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

Produced by

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

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 Hyde[1]

[1] Department of Public Health, Epidemiology & Biostatistics, University of Birmingham
[2] Department of Health Economics, University of Birmingham
[3] UK Cochrane Centre
[4] Cancer Sciences Clinical Trials Unit, University of Birmingham
[5] Electronic & Electrical Engineering, University of Birmingham

Correspondence to

Chris Hyde
Department of Public Health, Epidemiology & Biostatistics
University of Birmingham
Edgbaston
Birmingham B15 2TT
Fax: 0121 414 7878

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Details of review team

Lead/senior reviewer	Hyde, Chris, Dr	Senior Lecturer/Director of WMHTAC Tel: 0121 414 78708 C.J.Hyde@bham.ac.uk
Main reviewer	Pennant, Mary, Dr	Systematic Reviewer Tel: 0121 414 7497 m.pennant@bham.ac.uk
Administrator	Farren, Janet, Mrs	Project Administrator Tel: 0121 414 8434 J.A.Farren@bham.ac.uk
Senior statistical advisor	Deeks, Jon, Prof	Professor of Health Statistics Tel: 0121 414 5328 J.Deeks@bham.ac.uk
Statistical advisor	Yemisi Takawoingi, Ms	Research Fellow Tel: 0121 414 7864 y.takawoingi@bham.ac.uk
Modeller	Andronis, Lazaros, Dr	Research Associate Tel: 0121 414 3197 L.Andronis@bham.ac.uk
Information specialist	Fry-Smith, Anne, Ms	Information Specialist Tel: 0121 414 6769 A.S.Fry-Smith@bham.ac.uk
Information specialist	Eisinga, Anne, Mrs	Information Specialist Tel: (0)1865 516300 aeisinga@cochrane.co.uk
Clinical advisor	Rea, Dan, Dr	Senior Lecturer and Honorary Consultant in Medical Oncology Tel: (0) 121 414 4491 D.W.Rea@bham.ac.uk
Technical advisor	Arvanitis, Theodoros, Dr	Senior Lecturer Tel: 0121 414 4288 t.arvanitis@bham.ac.uk

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.[1] 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[1]).

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[2] and Isasi et al 2005[3]. 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 up-dated 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 asses 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. There is evidence that these types of studies exist since some are included in the review by Isasi et al. 2005. This approach is preferential as it allows direct comparison of PET or PET/CT test accuracy with the accuracy of other detection methods and it allows a more simple and direct modelling approach for the calculation of cost effectiveness (calculated from additional test accuracy and additional test cost).

Where there are sufficient studies that use a comparator test (in addition to the reference standard), these will be used to assess the incremental diagnostic accuracy of PET and PET/CT. The tests for comparison may be existing diagnostic strategies (as defined by UK treatment guidelines) such as clinical examination, mammography, bone scan, chest x-ray, liver ultrasound and CT. Studies will be excluded if:

- No comparator tests were undertaken.
- Not all the patients have undergone both the index and comparator test.
- Index tests and comparator tests were not undertaken during the same investigation period.

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 sub-group 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, 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:

1) Hierarchical methods are recommended[4] for meta-analyses of diagnostic test accuracy studies. The hierarchical summary receiver operating characteristic (HSROC) model[5] 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.

2) 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.

3) Studies of the relative cost effectiveness of PET or PET/CT versus other comparator tests will be subjected to narrative synthesis.

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Appendix: MEDLINE search strategy

Database: Ovid MEDLINE(R) 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 metasta$ or restag$ or re-stag$).mp. (633461)
16 14 and 15 (730)