A systematic review of PET and PET/CT for the diagnosis of breast cancer recurrence

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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Executive summary

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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

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) ($n = 10$). 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 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, $p = 0.157$). 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.

Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

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Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/34/01. The contractual start date was in July 2009. The draft report began editorial review in October 2009 and was accepted for publication in June 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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