CITs
In the patient-based analysis, absolute estimates of sensitivity and specificity were around 10% higher for PET compared with CIT and differences were statistically significant for both direct and indirect comparisons (Table 6). Lesion-based results were inconsistent with results for patient-based data and no significant differences were found in sensitivity or specificity for comparisons of PET with CIT (Appendix 4, Table 9). Lesion data are considered to be less reliable than patient data and may also relate more to the ability of tests to stage, rather than diagnose, disease. There was a high degree of heterogeneity between comparative studies presenting lesion data (Appendix 4, Figure 16) and, for the study in which PET had very poor lesion-based sensitivity (56%), patient-based data indicated a typical to high level of sensitivity (97%). Lesion-based data were not used for primary interpretation, not only owing to the small sample size and seemingly erratic nature of the data but also because of the wide recognition that patient-based data are a more true representation of the accuracy of patient diagnosis. From patient-based data, it appears that PET may give improved diagnostic accuracy compared with CIT for the diagnosis of BC recurrence, but there may be some constraints and uncertainties related to this.

In many of the included studies, sources of bias may bring some uncertainty around the apparent advantage of PET over CIT. In many of the studies comparing PET and CIT, it was unclear whether the patients selected were representative of those that might normally be examined in this context (Figure 4). Inclusion criteria were often not stated and it was unclear whether consecutive patients were enrolled or whether investigators selected particular individuals to take part in the study. Another aspect of quality identified as potentially important was the time delay between comparator tests and PET. Differences observed in some studies may be due partly to PET being conducted at a later time point, when disease was likely to be further developed and more detectable. In the sensitivity analysis including only studies in which PET and CIT were conducted within a 1-month time period, the difference in sensitivity between PET and CIT was reduced and became non-significant (Appendix 7, Table 11a and Figure 27), although the difference in specificity remained.

There may also be uncertainty around the magnitude of advantage of PET over different types of existing diagnostic tests. Relative accuracy may vary depending on the location of investigation and the accuracy of the particular comparative test conventionally used for diagnosis in that location. Included comparator groups classed as CIT fell into three categories: CW (a range of examination and imaging techniques), CT and bone scintigraphy. Further inspection identified that, for the three studies investigating the diagnosis of bone metastases, a less consistent pattern of effect was observed, with variable advantage in sensitivity and specificity over bone scintigraphy. A recent systematic review compared the diagnostic accuracy of PET with bone scintigraphy. In that review, for patient-based data, PET had similar sensitivity to bone scintigraphy (81%, 95% CI 70% to 89% and 78%, 95% CI 67% to 68%, respectively) and higher specificity but not significantly so (93%, 95% CI 84% to 97% and 79%, 95% CI 40% to 95% respectively). However, in formal statistical testing, there was no difference in the relative accuracy of PET when compared with CW, CT and bone scintigraphy (p = 0.50), suggesting that PET may have similar benefit when used in different contexts.

The absence of comparisons of PET with individual conventional diagnostic tests may be a limitation of this review. However, to some extent this may be counteracted by the benefit of making some estimation of the general advantage of adding PET to standard practice. The decision to combine studies of different conventional tests was made not only because of the limited number of available studies for each individual test but also so that the review might be more applicable to current practice. In practice it may be difficult to make distinctions in the use of PET for specific case presentations and there may be value in assessing whether there is likely to be a general advantage for its use for patients presenting with suspected recurrence.
It is likely that any potential advantage of PET should be considered in the context of its use in addition to, rather than instead of, existing strategies. The aim of this review was to assess comparative diagnostic accuracy in addition to standard practice but, in some of the included studies, assessors of PET were blinded to the results of previous imaging tests. This is displayed in the quality assessment as ‘relevant clinical information?’, i.e. were assessors blinded to previous clinical results? (Figure 4). In the subgroup analysis, the accuracy PET did not appear to be affected by whether assessors had knowledge of previous patient investigations (Appendix 8, Table 13c). Also, although the specificity of PET was lower in studies where previous imaging tests had shown negative compared with positive/equivocal findings, the level of sensitivity was similar (Appendix 8, Table 13a) suggesting that PET may be useful for disease diagnosis where previous imaging tests have failed. However, despite some suggestion that PET may be useful as a replacement technology, uncertainty remains around its comparative advantage in every setting and this does not warrant the recommendation of PET as a replacement to conventional imaging procedures.

Overall, PET appears to give improved diagnostic accuracy compared with CIT. However, there may be some uncertainty around these findings. There is currently insufficient evidence for the use of PET as a replacement for existing imaging technologies but, in addition to standard practice, it may give improved diagnostic accuracy compared with conventional imaging.

PET/CT compared with CITs

Positron emission tomography/computed tomography was compared with CT in four studies. PET/CT showed significantly improved sensitivity for both direct and indirect patient-based comparisons (absolute sensitivity was ~15% higher) but the absolute increase in specificity (~10%) was not statistically significant (Table 7). Differences were consistency shown across all of the four studies (Figure 8), with increases in sensitivity and specificity in each case where it could be achieved (in one study specificity was 100% for both PET/CT and CT).

In three of the four studies, patient samples appeared to be a representative spectrum of those that might be typical in clinical practice. CTs were performed as part of the PET/CT in three of the four studies but, in the other study, a separate CT was conducted earlier and the time interval before PET/CT in some of the patients was more than 1 month. After removal of this study in the sensitivity analysis, the increase in sensitivity compared with CT became non-significant (Appendix 7, Table 11b and Figure 28). However, a consistent pattern of effect was still observed for the remaining studies.

The poor availability of studies comparing the diagnostic accuracy of PET/CT with other imaging tests may to some extent limit the interpretation of findings. In comparative studies of PET/CT, the only CIT used was CT and there may be some uncertainty around the relative advantage of PET/CT over different individual CITs. In the indirect comparison, when PET/CT was compared with the range of conventional diagnostic tests (Table 7 and Appendix 3, Figure 14), sensitivity was 20% higher for PET/CT than for CIT ($p < 0.0001$). However, as this analysis was not based on direct comparison studies, the finding may be interpreted with caution, and uncertainty remains around the variation in benefit of PET/CT when compared with different conventional tests.

In three of the four studies, assessors of PET/CT were blind to CT results and previous clinical findings (Figure 7) and it may be that, in situations where the choice of CIT is CT, PET/CT can be used as a replacement test. However, the presence of uncertainty around the comparative advantage of PET/CT over other CITs is likely to make a conservative approach more appropriate. As for PET, it may be prudent to consider PET/CT in addition to, rather than instead of, conventional diagnostic tests.

Despite the small number of available studies, the consistent improvement in test accuracy for PET/CT compared with CT provides reasonable evidence for an advantage of PET/CT over CT. PET/CT may give diagnostic advantage over other CITs but currently there is no direct evidence of the comparative advantage of PET/CT over other imaging tests.

PET and PET/CT compared with MRI

In the current review only three studies compared PET and MRI on a patient basis and, as the types of MRI technology used were different, results of these studies could not be combined. There were no significant differences in sensitivity or
specificity between PET and MRI in any of these studies and further research may be required to assess their comparative diagnostic accuracy. Only one study compared the diagnostic accuracy of PET/CT with MRI and, for this study, data were presented on a lesion basis. Sensitivity and specificity were similar for PET/CT and MRI and further patient-based studies may be important to establish the comparative accuracy of PET/CT and MRI.

PET/CT compared with PET

In this review, for all studies comparing the diagnostic accuracy of PET with PET/CT ($n = 4$), PET/CT was consistently shown to have improved sensitivity compared with PET (Figure 12). Differences in sensitivity were significant for both direct and indirect comparisons, but differences in specificity were not (Table 8). In these studies, PET/CT was used for the diagnosis of local disease and metastases in different locations and the advantage of PET/CT over PET appears to be true when considered for the detection of disease over a range of locations.

In three of the four studies, patient samples appeared to be representative of patients that might be typical in clinical practice. All studies interpreted PET images obtained during the course of conducting PET/CT and, as tests were conducted simultaneously, none needed to be removed in the sensitivity analysis.

Despite the limited number of PET/CT studies, there appears to be reasonable evidence that PET/CT gives improved sensitivity compared with PET over the whole body. If it is found to be more cost-effective, PET/CT may be considered for use instead of PET in this context.

Diagnostic accuracy of PET and PET/CT

In the current review, the sensitivity and specificity of PET are very similar to those obtained in the most recently conducted systematic review19 (sensitivity 91% compared with 90% and specificity 86% compared with 87%), suggesting that more recent studies, not included in the previous review, have not influenced overall estimates of diagnostic accuracy. The criterion for inclusion in both of these reviews was that a dedicated PET machine was to have been used but, since the development of these types of instruments, there have been no major changes in the technology of PET (Dr Theodoros Arvanitis, University of Birmingham, 2009, personal communication). This review supports the suggestion that PET technology has reached a consistent level and confirms previous findings. No previous systematic review has attempted to meta-analyse the accuracy of PET/CT and the current review gives no indication as to whether the diagnostic accuracy of this technology has changed, or is likely to change, during its evolution.

Inspection of the individual results for PET studies (Appendix 5, Figure 20) shows heterogeneity in estimates of sensitivity and specificity (for some studies 95% CIs do not overlap). This was not observed with studies of PET/CT (Appendix 5, Figure 21) but the number of these studies was smaller. It appears likely that there are differences in the patient groups, study methods or mode of investigation in studies of PET and this may bring uncertainty around the overall estimates for test accuracy in this context.

Changes in patient management and outcome

Despite the reasonable data available to determine the diagnostic accuracy of PET and PET/CT, their impact on patient management is uncertain. Individual studies assert that these technologies do lead to changes in management, but it is difficult to determine to what extent these changes would have taken place with conventional diagnostic procedures and, more importantly, whether they resulted in changes in final patient outcome.

Some sense about impact on patient management may be gained by considering the consequences of FN and FP results, both of which appear to be reduced when comparing PET with conventional imaging and PET/CT with PET. FN results generally lead to delayed treatment, which is likely to be important where the condition is life threatening. In distantly recurring BC delaying treatments with palliative intent will make a considerable impact on quality of life over the short to medium term. For systemic treatments aiming to alter the course of metastatic disease, there are also likely to be modest gains in survival and thus FN CITs will delay these treatments. Some patients will suffer a sufficient fall in performance status by the time of diagnosis for there to be fewer appropriate treatment options available. The consequences of avoidance of FPs, which also appears to be achieved by the use of PET and PET/CT, are clearer. Avoiding unnecessary exposure
to costly and potentially harmful, occasionally life-threatening, treatment such as chemotherapy is clearly desirable and could be anticipated to bring about improvements in quality of life, if not survival. Avoiding the anxiety associated with treatment and the fact that BC has recurred adds to this. This prediction of impact on the patient assumes that there are no further steps in the diagnostic pathway beyond conventional imaging with or without PET/CT. Biopsies of possible BC recurrences following CITs are sometimes performed. In these cases, FNs can result in significant unnecessary risk and morbidity to patients. Overall, there appears to be a clear potential value for a diagnostic technique that reduces both the rate of FPs and FNs.

Of primary interest is the impact of PET and PET/CT on patient prognosis and survival. If detection of recurrence by PET or PET/CT gives patients additional quality of life or extends survival, these technologies may be important diagnostic tools. In order to directly assess the effects of PET or PET/CT on long-term outcomes, large-scale intervention studies may be required. Owing to the intensive follow-up and the large sample sizes required, these types of studies are expensive, and modelling work may be used to provide information on whether these trials are worthwhile. The construction of models relating diagnostic accuracy and features of disease progression to long-term patient outcomes would give information on the potential impact of PET and PET/CT on patient outcome. Where modelling findings suggest a potential benefit of PET or PET/CT, this may support the implementation of large-scale interventional studies to investigate long-term impacts.

**Variation in the diagnostic accuracy of PET**

The variation in estimates of test accuracy for PET was investigated by conducting subgroup analysis on this group of studies, but no conclusive pattern emerged to explain the variability. There was no apparent difference in the accuracy of PET in different locations of the body, although this analysis was conducted using lesion-based data (may be less reliable than patient-based data). The diagnosis of local disease may be considered more valuable than the diagnosis of disease in lymph nodes or distant metastases as surgical treatment may more realistically be employed for local recurrence. Findings suggest that the overall estimates of diagnostic accuracy for PET can be applied in the specific case of local recurrence and this may help to better predict the potential benefits from the use of PET. Data for the use of PET/CT for diagnosis in different locations were limited, and location-specific analysis could not be conducted. However, it may be anticipated that similar findings would be shown and PET/CT may have similar diagnostic accuracy for local recurrence as for metastatic disease.

PET had similar sensitivity in studies where patients had been negative on previous imaging tests compared with studies where previous findings were positive/equivocal but specificity was significantly reduced (Appendix 8, Table 13a). Specificity was also significantly reduced for studies in which patients were cleared of BC at the time of investigation compared with other studies (Appendix 8, Table 13b). Selective patient sampling by previous imaging testing in these studies may have had some impact on apparent specificity. However, it is difficult to ascertain whether these observations are due to random statistical significance of if they may be confounded by other potentially moderating factors. As numerous factors are likely to be involved in determining diagnostic accuracy of PET, it is difficult to identify specific factors responsible for the heterogeneity observed. Also, as subgroup analysis was not restricted to the group of comparative studies, it was not possible to examine whether these observations would result in a comparative difference in test accuracy between PET and CIT.

**Strengths and limitations of the review**

One strength of the current review was that it was likely to have included the majority of the relevant literature. This review included 14 of the 18 studies included in the most recent previous systematic review. The current review was restricted to studies performed in the secondary diagnostic setting and this led to the exclusion of the other four studies. The current report includes an additional 14 studies, not covered by the previous review and, for the first time, reviews evidence for the diagnostic accuracy of PET/CT.

A second strength of this work was the comparative nature of the review. Estimations of individual values for diagnostic accuracy may give some information on the likely benefit of these technologies. However, comparative analysis allows proper investigation of the possible advantage
of adopting PET or PET/CT over conventional diagnostic strategies.

A further strength of this review may be the use of direct comparisons. The large spread of results for test accuracy, particularly for PET, suggests that there are other important mediators of test accuracy that influence results. In indirect comparisons, where results from different studies are compared, the comparison of PET and PET/CT with CIT may be affected by many factors associated with the populations, study methods and technologies used. In direct comparisons, some of these moderating factors are avoided as index and comparator tests are conducted in the same populations and the same study methods are used.

Although direct comparisons are desirable and can eliminate between-study variability associated with indirect comparisons, methods currently recommended for meta-analysis of test accuracy studies do not exploit the paired nature of the data when all patients receive each of the two tests under evaluation as well as the reference standard. For such analyses to be possible, test accuracy data from primary studies must be presented in a suitable format, i.e. joint classification of the results of the tests, but this is rarely the case. Only six of the studies in this review presented data in this format, one comparing PET with PET/CT28 two comparing PET with MRI,50,52 one comparing PET with bone scintigraphy44 and two comparing PET with CW.49,50 Methods that combine evidence from both direct and indirect comparisons, such as the adjusted indirect comparison method and network meta-analysis techniques for comparing health-care interventions, make optimal use of all relevant data but such methods are lacking for test comparisons. Current methodology may result in a more conservative estimate of relative differences in test accuracy when analysis is restricted to direct comparisons and this may be a limitation of this review.

A limitation of this review was that subgroup analysis was conducted on the whole set of studies investigating PET (n = 25) and not on comparative studies for PET (n = 10) and PET/CT (n = 4). This was necessary as the number of comparative studies was limited. However, it is difficult to interpret subgroup findings because within-test analysis does not give information on the actual diagnostic advantage in different settings and patient populations. If more data were available, analysis of differences in the diagnostic accuracy of PET or PET/CT in different settings or groups relative to conventional tests may be useful to inform decision-making about specific contexts for their use.

A limitation in the interpretation of this review may be the distinction of results for direct and indirect comparisons. It should be noted that, particularly for PET/CT, studies included in the direct comparison analysis also largely constituted the studies included in the indirect comparison analysis. Because some of the study data are used in both analyses, although indirect comparisons may be taken to some extent to support comparative results, findings are not independent. Although they may be useful for corroborating findings, results for direct and indirect comparisons should not be interpreted as independent outcomes.

A further limitation of indirect comparisons in the current review is the exclusion of conventional imaging studies that were not compared with PET or PET/CT. Studies of CIT were only included in this review if they contained a comparison with PET or PET/CT, and it is unclear whether this could have had an impact on findings. In order to make true independent comparisons, an additional systematic review of all CIT studies would be necessary. However, owing to the large volume of evidence relating to each conventional diagnostic strategy, the workload involved would be sizable.

A further limitation of this review is the small size of the majority of included studies. The average (median) size of studies was 45 (10–291) and only 456 and 167 patients constituted the analysis groups for PET and PET/CT versus CIT respectively. Although sample sizes were adequate for testing statistical significance, they may, to some extent, limit the generalisability of these findings.

The short duration over which this review was conducted to some extent limited the number of included studies. As some studies appeared to have recorded the relevant information but not included it in publications, authors were contacted to request raw data for inclusion in the review. One investigator provided the relevant data33 but, in other cases, data were not retrieved and further follow-up may have proved successful in obtaining data and increasing the information available in this review.
Chapter 6

Conclusions

- For the detection of BC recurrence, in addition to conventional imaging techniques, PET may generally offer improved diagnostic accuracy compared with current standard practice. Uncertainty remains around its use as a replacement, rather than an add-on, to existing imaging technologies.
- PET/CT appears to show a clear advantage over CT for the diagnosis of BC recurrence. Although PET/CT may give an advantage over other conventional imaging strategies, its incremental value over other tests has yet to be assessed in studies directly. Concurrent use with, rather than replacement of, other conventional tests may be appropriate.
- PET/CT appears to show a clear advantage over PET and, if found to be more cost-effective, it may be preferred to PET for use in this context.
- PET and PET/CT appear to have some impact on patient management but there is currently no evidence of the effects of their use on patient outcome.

Recommendations for future research

- Further study of the diagnostic accuracy of PET/CT compared with specific CITs may help to assess the comparative advantage of PET/CT over different CITs.
- Further research may inform the use of PET/CT as a replacement technology. In future research, reading of scans with assessors both blinded and unblinded to previous results would allow assessment of the comparative accuracy of PET/CT as a replacement compared with an add-on technology. This may help to determine whether PET/CT may potentially be used as a replacement to tests currently used in clinical practice.
- Further research may investigate the application of MRI of the whole body compared with PET/CT in this context.
- Modelling work (to be published in another report) may be used to examine the potential impact of PET/CT on long-term patient outcomes. This work may be used to inform the implementation of large-scale intervention studies to examine the long-term impact of PET/CT.

Implications for policy

Positron emission tomography/computed tomography has largely superseded PET in current practice and the apparent advantage of PET/CT over PET found in this review supports this move. On the basis of some of the uncertainties observed, it may be premature to make recommendations about changes in the precise diagnostic role of PET/CT in current practice. However, current recommendations for its use following equivocal findings on conventional imaging techniques may be justified. It appears that PET/CT may be useful as an addition to current practice for the diagnosis of BC recurrence but this should be reassessed in light of the analysis of its cost-effectiveness.
Acknowledgements

We would like to thank Professor Pat Price and Dr Peter Clark for providing clinical comments and guidance on this report.

Contribution of authors

Mary Pennant contributed to the development of the protocol, conducted abstract and full-paper screening, data extraction and quality assessment, contributed to the interpretation of findings and was responsible for writing the report. Yemisi Takwoingi was responsible for the statistical analysis and reviewed the report. Lucy Pennant conducted the data extraction. Clare Davenport contributed to the interpretation of findings and reviewed the report. Anne Fry-Smith and Anne Eisinga devised the search strategy and Anne Fry-Smith carried out the searches. Lazaros Andronis reviewed the protocol and the report. Theo Arvanitis gave technical guidance on imaging technologies and reviewed the report. Jon Deeks gave guidance for statistical analysis and reviewed the report. Chris Hyde developed the protocol, conducted quality assessment, contributed to the interpretation of findings and reviewed the report.
References


23. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a
References


# Appendix 1

## MEDLINE search strategy

**Database: Ovid MEDLINE 1950 to Week 2 May 2009**

1. exp tomography, emission-computed/ (52882)
2. (emission adj2 comput$ adj2 tomograph$).tw. (9710)
3. (tomograph$ adj2 emission adj2 comput$).tw. (9941)
4. (radionuclide-comput$ adj2 tomograph$).tw. (19)
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10. or/1–9 (65938)
11. exp breast neoplasms/ (162433)
12. (breast$ adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$ or malignan$ or tumo?r$ or neoplas$)).tw. (149035)
13. or/11–12 (191059)
14. 10 and 13 (1422)
15. (recur$ or relaps$ or metasta$ or restag$ or re-stag$).mp. (633461)
16. 14 and 15 (750)
Appendix 2

Characteristics of FDG-PET technology
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<th>Study and date</th>
<th>Camera</th>
<th>Attenuation correction</th>
<th>Interpretation</th>
<th>Image reconstruction</th>
<th>Positive scan definition given?</th>
<th>BG testing and fasting</th>
<th>FDG dose</th>
<th>Uptake time</th>
<th>Acquisition time</th>
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<tbody>
<tr>
<td>Abe 2005⁴⁻</td>
<td>ECAT EXACT HR+</td>
<td>Y</td>
<td>Visual</td>
<td>Ordered-subset expectation maximisation (OSEM) algorithm</td>
<td>N</td>
<td>BG measured as 87–135 mg/dl, &gt; 4-hour fast</td>
<td>101–434 MBq</td>
<td>60 minutes</td>
<td>2 minutes</td>
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<tr>
<td>Aide 2007⁵⁻</td>
<td>HR+ CTI siemens</td>
<td>Y</td>
<td>Visual</td>
<td>Iterative</td>
<td>N</td>
<td>BG &lt; 120 mg/dl, fast &gt; 6hour</td>
<td>2 MBq/kg</td>
<td>60 minutes</td>
<td>7 minutes</td>
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<tr>
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<td>ECAT EACT 927/47</td>
<td>Y</td>
<td>Visual</td>
<td>Filtered back projection</td>
<td>Y</td>
<td>Given BG test, don’t give results, fasting</td>
<td>185–370 MBq</td>
<td>45–60 minutes</td>
<td>10 minutes per position</td>
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<td>BG &lt; 150 mg/dl, fasting</td>
<td>370 MBq</td>
<td>50 minutes</td>
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<td>Fueger 2005⁸⁻</td>
<td>REVEAL RT PET/CT scanner</td>
<td>Y</td>
<td>Visual</td>
<td>Filtered backprojection for CT. Iterative algorithms (OSEM) for PET</td>
<td>Y</td>
<td>Only those &lt; 200 mg/dl included, fast &gt; 6hours</td>
<td>7.77 MBq/kg</td>
<td>60 minutes</td>
<td>NR</td>
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<tr>
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<td>ECAT ART Siemens CTI MS</td>
<td>Y</td>
<td>Visual</td>
<td>Iterative</td>
<td></td>
<td>BG &lt; 130 mg/dl, fasting</td>
<td>200 MBq</td>
<td>70 minutes</td>
<td>9 minutes</td>
</tr>
<tr>
<td>Goerres 2003¹⁰⁻</td>
<td>GE Advance</td>
<td>Y</td>
<td>Visual</td>
<td>Iterative OSEM algorithm</td>
<td>Y</td>
<td>4 hours fasting</td>
<td>386 MBq</td>
<td>45 minutes</td>
<td>4 minutes per field of view</td>
</tr>
<tr>
<td>Guillemard 2006¹¹⁻</td>
<td>Biograph PET/CT, Siemens AG</td>
<td>Y</td>
<td>Visual</td>
<td>NR</td>
<td>N</td>
<td>BG controlled before, &gt; 6-hour fast</td>
<td>300–520 MBq</td>
<td>60 minutes</td>
<td>~2 minutes</td>
</tr>
<tr>
<td>Hathaway 1999¹²⁻</td>
<td>GE Advance</td>
<td>Y</td>
<td>Visual and SUV</td>
<td>Filtered back-projection</td>
<td>Y</td>
<td>BG &gt; 80&lt; 140 mg/dl, &gt; 4-hour fast</td>
<td>260–370 MBq</td>
<td>45–60 minutes</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Haug 2007¹³⁻</td>
<td>Phillips Gemini</td>
<td>Y</td>
<td>Visual and SUV</td>
<td>NR</td>
<td>Y</td>
<td>Tested ensure &lt; 120 mg/dl, &gt; 6-hour fast</td>
<td>200 MBq</td>
<td>60 minutes</td>
<td>3 minutes</td>
</tr>
<tr>
<td>Hubner 2000¹⁴⁻</td>
<td>ECAT/EACT 921</td>
<td>Y</td>
<td>Visual and SUV</td>
<td>Using 0.4 Hann filter and 1.5 zoom</td>
<td>Y</td>
<td>BG recorded but not given, 4-hour fast</td>
<td>185–370 MBq</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kamel 2003¹⁵⁻</td>
<td>GE Advance</td>
<td>Y</td>
<td>Visual</td>
<td>Iterative and some standard filtered back projection</td>
<td>Y</td>
<td>4-hour fast</td>
<td>300–400 MBq</td>
<td>45 minutes</td>
<td>4 minutes</td>
</tr>
<tr>
<td>Kim 2001¹⁶⁻</td>
<td>ECAT EXACT 47</td>
<td>Y</td>
<td>Visual and SUV</td>
<td>NR</td>
<td>Y</td>
<td>Overnight fast</td>
<td>370–555 MBq</td>
<td>60 minutes</td>
<td>6 minutes, 30 minutes if evidence</td>
</tr>
<tr>
<td>Study and date</td>
<td>Camera</td>
<td>Attenuation correction</td>
<td>Interpretation</td>
<td>Image reconstruction</td>
<td>Positive scan definition given?</td>
<td>BG testing and fasting</td>
<td>FDG dose</td>
<td>Uptake time</td>
<td>Acquisition time</td>
</tr>
<tr>
<td>---------------</td>
<td>--------</td>
<td>------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-------------------------------</td>
<td>------------------------</td>
<td>----------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Lin 2002&lt;sup&gt;27&lt;/sup&gt;</td>
<td>GE Advance whole body</td>
<td>N</td>
<td>Visual</td>
<td>Standard filtered back projection</td>
<td>N</td>
<td>4-hour fast</td>
<td>370 MBq</td>
<td>NR</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Liu 2002&lt;sup&gt;28&lt;/sup&gt;</td>
<td>CTI-Siemens ECAT HR +</td>
<td>Y</td>
<td>Visual</td>
<td>NR</td>
<td>Y</td>
<td>Fast &gt; 4 hours</td>
<td>370 MBq</td>
<td>30–45 minutes</td>
<td>7 minutes</td>
</tr>
<tr>
<td>Lonneux 2000&lt;sup&gt;29&lt;/sup&gt;</td>
<td>ECAT EXACT HR, CTI</td>
<td>Y, N</td>
<td>Visual</td>
<td>Filtered backprojection (no attenuation correction) or attenuation-weighted OSEM</td>
<td>Y</td>
<td>&gt; 6-hour fast</td>
<td>370 MBq</td>
<td>60 minutes</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Moon 1998&lt;sup&gt;30&lt;/sup&gt;</td>
<td>ECAT 931 (67%) and ECAT 961</td>
<td>N</td>
<td>Visual</td>
<td>NR</td>
<td>N</td>
<td>No exclusions, &gt; 6-hour fast</td>
<td>370–555 MBq</td>
<td>40 minutes</td>
<td>4 minutes (931) or 6 minutes (961)</td>
</tr>
<tr>
<td>Ohta 2001&lt;sup&gt;31&lt;/sup&gt;</td>
<td>ECAT EXACT 47</td>
<td>NR</td>
<td>Visual</td>
<td>NR</td>
<td>N</td>
<td>?, &gt; 4-hour fast</td>
<td>260–370 MBq</td>
<td>45 minutes</td>
<td>7 minutes</td>
</tr>
<tr>
<td>Pecking 2004&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Discovery LS</td>
<td>Y</td>
<td>SUV</td>
<td>NR</td>
<td>Y</td>
<td>NR</td>
<td>296–407 MBq</td>
<td>60 minutes</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Radan 2006&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Discovery LS</td>
<td>Y</td>
<td>Visual</td>
<td>Order subsets expectation maximisation</td>
<td>Y</td>
<td>BG &lt; 11 mmol/l, fasting 4–6 hours</td>
<td>370–666 MBq</td>
<td>60 minutes</td>
<td>4 minutes</td>
</tr>
<tr>
<td>Raileanu 2004&lt;sup&gt;34&lt;/sup&gt;</td>
<td>ADAC-philips</td>
<td>NR</td>
<td>Visual</td>
<td>NR</td>
<td>N</td>
<td>NR</td>
<td>2 MBq/kg</td>
<td>1 hour</td>
<td>NR</td>
</tr>
<tr>
<td>Santiago 2006&lt;sup&gt;35&lt;/sup&gt;</td>
<td>GE Advance</td>
<td>NR</td>
<td>Visual</td>
<td>Filtered backprojection</td>
<td>N</td>
<td>BG &lt; 200 mg/dl, &gt; 6-hour fast</td>
<td>370–550 MBq</td>
<td>45–60 minutes</td>
<td>6 minutes</td>
</tr>
<tr>
<td>Schmidt 2008&lt;sup&gt;36&lt;/sup&gt;</td>
<td>2-detector row scanner (Gemini)</td>
<td>Y</td>
<td>Visual + SUV</td>
<td>Row action maximum likelihood algorithm</td>
<td>Y</td>
<td>Fast &gt; 6 hours</td>
<td>202–378 MBq</td>
<td>60 minutes</td>
<td>NR</td>
</tr>
<tr>
<td>Suarez 2002&lt;sup&gt;37&lt;/sup&gt;</td>
<td>ADAC C-PET-250</td>
<td>Y</td>
<td>Visual and SUV</td>
<td>Iterative</td>
<td>Y</td>
<td>BG &lt; 120 mg/dl, &gt; 6-hour fast</td>
<td>2 MBq/kg</td>
<td>60 minutes</td>
<td>NR</td>
</tr>
<tr>
<td>Veit-Haibach 2007&lt;sup&gt;38&lt;/sup&gt;</td>
<td>CT - Somatom emotion PET -ECAT HR+</td>
<td>Y</td>
<td>Visual and SUV</td>
<td>Iterative</td>
<td>Y</td>
<td>BG measured to ensure normal, fast 4 hours</td>
<td>340 MBq</td>
<td>1 hour</td>
<td></td>
</tr>
<tr>
<td>Vranjesevic 2002&lt;sup&gt;39&lt;/sup&gt;</td>
<td>ECAT EXACT or HR+</td>
<td>N (20% with)</td>
<td>Visual</td>
<td>Filtered backprojection</td>
<td>N</td>
<td>&gt; 6-hour fast</td>
<td>370–555 MBq</td>
<td>45–60 minutes</td>
<td></td>
</tr>
<tr>
<td>Wolfort 2006&lt;sup&gt;40&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Yang 2002&lt;sup&gt;41&lt;/sup&gt;</td>
<td>ECAT HR+</td>
<td>NR</td>
<td>Visual</td>
<td>NR</td>
<td>Y</td>
<td>&gt; 4-hour fast</td>
<td>370 MBq</td>
<td>30–45 minutes</td>
<td>3 minutes</td>
</tr>
</tbody>
</table>

BG, blood glucose; N, no; NR, not reported; SUV, standardised uptake value; Y, yes
Appendix 3

Figures for indirect comparisons of patient-based data

PET versus conventional imaging tests

![PET vs. Conventional Imaging Diagram]

**FIGURE 13** Summary receiver operating characteristic plane for indirect comparison of the diagnostic performance of PET (□) and CIT (◊) for patients with suspected BC recurrence.

PET/CT versus conventional imaging tests

![PET/CT vs. Conventional Imaging Diagram]

**FIGURE 14** Summary receiver operating characteristic plane for indirect comparison of the diagnostic performance of PET/CT (□) and CIT (◊) for patients with suspected BC recurrence.
Appendix 3

PET versus PET/CT

FIGURE 15 Summary receiver operating characteristic plane for indirect comparison of the diagnostic performance of PET (□) and PET/CT (◊) for patients with suspected BC recurrence.
Appendix 4

Comparative lesion-based data

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Test</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe 2005</td>
<td>24</td>
<td>PET</td>
<td>38</td>
<td>2</td>
<td>7</td>
<td>140</td>
<td>0.84 (0.71 to 0.94)</td>
<td>0.99 (0.95 to 1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallowitsch 2003</td>
<td>29</td>
<td>PET</td>
<td>61</td>
<td>3</td>
<td>47</td>
<td>24</td>
<td>0.56 (0.47 to 0.66)</td>
<td>0.89 (0.71 to 0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallowitsch 2003</td>
<td>29</td>
<td>CIT</td>
<td>97</td>
<td>7</td>
<td>11</td>
<td>20</td>
<td>0.90 (0.83 to 0.95)</td>
<td>0.74 (0.54 to 0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang 2002</td>
<td>51</td>
<td>PET</td>
<td>100</td>
<td>2</td>
<td>5</td>
<td>20</td>
<td>0.95 (0.89 to 0.98)</td>
<td>0.91 (0.71 to 0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang 2002</td>
<td>51</td>
<td>CIT</td>
<td>98</td>
<td>20</td>
<td>7</td>
<td>2</td>
<td>0.93 (0.87 to 0.97)</td>
<td>0.09 (0.01 to 0.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 16** Lesion data for the diagnostic accuracy of PET and CITs in comparative studies. Note: no studies comparing the accuracy of PET/CT and CIT presented lesion data.

**TABLE 9** Lesion data for direct and indirect comparisons of PET compared to CITs

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PET sensitivity % (95% CI)</th>
<th>CIT sensitivity % (95% CI)</th>
<th>Relative sensitivity (95% CI), p-value</th>
<th>PET specificity% (95% CI)</th>
<th>CIT specificity % (95% CI)</th>
<th>Relative specificity (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct PET vs CIT: lesion data</td>
<td>83 (56 to 95), n=3</td>
<td>90 (84 to 94), n=3</td>
<td>0.93 (0.76 to 1.13) p=0.447</td>
<td>95 (87 to 98)</td>
<td>74 (10 to 99)</td>
<td>1.29 (0.57 to 2.90) p=0.540</td>
</tr>
<tr>
<td>Indirect PET vs CIT: lesion data</td>
<td>89 (78 to 95), n=7</td>
<td>91 (86 to 94), n=3</td>
<td>0.98 (0.90 to 1.07) p=0.624</td>
<td>91 (83 to 95)</td>
<td>35 (3 to 91)</td>
<td>2.57 (0.41 to 6.07) p=0.313</td>
</tr>
</tbody>
</table>

**FIGURE 17** Summary receiver operating characteristic plane for studies directly comparing the diagnostic performance of PET (-) and CITs (◊) for lesions with suspected disease.
TABLE 10  Lesion data for the indirect comparison of PET with PET/CT

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PET/CT sensitivity% (95% CI)</th>
<th>PET sensitivity % (95% CI)</th>
<th>Relative sensitivity (95% CI)</th>
<th>PET/CT specificity% (95% CI)</th>
<th>PET specificity% (95% CI)</th>
<th>Relative specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect PET/CT vs PET</td>
<td>97 (86 to 99), n=2</td>
<td>89 (78 to 95), n=7</td>
<td>1.1 (1.0 to 1.2) p=0.137</td>
<td>84 (62 to 94)</td>
<td>91 (83 to 95)</td>
<td>0.9 (0.8 to 1.1) p=0.414</td>
</tr>
</tbody>
</table>

FIGURE 18  Summary receiver operating characteristic plane for indirect comparison of the diagnostic performance of PET (□) and CIs (◊) for lesions with suspected disease.

FIGURE 19  Lesion data for the diagnostic accuracy of PET/CT and MRI in the comparative study of PET/CT and MRI. Note: no studies comparing the accuracy of PET and MRI presented lesion data.
### Appendix 5

Study data and figures for independent estimates of PET and PET/CT

#### Patient data

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe 2005</td>
<td>14</td>
<td>1</td>
<td>29</td>
<td>0.0 0.2 0.4 0.6 0.8 1.0</td>
<td>0.0 0.2 0.4 0.6 0.8 1.0</td>
<td></td>
</tr>
<tr>
<td>Aide 2007</td>
<td>21</td>
<td>2</td>
<td>7</td>
<td>0.75 0.55 to 0.89</td>
<td>0.71 0.29 to 0.96</td>
<td></td>
</tr>
<tr>
<td>Bender 1997</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>0.93 0.66 to 1.00</td>
<td>0.97 0.88 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Dirisamer 2010</td>
<td>34</td>
<td>0</td>
<td>8</td>
<td>0.81 0.66 to 0.91</td>
<td>1.00 0.69 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Fueger 2005</td>
<td>28</td>
<td>7</td>
<td>5</td>
<td>0.85 0.68 to 0.95</td>
<td>0.72 0.51 to 0.88</td>
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</tr>
<tr>
<td>Gallowitsch 2003</td>
<td>33</td>
<td>5</td>
<td>1</td>
<td>0.97 0.85 to 1.00</td>
<td>0.82 0.63 to 0.94</td>
<td></td>
</tr>
<tr>
<td>Goerres 2003</td>
<td>14</td>
<td>5</td>
<td>0</td>
<td>1.00 0.77 to 1.00</td>
<td>0.72 0.47 to 0.90</td>
<td></td>
</tr>
<tr>
<td>Guillemand 2006</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>0.88 0.47 to 1.00</td>
<td>1.00 0.54 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Hathaway 1999</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1.00 0.54 to 1.00</td>
<td>1.00 0.03 to 1.00</td>
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</tr>
<tr>
<td>Haug 2007</td>
<td>23</td>
<td>1</td>
<td>3</td>
<td>0.88 0.70 to 0.98</td>
<td>0.88 0.47 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Hubner 2000</td>
<td>36</td>
<td>6</td>
<td>6</td>
<td>0.86 0.71 to 0.95</td>
<td>0.73 0.50 to 0.89</td>
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</tr>
<tr>
<td>Kamel 2003</td>
<td>25</td>
<td>2</td>
<td>2</td>
<td>0.93 0.76 to 0.99</td>
<td>0.92 0.74 to 0.99</td>
<td></td>
</tr>
<tr>
<td>Kim 2001</td>
<td>16</td>
<td>2</td>
<td>1</td>
<td>0.94 0.71 to 1.00</td>
<td>0.80 0.44 to 0.97</td>
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</tr>
<tr>
<td>Lin 2002</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1.00 0.40 to 1.00</td>
<td>0.97 0.84 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Liu 2002</td>
<td>27</td>
<td>2</td>
<td>1</td>
<td>0.96 0.82 to 1.00</td>
<td>0.00 0.00 to 0.84</td>
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</tr>
<tr>
<td>Lonneux 2000</td>
<td>31</td>
<td>3</td>
<td>2</td>
<td>0.94 0.80 to 0.99</td>
<td>0.50 0.12 to 0.88</td>
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</tr>
<tr>
<td>Moon 1999</td>
<td>27</td>
<td>6</td>
<td>2</td>
<td>0.93 0.77 to 0.99</td>
<td>0.79 0.59 to 0.92</td>
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</tr>
<tr>
<td>Ohta 2001</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>0.78 0.40 to 0.97</td>
<td>0.98 0.88 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Pecking 2004</td>
<td>260</td>
<td>12</td>
<td>7</td>
<td>0.97 0.95 to 0.99</td>
<td>0.50 0.29 to 0.71</td>
<td></td>
</tr>
<tr>
<td>Raileanu 2004</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0.86 0.42 to 1.00</td>
<td>1.00 0.75 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Santiago 2006</td>
<td>68</td>
<td>7</td>
<td>30</td>
<td>0.69 0.59 to 0.78</td>
<td>0.80 0.63 to 0.92</td>
<td></td>
</tr>
<tr>
<td>Suarez 2002</td>
<td>24</td>
<td>3</td>
<td>2</td>
<td>0.92 0.75 to 0.99</td>
<td>0.75 0.43 to 0.95</td>
<td></td>
</tr>
<tr>
<td>Veit-Haibach 2007</td>
<td>17</td>
<td>6</td>
<td>2</td>
<td>0.89 0.67 to 0.99</td>
<td>0.76 0.55 to 0.91</td>
<td></td>
</tr>
<tr>
<td>Vranjesivic 2002</td>
<td>39</td>
<td>3</td>
<td>3</td>
<td>0.93 0.81 to 0.99</td>
<td>0.84 0.60 to 0.97</td>
<td></td>
</tr>
<tr>
<td>Wolfert 2006</td>
<td>13</td>
<td>0</td>
<td>3</td>
<td>0.81 0.54 to 0.96</td>
<td>1.00 0.59 to 1.00</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 20** Study data for the accuracy of PET on a patient basis.

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% Cl)</th>
<th>Specificity (95% Cl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dirisamer 2010</td>
<td>40</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>0.95 0.84 to 0.99</td>
<td>1.00 0.69 to 1.00</td>
</tr>
<tr>
<td>Fueger 2005</td>
<td>31</td>
<td>4</td>
<td>2</td>
<td>21</td>
<td>0.94 0.80 to 0.99</td>
<td>0.84 0.64 to 0.95</td>
</tr>
<tr>
<td>Haug 2007</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>0.96 0.80 to 1.00</td>
<td>0.89 0.52 to 1.00</td>
</tr>
<tr>
<td>Radan 2006</td>
<td>17</td>
<td>4</td>
<td>3</td>
<td>13</td>
<td>0.85 0.62 to 0.97</td>
<td>0.76 0.50 to 0.93</td>
</tr>
<tr>
<td>Veit-Haibach 2007</td>
<td>19</td>
<td>4</td>
<td>0</td>
<td>21</td>
<td>1.00 0.82 to 1.00</td>
<td>0.84 0.64 to 0.95</td>
</tr>
</tbody>
</table>

**FIGURE 21** Study data for the accuracy of PET/CT on a patient basis.
FIGURE 22 Summary receiver operating characteristic plane for studies measuring the diagnostic performance of PET (○) for patients with suspected BC recurrence.

FIGURE 23 Summary receiver operating characteristic plane for studies measuring the diagnostic performance of PET/CT (□) for patients with suspected BC recurrence.
Lesion data

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe 2005</td>
<td>38</td>
<td>2</td>
<td>7</td>
<td>140</td>
<td>0.84 (0.71 to 0.94)</td>
<td>0.99 (0.95 to 1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallowitch 2003</td>
<td>61</td>
<td>3</td>
<td>47</td>
<td>24</td>
<td>0.56 (0.47 to 0.66)</td>
<td>0.89 (0.71 to 0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kamel 2003</td>
<td>43</td>
<td>3</td>
<td>2</td>
<td>13</td>
<td>0.96 (0.85 to 0.99)</td>
<td>0.81 (0.54 to 0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim 2001</td>
<td>46</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>0.96 (0.86 to 0.99)</td>
<td>0.85 (0.55 to 0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin 2002</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>28</td>
<td>0.89 (0.52 to 1.00)</td>
<td>0.93 (0.78 to 0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moon 1998</td>
<td>35</td>
<td>8</td>
<td>6</td>
<td>31</td>
<td>0.85 (0.71 to 0.94)</td>
<td>0.79 (0.64 to 0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang 2002</td>
<td>100</td>
<td>2</td>
<td>5</td>
<td>20</td>
<td>0.95 (0.89 to 0.98)</td>
<td>0.91 (0.71 to 0.99)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 24** Study data for the accuracy of PET on a lesion basis.

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radan 2006</td>
<td>151</td>
<td>5</td>
<td>2</td>
<td>13</td>
<td>0.99 [0.95 to 1.00]</td>
<td>0.72 [0.47 to 0.90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt 2008</td>
<td>179</td>
<td>8</td>
<td>16</td>
<td>69</td>
<td>0.92 [0.87 to 0.95]</td>
<td>0.90 [0.81 to 0.95]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 25** Summary receiver operating characteristic plane for studies measuring the diagnostic performance of PET (■) for lesions with suspected disease.

**FIGURE 26** Study data for the accuracy of PET/CT on a lesion basis.
# Appendix 6

## Changes in patient management

<table>
<thead>
<tr>
<th>Additional gain</th>
<th>Patients with overall changes in management n (%)</th>
<th>Start/changed medical therapy n (%)</th>
<th>Changed to surgery n (%)</th>
<th>Avoided medical treatment n (%)</th>
<th>Avoided surgery n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dirisamer 2010&lt;sup&gt;27&lt;/sup&gt;</td>
<td>N 52</td>
<td>7 (13%)</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>Bělohlávek 2002&lt;sup&gt;33&lt;/sup&gt;</td>
<td>N 51</td>
<td>31 (60%)</td>
<td>2 (2%)</td>
<td>14 (11%)</td>
<td></td>
</tr>
<tr>
<td>Eubank 2004&lt;sup&gt;45&lt;/sup&gt;</td>
<td>N 125</td>
<td>40 (32%)</td>
<td>22 (18%)</td>
<td>14 (11%)</td>
<td></td>
</tr>
<tr>
<td>Eubank 2004&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Y&lt;sup&gt;4&lt;/sup&gt; 20</td>
<td>5 (25%)</td>
<td>4 (16%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Gallowitsch 2003&lt;sup&gt;29&lt;/sup&gt;</td>
<td>N 62</td>
<td>13 (21%)</td>
<td>6 (3%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Grahek 2004&lt;sup&gt;34&lt;/sup&gt;</td>
<td>N 75</td>
<td>25 (33%)</td>
<td>10 (13%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Kim 2001&lt;sup&gt;46&lt;/sup&gt;</td>
<td>N 27</td>
<td>13 (48%)</td>
<td>6 (22%)</td>
<td>7 (26%)</td>
<td></td>
</tr>
<tr>
<td>Radan 2006&lt;sup&gt;45&lt;/sup&gt;</td>
<td>N 47</td>
<td>24 (51%)</td>
<td>17 (36%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Santiago 2006&lt;sup&gt;45&lt;/sup&gt;</td>
<td>N 133</td>
<td>99 (74%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Veit-Haibach 2007&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Y&lt;sup&gt;4&lt;/sup&gt; 44</td>
<td>5 (11%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vranješevic 2002&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Y&lt;sup&gt;4&lt;/sup&gt; 61</td>
<td>10 (16%)</td>
<td>10 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yap 2001&lt;sup&gt;52&lt;/sup&gt;</td>
<td>N 50</td>
<td>29 (58%)</td>
<td>22 (44%)</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

N, no; Y, yes.

- In patients not correctly identified by conventional imaging.
- Half of patients referred for initial staging of BC.
### Appendix 7

Sensitivity analysis

#### TABLE 11a  Diagnostic accuracy of PET and CIT for studies in which tests were conducted within a 1-month time period

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PET sensitivity % (95% CI)</th>
<th>CIT sensitivity % (95% CI)</th>
<th>Relative sensitivity (95% CI), p-value</th>
<th>PET specificity % (95% CI)</th>
<th>CIT specificity % (95% CI)</th>
<th>Relative specificity (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct PET vs CIT</td>
<td>87 (79 to 93) n=6</td>
<td>84 (72 to 91) n=6</td>
<td>1.04, (0.92 to 1.15) p=0.4797</td>
<td>96 (83 to 99)</td>
<td>87 (75 to 94)</td>
<td>1.10, (1.01 to 1.17) p=0.022</td>
</tr>
</tbody>
</table>

#### TABLE 11b  Diagnostic accuracy of PET/CT and CIT for studies in which tests were conducted within a 1-month time period

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PET/CT sensitivity % (95% CI)</th>
<th>CIT sensitivity % (95% CI)</th>
<th>Relative sensitivity (95% CI), p-value</th>
<th>PET/CT specificity % (95% CI)</th>
<th>CIT specificity % (95% CI)</th>
<th>Relative specificity (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct PET/CT vs CIT (CT)</td>
<td>97 (90 to 99) n=3</td>
<td>84 (66 to 94) n=3</td>
<td>1.13 (0.99 to 1.26), p=0.063</td>
<td>93 (65 to 99)</td>
<td>86 (59 to 97)</td>
<td>1.07 (0.91 to 1.22), p=0.367</td>
</tr>
</tbody>
</table>

#### TABLE 11c  Diagnostic accuracy of PET/CT and PET for studies in which tests were conducted within a 1-month time period

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PET/CT sensitivity % (95% CI)</th>
<th>PET sensitivity % (95% CI)</th>
<th>Relative sensitivity (95% CI), p-value</th>
<th>PET/CT specificity % (95% CI)</th>
<th>PET specificity % (95% CI)</th>
<th>Relative specificity (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct PET/CT vs PET</td>
<td>96 (90 to 98) n=4</td>
<td>85 (77 to 91) n=4</td>
<td>1.11 (1.03 to 1.18), p=0.006</td>
<td>89 (74 to 96)</td>
<td>82 (64 to 92)</td>
<td>1.08 (0.94 to 1.20), p=0.267</td>
</tr>
</tbody>
</table>
Figure 27 Summary receiver operating characteristic plane for direct comparison of the diagnostic performance of PET (□) and CITs (◊) for patients with suspected BC recurrence for studies where PET and CIT were conducted within a 1-month time period.

Figure 28 Summary receiver operating characteristic plane for direct comparison of the diagnostic performance of PET/CT (□) and CT (◊) for patients with suspected BC recurrence for studies where PET/CT and CT were conducted within a 1-month time period.
Appendix 8

Subgroup analysis

TABLE 12  Indirect comparison of the diagnostic accuracy of PET for detecting lesions of disease in different locations in the body

<table>
<thead>
<tr>
<th></th>
<th>Local (n = 4 studies)</th>
<th>p</th>
<th>Lymph nodes (n = 3 studies)</th>
<th>p</th>
<th>Distant metastases (n = 7 studies)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative specificity (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>–</td>
<td>1.01</td>
<td>0.936</td>
<td>1.02</td>
<td>0.744</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.81 to 1.17)</td>
<td></td>
<td>(0.9 to 1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>0.99</td>
<td>0.936</td>
<td>–</td>
<td>0.98</td>
<td>0.874</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.83 to 1.19)</td>
<td></td>
<td></td>
<td>(0.75 to 1.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>0.98</td>
<td>0.744</td>
<td>1.02</td>
<td>0.874</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.88 to 1.10)</td>
<td></td>
<td></td>
<td>(0.83 to 1.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relative sensitivity (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>–</td>
<td>0.91</td>
<td>0.334</td>
<td>0.93</td>
<td>0.442</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.69 to 1.09)</td>
<td></td>
<td>(0.74 to 1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>1.09</td>
<td>0.334</td>
<td>–</td>
<td>1.02</td>
<td>0.822</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.91 to 1.31)</td>
<td></td>
<td></td>
<td>(0.89 to 1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>1.07</td>
<td>0.442</td>
<td>0.98</td>
<td>0.822</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.91 to 1.26)</td>
<td></td>
<td></td>
<td>(0.84 to 1.11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 29  Indirect comparison of the diagnostic accuracy of PET for the detection of local (□), lymph node (○) or distant metastatic (◊) lesions.
Variability of PET with study characteristics

**TABLE 13a** Indirect comparisons of the variability of PET with the outcome of previous imaging investigations

<table>
<thead>
<tr>
<th></th>
<th>PET positive on previous imaging (n = 5)</th>
<th>PET negative on previous imaging (n = 5)</th>
<th>Relative sensitivity/specificity</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>94% (82 to 98)</td>
<td>93% (84 to 97)</td>
<td>0.99 (0.90 to 1.09)</td>
<td>0.859</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>90% (77 to 96)</td>
<td>66% (48 to 80)</td>
<td>0.73 (0.56 to 0.96)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

**TABLE 13b** Indirect comparisons of the variability of PET with patient disease status at the time of investigation

<table>
<thead>
<tr>
<th></th>
<th>PET in patients with known BC or diagnosis unclear (n = 11)</th>
<th>PET in patients cleared of BC (n = 14)</th>
<th>Relative sensitivity/specificity</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>91% (82 to 95)</td>
<td>91% (86 to 94)</td>
<td>1.00 (0.92 to 1.09)</td>
<td>0.920</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>92% (85 to 95)</td>
<td>77% (66 to 86)</td>
<td>0.84 (0.73 to 0.97)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

**TABLE 13c** Indirect comparisons of the variability of PET with assessors knowledge of previous clinical and imaging investigations at the time of study

<table>
<thead>
<tr>
<th></th>
<th>PET assessors with knowledge of previous findings/knowledge unclear (n = 16)</th>
<th>PET assessors blinded to previous findings (n = 9)</th>
<th>Relative sensitivity/specificity</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>92% (87 to 95)</td>
<td>88% (81 to 93)</td>
<td>0.96 (0.87 to 1.04)</td>
<td>0.346</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>85% (75 to 91)</td>
<td>88% (76 to 95)</td>
<td>1.05 (0.91 to 1.20)</td>
<td>0.533</td>
</tr>
</tbody>
</table>
FIGURE 30  Summary receiver operating characteristic plane for comparison of the diagnostic performance of PET in studies where all patients had been positive or equivocal (□) or negative (◊) for breast cancer recurrence in previous imaging tests.

FIGURE 31  Summary receiver operating characteristic curve for comparison of the diagnostic performance of PET in studies of patients previously cleared of BC (□) or of patients with known BC or where disease status was unclear (◊).
## Appendix 9

### False-positives and false-negatives

**TABLE 14** Causes of FPs in PET and PET/CT studies

<table>
<thead>
<tr>
<th></th>
<th>Infection/inflammation</th>
<th>Physiological activity</th>
<th>Degenerative process/old fractures</th>
<th>Other artefacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bender 1997</td>
<td>4</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Dirisamer 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fueger 2005</td>
<td>5</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Gallowitsch 2003</td>
<td>3</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Goerres 2003</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grahek 2004</td>
<td>2</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hubner 2000</td>
<td>2</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Kamel 2003</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim 2001</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Lin 2002</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu 2002</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lonneux 2000</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Moon 1998</td>
<td>4</td>
<td>5</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Ohta 2001</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radan 2006</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suarez 2002</td>
<td>1</td>
<td>4</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Veit-Haibach 2007</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vranjevic 2002</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>41%</strong></td>
<td><strong>29%</strong></td>
<td><strong>10%</strong></td>
<td><strong>20%</strong></td>
</tr>
</tbody>
</table>

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### TABLE 15 Sites of FN s in PET and PET/CT scans

<table>
<thead>
<tr>
<th>Study</th>
<th>Local/ regional</th>
<th>Cutaneous/subcutaneous/soft tissue</th>
<th>Peritoneal</th>
<th>Lymph node</th>
<th>Lung</th>
<th>Bone</th>
<th>Liver</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bender 1997</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dirisamer 2010</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallowitsch 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grahek 2004</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hubner 2000</td>
<td>1</td>
<td></td>
<td>3</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kamel 2003</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim 2001</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu 2002</td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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Appendix 10

Protocol

Positron emission tomography (PET) and PET/CT in breast cancer recurrence: draft protocol

Produced by West Midlands Health Technology Assessment Collaboration, Department of Public Health, Epidemiology & Biostatistics, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Authors: Mary Pennant,1 Yemisi Takwoingi,1 Lazaros Andronis,2 Anne Fry-Smith,1 Anne Eisinga,3 Daniel Rea,4 Theo Arvanitis,5 Jon Deeks,1 Chris Hyde1

Details of review team

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Institution</th>
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<tr>
<td>Lead/senior reviewer</td>
<td>Hyde, Chris, Dr</td>
<td>Senior Lecturer/Director of WMHTAC</td>
</tr>
<tr>
<td>Main reviewer</td>
<td>Pennant, Mary, Dr</td>
<td>Systematic Reviewer</td>
</tr>
<tr>
<td>Administrator</td>
<td>Farren, Janet, Mrs</td>
<td>Project Administrator</td>
</tr>
<tr>
<td>Senior statistical advisor</td>
<td>Deeks, Jon, Professor</td>
<td>Professor of Health Statistics</td>
</tr>
<tr>
<td>Statistical advisor</td>
<td>Yemisi Takwoingi, Mrs</td>
<td>Research Fellow</td>
</tr>
<tr>
<td>Health economist</td>
<td>Andronis, Lazaros, Mr</td>
<td>Research Associate</td>
</tr>
<tr>
<td>Information specialist</td>
<td>Fry-Smith, Anne, Ms</td>
<td>Information Specialist</td>
</tr>
<tr>
<td>Information specialist</td>
<td>Eisinga, Anne, Mrs</td>
<td>Information Specialist</td>
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<tr>
<td>Clinical advisor</td>
<td>Rea, Dan, Dr</td>
<td>Senior Lecturer and Honorary Consultant in Medical Oncology</td>
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<tr>
<td>Technical advisor</td>
<td>Arvanitis, Theodoros, Dr</td>
<td>Senior Lecturer</td>
</tr>
</tbody>
</table>

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³UK Cochrane Centre
⁴Cancer Sciences Clinical Trials Unit, University of Birmingham
⁵Electronic & Electrical Engineering, University of Birmingham

Correspondence to: Chris Hyde

Date completed: June 2009

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**Background**

Breast cancer is a serious life-threatening disease. Treatment options have developed significantly over the past decade, and have impacted on survival. Inevitably, recurrence of breast cancer has increased and its diagnosis is important, as early appropriate treatment also has small but clear associated advantage for survival.

For women who have suffered with breast cancer, following clearance, NICE recommends continued access to a breast cancer nurse for an indefinite period of time. This nurse is to provide advice, support and counselling via the telephone and, where appropriate, to arrange additional hospital appointments. Women also undergo the normal population-wide screening programme (mammography every 3 years for those aged 50–64 years).

Breast cancer recurrence may be local (in the breast), regional (lymph nodes, collar bone, etc., same side of body as original cancer) or distant (in other body organs such as bone, liver, lungs and brain) and is associated with symptoms such as weight loss, abdominal pain, respiratory symptoms, bone pain and neurological signs. Women with a past history of breast cancer may present with symptoms which may be innocent or the first indication of recurrence. The nature of these symptoms will dictate the nature of the investigation but tests will often include bone scans, chest X-ray, CT scans, MRI scans and ultrasound.

PET and, more recently, PET/CT are new tools that may be used to diagnose breast cancer recurrence. These technologies trace radioactive isotopes in the body. Isotopes of glucose, most commonly fluorodeoxyglucose (FDG), are used for the detection of tumours since glucose is taken up and retained in tumour tissue, making it visible in PET images. Whether PET or PET/CT offer advantages over existing diagnostic approaches depends in the first instance on whether their diagnostic accuracy is good. However, ultimately, these need to be translated into more appropriate applications of effective treatment strategies, leading in turn to improved patient outcomes. As well as detecting recurrence, a new diagnostic tool may also be able to improve outcomes by correctly differentiating solitary recurrences from multiple metastases.

We have reviewed existing systematic reviews assessing the effectiveness of PET and PET/CT in the diagnosis of recurrent breast cancer. The two most relevant were Blue Cross/Blue Shield 2001 and Isasi et al, 2005. The latter provides the most up-to-date assessment of test accuracy in evaluations up to 2004, with pooled sensitivity and specificity for PET both in the region of 90%. Although this review could be updated and improved on, the key outstanding issue is the amount of improvement PET and PET/CT offer over existing diagnostic approaches and this is the focus of the research proposed in this protocol.

**Objectives**

1. To assess the diagnostic accuracy of PET and PET/CT in the diagnosis of breast cancer recurrence.
   - The primary aim is to assess the incremental diagnostic accuracy of PET and PET/CT compared to existing diagnostic strategies.
   - If there are insufficient within-study comparisons to assess incremental diagnostic accuracy, basic test accuracy values will be reported.

2. To assess the impact of PET and PET/CT on the type of patient diagnosis, treatment and outcome.

3. To assess the cost-effectiveness of PET and PET/CT in the diagnosis and treatment of breast cancer recurrence.

A further objective, to be met by conducting an additional modelling review, is:

4. To model the effectiveness and cost-effectiveness of PET and PET/CT relative to existing diagnostic strategies in suspected breast cancer recurrence.

**Population**

The population to be studied are patients with a history of breast cancer but who have been cleared of having the disease and, at the time of study, have not been diagnosed with breast cancer recurrence. Breast cancer recurrence may or may not be suspected at the time of study and tests may be conducted as part of follow-up examinations or in response to presentation of symptoms suggestive of breast cancer recurrence.

Studies will be excluded if:

- Patients have confirmed breast cancer.
- Patients have never suffered from breast cancer.
Populations include both patients with and without breast cancer but data from the two patient types cannot be differentiated.

Populations include patients undergoing tests to diagnose primary breast cancer and breast cancer recurrence but data from the two patient types cannot be differentiated.

Patients may have impaired glucose tolerance/diabetes or may not have been fasting at the time of PET or PET/CT scanning.

Index tests

The index tests under assessment are PET and PET/CT and these will be considered separately. They may be used in addition to standard tests, e.g. in combination with clinical examination/bone scanning, etc., and also instead of standard tests. Studies where whole body PET and PET/CT are conducted as well as studies using only breast imaging may be considered. Studies will be excluded if:

- FDG is not the radioactive tracer used.
- Planar (not tomographic) imaging is used.

Reference standard

The reference standard used to define the true disease status of patients may be histological diagnosis (operation/biopsy) or long term clinical follow-up/autopsy findings. Studies will be excluded if:

- Other diagnostic tests, e.g. CT, are used as the reference standard.
- It is not clear what reference standard has been used.

Comparator

In order to be able to directly compare the accuracy of PET and PET/CT for the detection of recurrent breast cancer with other diagnostic strategies, in the first instance, studies investigating both PET or PET/CT and another method of detection (and both compared to the same reference standard – see above), will be included. If sufficient studies with comparator groups are not available then it is anticipated that the emphasis of the review will be changed to include studies with no additional comparator test (but still with a reference standard).

Target condition

The outcome to be assessed by studies is breast cancer recurrence as defined by the reference standard (see above). Recurrence may be local, regional or distant but must be considered to be a consequence of the originally diagnosed breast cancer. It is anticipated that, in the majority of studies, PET or PET/CT will have been used to detect distant recurrence. Studies will be excluded if they investigate:

- The diagnosis of primary breast cancer in previously disease-free individuals.
- Diagnosis of lymph node/distant metastases in breast cancer patients who have not been cleared of having breast cancer.
- Diagnosis of tumours that are not considered to be related to the initial breast cancer.

Study design

Studies in which subjects undergo the index test (PET or PET/CT), a comparison test (e.g. mammography) and the reference standard (histology/long-term follow-up) will be included. If there are insufficient tests with comparator groups, studies where subjects only undergo the index test and the reference standard will also be included.
All study designs assessing test accuracy will be considered for inclusion. Additionally, all study designs providing information on cost-effectiveness or relevant outcomes related to diagnosis, treatment or outcome will also be considered. Studies will be excluded if:

- Data is not available to determine test accuracy, cost-effectiveness or other relevant outcomes.
- They are not published in peer-reviewed journals.
- They are case-control studies comparing test results in diseased versus non-diseased individuals.

Subgroup analysis

Subgroup analysis may be conducted to assess the differential diagnostic accuracy of PET and PET/CT in different patient groups, settings or methods of use.

PET and PET/CT may have different diagnostic accuracy depending on the mode of presentation. The primary focus for subgroup analysis may be differentiation on the basis of presentation at the time of the index test. Groups have been identified as:

- Patients undergoing a follow-up examination with no clinical symptoms of recurrence.
- Patients presenting with clinical symptoms suggestive of breast cancer recurrence, e.g. bone pain, shortness of breath, weight loss and neurological symptoms.
- Patients with a rise in tumour marker levels.
- Patients testing positive for other imaging techniques (mammography, ultrasonography, CT or bone scintigraphy).

Studies may present patient or lesion-based data, i.e. either recurrence in one patient or one lesion of recurrence in a patient can be taken as the unit of measurement. If this is the case, studies presenting patient and lesion based data will be separated in the analysis of data.

Other possible subgroup analysis

The diagnostic accuracy of PET and PET/CT may depend on the location of recurrence. It may be that studies do not differentiate between patients on the basis of recurrence location, especially where whole-body scans have been conducted. However, where possible, subgroup analysis may be conducted to assess the differential diagnostic accuracy for breast cancer recurrence in the bone, liver, lung and brain.

PET scans may be interpreted by quantitative (using standard uptake values) or qualitative (visual assessment) methods. The mode of interpretation may influence diagnostic accuracy and subgroup analysis may include comparison of PET and PET/CT diagnostic accuracy using quantitative versus qualitative methodology.

The methodological quality, e.g. presence of blinding, length of reference standard follow-up etc. of included studies may affect the apparent accuracy. Other possible subgroup analysis are to examine the diagnostic accuracy of PET and PET/CT in studies that differ for aspects of methodological quality.

Method

A systematic review of the literature will be conducted to identify studies assessing:

1. The test accuracy of PET and PET/CT. In the first instance, only studies in which PET or PET/CT are compared to existing methodologies will be included in the review. If there are insufficient studies to provide useful information, the review will be extended to include studies of PET or PET/CT without comparator groups.
2. The impact of PET and PET/CT on patient diagnosis, treatment and outcome.
3. The cost-effectiveness of PET and PET/CT.

In a separate piece of work, the results of this review will be used to devise a simple decision tree model to explore health effects and costs associated with changes in diagnostic error. A further protocol will be developed to detail methodology for this modelling review, including further targeted searches to identify best available parameters, e.g. effects of treatments, side-effects and costs.

Standard Cochrane and diagnostic test accuracy methods will be used to conduct the review. The possibility of this work being conducted as a Cochrane review will also be explored.

Search strategy

Relevant primary studies will be sought in MEDLINE (Ovid) and EMBASE (Ovid). Search strategies will be devised by combining index and text words defining the index test: PET and PET/
CT; and the population: suspected breast cancer recurrence. There will be no language restrictions and searches will be done from inception of the databases up to the current date. Details of the proposed search strategy for MEDLINE is available in the appendix.

**Selection of studies**

Titles/abstracts obtained from the literature search will be scanned for inclusion. Full articles will be retrieved for further assessment if the information given suggests that the study: 1) includes patients who have had breast cancer in the past, 2) conducts PET or PET/CT scans in those patients, and 3) assesses test accuracy, cost-effectiveness or one or more relevant clinical outcome measure. If there is any doubt regarding inclusion from the title and abstract, the full article will be retrieved for clarification. Full paper articles will be screened with another checklist, using inclusion/exclusion criteria as detailed in this protocol.

**Quality assessment**

Quality assessment will be conducted using the QADAS tool that includes criteria relating to patient selection, use of the reference standard, detail of reporting, blinding, follow-up and external validity. Since this quality assessment tool does not address issues related to the use of an additional comparator test, a small number of additional quality criteria will be added.

**Data analysis**

PET and PET/CT will be considered as separate technologies in data analysis. For the stated research objectives, data analysis will be undertaken as follows:

- Hierarchical methods are recommended for meta-analyses of diagnostic test accuracy studies. The HSROC model which takes account of both within- and between-study variation in test performance will be used to quantitatively combine data from eligible studies. The relative accuracy of PET and PET/CT compared to the comparator tests will be determined and potential sources of heterogeneity investigated using extensions of this model where possible.
- Narrative synthesis will be used to combine information from studies assessing the impact of PET or PET/CT on patient diagnosis (e.g. differentiating solitary recurrences and multiple metastases), treatment and outcome.
- Studies of the relative cost-effectiveness of PET or PET/CT versus other comparator tests will be subjected to narrative synthesis.

**References**


**Appendix: MEDLINE search strategy**

**Database: Ovid MEDLINE 1950 to May Week 2 2009**

1. exp tomography, emission-computed/(52882)
2. (emission adj2 comput$ adj2 tomograph$).tw. (9710)
3. (tomograph$ adj2 emission adj2 comput$).tw. (9941)
4. (radionuclide-comput$ adj2 tomograph$).tw. (19)
5. (radionuclide adj2 cat scan$).tw. (4)
6. (radionuclide adj2 ct scan$).tw. (29)
7. (scintigraph$ adj2 comput$ adj2 tomograph$).tw. (373)
8. (positron adj2 emission adj2 tomograph$).tw. (21399)
9. (pet or petct).tw. (30218)
10. or/1–9 (65938)
11. exp breast neoplasms/(162433)
12. (breast$ adj5 (cancer$ or carcinoma$ or adenocarcinoma$ or carcinogen$ or sarcoma$...
or malignan$ or tumo?r$ or neoplas$),tw. (149035)

13. or/11–12 (191059)
14. 10 and 13 (1422)

15. (recur$ or relaps$ or metast$ or restag$ or re-stag$).mp. (633461)
16. 14 and 15 (730)
## Appendix II

### Excluded studies

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<td>Basu S, Mavi A, Cermik T, Housen M, Alavi A</td>
<td>In patients with newly diagnosed BC</td>
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<td>Belohlavek O, Kantorova I.</td>
<td>No test accuracy data (included for data on patient management)</td>
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<td>Bos R, Van der Hoeven JJ, van der WE, van Der GP, Van Diest PJ, Comans EF, et al.</td>
<td>Pre-operative PET, primary setting</td>
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<td>Can N, Kapucu LO, Uner A, Unlu M.</td>
<td>No relevant outcomes for patients</td>
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<td>Chae BJ, Bae JS, Kang BJ, Kim SH, Jung SS, Song BJ.</td>
<td>For primary staging</td>
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<td>Danforth DN, Jr., Aloj L, Carrasquillo JA, Bacharach SL, Chow C, Zujewski J, et al.</td>
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<td>Dizendorf EV, Baumert BG, Von Schuelthess GK, Lutolf UM, Steinert HC, Dizendorf EV, et al.</td>
<td>Staging in primary setting</td>
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<td>Uematsu T, Kasami M, Yuen S. Comparison of FDG PET and MRI for evaluating the tumor extent of breast cancer and the impact of FDG PET on the systemic staging and prognosis of patients who are candidates for breast-conserving therapy. <em>Breast Cancer</em> 2009;16(2):97–104</td>
<td>Setting of primary BC staging</td>
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<td>Weir L, Worsley D, Bernstein V. The value of FDG positron emission tomography in the management of patients with breast cancer. <em>Breast</em> 2005;11(3):204–9</td>
<td>PET for staging or unclear reason for referral</td>
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a A full list of the 185 excluded hard-copy references with reasons for exclusion can be provided on request.
Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawon T, Forsmaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner J, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down’s syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, Mcguire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.

No. 4

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By Macleod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, et al.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.
No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.

No. 4

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zoumer D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.

No. 13
‘Early warning systems’ for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.

No. 19
What role for statins? A review and economic model.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kinioka S, et al.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
   A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
   By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
   A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
   By Petticrew MP, Swaminathan R.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
   By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.

No. 8
An introduction to statistical methods for health technology assessment.
   A review by White SJ, Ashby D, Brown P.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
   By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
   A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
   By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
   By Coster S, Gulliford MC, Seed PT, Powrie JF, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
   A rapid review by Song F, O’Meara S, Wilson P, Golder S, Kleijnen J.

No. 16

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
   By Lister-Sharp D, McDonagh MS, Khani KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
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We look forward to hearing from you.