NETSCC, HTA

2 June 2009

HTA MAMMOGRAPHY SURVEILLANCE PROTOCOL FOR REVIEW 2: DIAGNOSTIC ACCURACY

Title: Surveillance mammography for diagnosing ipsilateral breast cancer tumour recurrence and metachronous contralateral breast cancer in women previously treated for primary breast cancer.

Table of Contents

1 Background

1.1 Target condition

There are 45,000 new cases of breast cancer in the UK each year with 8 in 10 breast cancers being diagnosed in women aged 50 and over.[1] Approximately 25% of patients will develop metastatic disease and die within five years.[2] It appears that early detection of ipsilateral breast cancer tumour recurrence (IBTR) and of metachronous contalateral breast cancer (MCBC) is beneficial for survival.[3,4] This raises the question as to how best to identify recurrent and contralateral disease. Local recurrences can be detected by either clinical examination and/or mammography. Although published figures vary it has been estimated that approximately 50% of local disease recurrences in the conserved breast will be detected by mammography, with the remainder being detected by clinical examination.[5-8] Recurrent tumours detected by mammography are generally smaller and less invasive then those found on clinical examination.[6,7] It has been presumed, therefore, that mammography and clinical examination allow the earliest possible diagnosis of local disease recurrence and also allows surveillance of the contralateral breast. Whether such surveillance reduces mortality remains unclear.

1.2 Index test

Mammography has been in use for over 30 years and is the reference standard imaging technique for breast cancer detection.[9] In women previously treated for breast cancer, surveillance mammography is useful for early detection of tumour recurrence or for confirming the absence of recurrent cancer.

Mammography involves low dose X-ray imaging of the breast to create detailed soft tissue, high contrast, high resolution images, which are produced onto photographic film. Mammograms are typically produced by a radiographer or assistant practitioner and interpreted by a radiologist or other trained film reader for clinical abnormalities in the primary, secondary care outpatient or community setting. Recent developments in the field of mammography have led to an increasing use of digital mammography. Digital mammography or full-field digital mammography (FFDM) uses solid state detectors rather than x-ray film. These convert x-rays into electrical signals. The images produced are viewed on a computer screen but can be printed out to look like conventional mammograms. It is possible to manipulate digital images on-screen to enhance visibility of certain areas. Digital mammography is quicker to produce than film mammography, uses lower doses of radiation and digital images are easier to

store than traditional films. Digital mammography systems are, however, one to four times as costly as film mammography systems.[10] In the screening population, digital mammography has improved performance over film mammography in younger women and women with dense breasts. Overall, however, the diagnostic accuracy of digital mammography is not significantly greater than film mammography.[11]

Computer-aided detection (CAD) has also been developed to assist in the interpretation of mammograms. A computer algorithm highlights abnormal areas of density, mass or calcification, which are suspicious of cancer. Such areas may then be further analysed by the radiologist. CAD is not currently used in the UK symptomatic setting.

.
In detecting local recurrence, mammography has a reported sensitivity of 55 to 70%.[12] Approximately 10% of palpable tumours are not clearly visible on mammography and require additional imaging techniques. While tumour recurrence displays similar mammographic features to the primary lesion,[13] interpretation of the surveillance mammogram is hindered by changes in the breast caused by post-operative scarring and changes to breast density caused by primary treatment.[14] For example, following surgery and/or radiotherapy detectable abnormalities on mammography include haematoma, scar formation, fat necrosis, skin thickening, increased soft tissue density in the breast and microcalcifications.[15] Thus surveillance mammography is also associated with the possibility of false positive results causing further unnecessary investigations (invasive and non-invasive).

Radiation doses are presented as the Mean Glandular Dose (MGD). The mean dose of radiation for a woman undergoing two-view mammography of each breast is 2.35mGy. 12 mGy and 22 mGy represent the doses exceeded by the top 2% and 0.1% of the population who receive higher doses of radiation primarily because of their greater breast size.[15] The risk of developing cancer due to the radiation exposure associated with mammography varies with age, with risk being higher for women under 20 years and lowest for those over 50 years.[16] The risk of radiation induced breast cancer is considered to be low (in the screening programme this is 1 in 20,000 per visit) and the number of cancers detected by mammography greatly exceeds the total number induced by radiation.[16, 17]

Mammography is generally an uncomfortable procedure and can be painful in some women. Surveillance mammography may also be associated with psychological benefits and harms, for example reassurance of being monitored/remaining disease free and anxiety that cancer has returned.

Guidance for frequency of mammography surveillance is varied, but is broadly recommended as every one to two years for up to 10 years.[18-21]

1.3 Comparator tests

1.3.1 Imaging Tests

- Ultrasound

Breast ultrasound (or sonography) is an imaging technique for diagnosing breast cancer. It uses harmless, high frequency sound waves to form an image (sonogram). The sound waves pass through the breast and are reflected back or echo from various tissue surfaces to form a picture of the internal structures. It is not invasive and involves no radiation. A hand held transducer is pressed against the surface of the breast to produce an image. The transducer is linked to a computer so that images can be viewed on a monitor screen. The operator can move the sensor over the skin to view the whole breast. A hard copy of the image can be produced or a digital copy can be kept for archive. A radiologist or radiographer is responsible for interpreting the ultrasound image. Ultrasound is usually performed in an outpatient setting.

Breast ultrasonography is reportedly the best imaging method for evaluating the chest wall and axilla, which cannot be visualised on mammograms[22] but it does not consistently detect early signs of breast cancer such as microcalcifications. Ultrasound also has a lower positive predictive value for recommended biopsies than mammography.[23] Its use in routine practice is, therefore, mainly as an adjunct to mammography to investigate a specific area of the breast under suspicion. Here, ultrasound acts as an additional diagnostic tool in determining whether a structure identified on mammography requires further investigation, for example in distinguishing between a fluid-filled cyst and a solid mass. It can also identify small non-palpable lesions. Breast ultrasound is also particularly useful in evaluating women whose mammograms are difficult to interpret due to the density of their breasts. [24-26] It is considered to be more useful for women who have had a previous cancer for identifying recurrence than in women over 35 who have never had breast cancer [27]

Ultrasound is a low cost technique and unlike mammography does not involve any harm or discomfort to the patient. Test performance is, however, operator dependent

and is less consistent than mammography. Ultrasound is also time consuming (30min per ultrasound).

- Magnetic Resonance Imaging (MRI)

MRI uses a powerful magnetic field and radio frequencies to produce detailed images of the breast and can provide valuable information that is unobtainable by mammography or ultrasound. Breast imaging is undertaken with dedicated breast coils with the patient lying prone on the examination table. The body coil around the base of the magnet sends radio waves into the breast tissues. The breast coils, receive radio waves recording signals from the breast tissue. A computer then processes the signals and generates a series of images each of which shows a thin slice of the breast, which can be viewed in different planes. A contrast agent is used during the examination to improve the conspicuity of cancers against the glandular tissue. The examination is carried out in the second week of the menstrual cycle to reduce background tissue enhancement.

MRI is used in women who are at high risk of developing breast cancer in distinguishing between scar tissue and recurrent tumour; in women where ultrasound and mammography findings are discordant and as a preoperative staging tool in patients with lobular cancer or where there is suspected multifocal disease . MRI has greater sensitivity than mammography or ultrasound, making it a particularly useful imaging modality for detecting small tumours and in women with dense breast tissue. Specificity has been reported as being as low as 37%, however, as MRI is poor at distinguishing between cancer and benign breast disease.[23]

The magnetic field used in MRI is not harmful, although internal medical devices that contain metal may malfunction or cause problems during an MRI exam. Some women may find the procedure uncomfortable and claustrophobic. There is also a small risk of mild allergic reaction if contrast material is injected. MRI investigations carry a greater financial cost than mammography or ultrasound and are more time consuming to perform (30-40 minutes).

1.3.2 Physical Examination Tests

- Specialist led clinical exam

A small percentage of breast cancers are not detected by mammography but can be felt during a clinical breast examination. The clinical exam involves both a physical breast examination coupled with individual medical history taking and review. It also provides an opportunity for monitoring treatment outcomes and providing psychological reassurance for the patient. A clinical breast examination is a physical examination conducted by a trained specialist clinician or a nurse practitioner. This involves visual inspection and palpation of the entire breast/chest area including the lymph node areas above and below the collarbone, and under each arm. Special attention is given to any change in shape and texture of the breasts, location of any lumps, and whether such lumps are attached to the skin or to deeper tissues. A noted cause for concern is usually investigated with an additional imaging test, such as mammography, ultrasound or MRI. There is broad agreement for frequent clinical examination, initially 6 monthly and then annually for up to 3-5 years.[18--20]

- Unstructured primary care follow up (including primary care follow-up and self-examination)

(i) Primary care follow up

Clinical follow up of breast cancer patients is routinely coordinated and conducted in the secondary care hospital outpatient setting. Patients often detect recurrences themselves, however, during the interval between clinic visits. Consequently, there have been calls to transfer follow up to the primary care setting, with the General Practitioner performing a similar role to the specialist clinician during the clinical exam. If a GP detects a possible recurrence, the woman should be referred back to the secondary care breast unit for further investigation. Primary care follow up also encompasses the role of the GP in assessment and referral of patients presenting in primary care with self-reported symptoms. These patients may be under secondary care supervision or may have been lost from the follow up regime for varying reasons. This latter group of women are classified as undergoing unstructured primary care follow up as they commonly self present with symptoms in the GP setting.[28]

(ii) Self examination

The breast self examination is a physical examination performed by the woman to detect any changes in the breast. Special training is given to the woman in palpation techniques and to promote breast self awareness. Training teaches women how to identify new lumps in the breast or underarm that may be potentially cancerous, and

to identify any surface changes such as skin rash or nipple discharge. In follow up, women are also taught to recognise additional symptoms such as bone, chest or abdominal pain, difficulty breathing and persistent coughs or headaches that may be indicative of cancer. It is recommended that women perform a self exam every month in addition to scheduled imaging and clinical examinations.

1.4 Reference standard test

Histopathological examination is the commonly agreed reference standard for diagnosing recurrent breast cancer based on tissue from a biopsy or needle aspiration and cell cytology. Histopathology is usually conducted due to suspicion of malignancy on a prior surveillance test.

There is, however, no reference standard for ascertaining the true negative and false negative measures of a surveillance test for recurrent breast cancer, although this is usually ascertained by a negative result or a positive test result at subsequent testing after a period of follow up has elapsed (e.g. 1 year mammography interval, 2-3 year MRI interval, etc). A pragmatic reference standard is diagnosis of IBTR or MCBC up to 3 years post surveillance.

2 Objectives

To determine the diagnostic accuracy of surveillance mammography for detecting ipsilateral breast cancer tumour recurrence (IBTR) and metachronous contralateral breast cancer (MCBC) in women previously treated for primary breast cancer.

Primary Objective

To determine the performance of surveillance mammography, alone or in combination with other tests, in detecting IBTR & MCBC.

Secondary Objective

To determine the performance of surveillance mammography, alone or in combination with other tests, in comparison with the performance of alternative tests, alone or in combination, in detecting IBTR & MCBC.

3 Methods

3.1 Inclusion criteria for considering studies for the review

3.1.1 Types of study

We will include randomised controlled trials (RCTs) in which women are randomised to the index and comparator test(s) and all receive the reference standard test.

We will also consider diagnostic consecutive cohort studies in which both index and comparator tests are evaluated against the reference standard test in the same study population (head-to-head design). We will also consider indirect (between-study) comparisons by comparing cohort studies where women have received either the index test, or the comparator test, or a combination of tests with the reference standard test, and have included at least 100 participants in the analysis of test performance. This type of study design is less reliable than direct studies, however, as differences in diagnostic accuracy are susceptible to confounding factors between studies. [29]

If the number of studies meeting our inclusion criteria is sufficiently large, we may limit them by type of study design and taking into account the importance of other factors such as study quality and sample size.

Case reports and studies investigating technical aspects of a test will not be considered.

3.1.2 Types of participants

Women previously treated for primary breast cancer without detectable metastatic disease.

We will consider test performance in all settings.

3.1.3 Index Test

The index test for this review is surveillance mammography.

3.1.4 Comparator Test(s)

The following comparator tests will be considered:

Ultrasound

MRI

Specialist led clinical exam

- Hospital clinician led
- Hospital nurse led

Unstructured primary care follow up (which may or may not involve mammography)

- GP led follow up
- Self presentation
- Self examination

Comparisons of both individual and combinations of tests will be considered.

3.1.5 Target condition

Ipsilateral breast tumour recurrence and metachronous contralateral breast cancer following treatment for primary breast cancer.

3.1.6 Reference Standard

The reference standard for this review is histopathological assessment for test positives along with a follow-up period of up to 3 years for test negatives (in order to differentiate between true negatives and false negatives).

3.1.7 Outcomes

The following types of outcome will be considered:

- Test performance in diagnosing IBTR
- Test performance in diagnosing MCBC

Studies must report the absolute numbers of true positives, false positives, false negatives and true negatives, or provide information allowing their calculation, and report a per-patient analysis.

In studies reporting the above outcomes, the following outcomes will also be recorded, if reported:

- Adverse effects of mammography and other tests
- Acceptability of the tests
- Reliability
- Radiological/operator expertise (who conducts the test and previous experience)
- Interpretability/readability of the tests

3.2 Search strategy

We will conduct extensive electronic searches to identify reports of published, unpublished and ongoing studies. The search strategies will be designed to be highly

sensitive, including both appropriate subject heading and text word terms to identify diagnostic accuracy studies of mammography and comparative tests when used in surveillance. Searches will be restricted to English language reports published from 1990 onwards. Conference abstracts will not be included. The following databases will be searched: Medline, Medline In process, Embase, Biosis, Science Citation Index, Cancerlit, Medion, Health Management Information Consortium and the HTA Database. Reports of ongoing and recently completed trials will be sought from the Current Controlled Trials, Clinical Trials, WHO International Clinical Trials Registry Platform, NCI Clinical Trials Database, NRR Archive and NIHR Portfolio Database. The search strategy to be used in Medline and Embase is detailed (Appendix 1) and will be adapted for other databases.

In addition, relevant websites will be searched and will include National Cancer Institute, National Comprehensive Cancer Network, CancerWEB, Breast Cancer Surveillance Consortium, and National Library for Health as well as relevant professional organisations including the Royal College of Radiologists, Association of Breast Surgery at the British Association of Surgical Oncology, American Society of Clinical Oncology, American Society of Breast Disease, American College of Radiology and European Society for Clinical Oncology. Reference lists of all included studies will also be scanned for additional reports.

3.3 Data Collection and analysis

3.3.1 Data extraction and management

One reviewer will screen the titles and abstracts (if available) of all reports identified by the search strategy (Appendix 2). We will obtain full text copies of all studies deemed to be potentially relevant and one reviewer will independently assess them for inclusion. We will carry out a 10% check of inclusion assessment for all potentially relevant studies. Any disagreements will be resolved by consensus or arbitration by a third party.

We will develop and pilot a data extraction form (Appendix 3 and 4). One reviewer will independently extract details of study design, participants, index, comparator and reference standard tests, and participant flow and outcome data. A second reviewer will check the extracted data. When uncertainty exists regarding the data extraction, a third reviewer will advise and validate data extraction.

3.3.2 Assessment of methodological quality

The QUADAS tool was designed to assess the methodological quality of diagnostic accuracy studies included in systematic reviews. Two reviewers will independently assess the quality of all included studies, using a modified version of QUADAS (Appendix 5), adapted for appropriateness in assessing the quality of studies of tests for detecting breast cancer. Any disagreements will be resolved by consensus or arbitration by a third party. We will use a separate quality assessment tool (Appendix 6) for any RCT studies to assess the quality of randomisation.

3.3.3 Statistical analysis and data synthesis

For studies of diagnostic accuracy, we will tabulate the results of each individual study in a 2 x 2 table, an example of which is shown in Table 1. For each study we will attempt to calculate sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios and their 95% confidence intervals (CIs). We will also attempt to derive separate 2 x 2 tables for each subgroup to be considered in the analysis, where such information is reported.

We will use summary receiver operating characteristic (SROC) curves for the meta-analysis of data from studies reporting estimates of true and false positives and negatives. This approach characterises the relationship between sensitivity and 1-specificity across studies and takes into account variation in the threshold for test positivity between studies. ROC curves will be generated, where possible, for each testing procedure. Where data are available, potential sources of heterogeneity will be investigated by extending the SROC regression models to include study level covariates. These potential sources of heterogeneity include characteristics of the population such as age, race, family history and whether the patient had other screening tests.

Where appropriate, models will be fitted using the hierarchical summary receiver operating characteristic (HSROC) framework, which takes proper account of the diseased and non-diseased sample sizes in each study, and allows estimation of random effects for the threshold and accuracy effects, and testing of the impact of potential sources of heterogeneity. Pooled estimates and their 95%? CIs for the average operating points, expressed as sensitivity, specificity and likelihood ratios will be obtained by combining these estimates.

Average and ranges of feasible operating points will be identified on the fitted ROC points to convert ROC curve values into estimates of true positive and false positive rates which will serve as parameters within the economic model.

Table 1 Example of 2 x 2 table

		True disease status		
		Diseased	**Non-diseased**	***Total***
Test result	**Positive**	True positive, A	False positive, b	a+b
	Negative	False negative, c	True negative, d	c+d
	Total	a+c	b+d	

3.3.3 Subgroup analyses

We plan to conduct the following subgroup analyses, if there is sufficient evidence:

- Patient characteristics

  Breast density

  Age
  - Under 50 years
  - 50 years and over

  Menopausal status
  - Premenopausal
  - Postmenopausal

  HRT status
  - Previous hormone replacement therapy
  - Current hormone replacement therapy
  - No history of hormone replacement therapy

- Patient management

  Treatment for primary breast cancer (e.g. radiotherapy, neo/adjuvant therapy, endocrine therapy)

  Surgical treatment for primary breast cancer
  - Mastectomy
  - Breast conserving surgery

- Second tumour type (DCIS, Invasive, Size, Grade)

- Reference standard

  Duration of follow-up period

References

1 *UK beast cancer statistics [webpages on the Internet].* Cancer Research UK; 2007. [accessed July 2007] Available from: URL: http://info.cancerresearchuk.org/cancerstats/types/breast/?a=5441.

2 Heys SD, Chaturvedi S, Hutcheon AW, Sarkar TK. Guidelines, guidelines and more guidelines: and we still do not know how to follow-up patients with breast cancer. *World J Surg Oncol [journal on the Internet]* 2005;3(54):23rd Aug 2005.

3 Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366(9503):2087-106.

4 Schootman M, Fuortes L, Aft R. Prognosis of metachronous contralateral breast cancer according to stage at diagnosis: the importance of early detection. *Breast Cancer Res Treat* 2006;99(1):91-5.

5 Joseph E, Hyacinthe M, Lyman GH, Busch C, Demps L, Reintgen DS et al. Evaluation of an intensive strategy for follow-up and surveillance of primary breast cancer. *Ann Surg Oncol* 1998;5(6):522-8.

6 Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. *Int J Radiat Oncol Biol Phys* 1990;19(4):833-42.

7 Orel SG, Troupin RH, Patterson EA, Fowble BL. Breast cancer recurrence after lumpectomy and irradiation: role of mammography in detection. *Radiology* 1992;183(1):201-6.

8 *Breast cancer survival statistics[webpage on the Internet].* Cancer Research UK; 2--5. [accessed July 2007] Available from: URL: http://info.cancerresearchuk.org/cancerstats/types/breast/survival/

9 Flobbe K, Van der Linden ES, Kessels EG, van Engelshoven JM. Diagnostic value of radiological breast imaging in a non-screening population. Int J Cancer 2001, 92(4):616-8.

10 Bartella L, Smith CS, Dershaw DD, Liberman L. Imaging breast cancer Radiol Clin North Am 2006;45:45-67

11 Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 2005; 353 (17) 1773-83. Samei E, Poolla A, Ulissey MJ, et al; Digital Mammography: Comparative Performance of Color LCD and Monochrome CRT Displays. Acad Radiol. 2007 May;14(5):539-46

12 Berenberg AL, Jochelson MS, Harris JR: Mammographic detecion of recurrent cancer in the irradiated breast> AJR Am J Roentgenol 148:39-43 1987)

13 Orel SG, Troupin RH, Patterson EA, et al: Breast cancer recurrence after lumpectomy and irradiation: role of mammography in detection. Radiology 1992,183:201-206,

14 Burrell HC, Sibbering DM, Evans A *et al* Mammographic features of locally recurrent breast cancer following treatment by conservative surgery. *Clin Radiol* 1994 49:741.

15 Kunci CC, Weisensee AM, Lee CK Mammographic changes following conservative surgery and radiation therapy for breast cancer. *Breast Dis* 1992 5:169-181

16 Law & Faulkner (2002) Two-view screening and extending the age range: the balance of benefit and risk. Br J Radiol 2002, 889-894

17 Review of radiation risk in breast screening: Report by a joint working party of the NHSBSP National Coordinating Group for Physics Quality Assurance and the National Radiological Protection Board. NHSBSP Publication No 54 Feb 2003

18 I*mproving outcomes in breast cancer. Guidance on cancer services: manual update [document on the Internet].* London: National Institute for Clinical Excellence; 2002. [accessed July 2007]Availablefrom: URL: http://www.nice.org.uk/pdf/Improving_outcomes_breastcancer_manual.pdf

19 *Management of breast cancer in w. SIGN Guideline no 84. [document on the Internet].* Edinburgh: Scottish Intercollegiate Guiselines Network; 2005. [accessed July 2007] Avaialable from: URL: www.sign.ac.uk/pdf/sign84.pdf.

20 Association of Breast Surgery @ BASO RCoSoE. Guidelines for the management of symptomatic breast disease. *Eur J Surg Oncol* 2005;31(Suppl 1):1-21.

21 Board of the Faculty of Clinical Radiology. *Guidance on screening and symptomatic breast imaging [document on the Internet].* London: The Royal College of Radiologists; 2003. [accessed July 2007] Available from: URL: http://www.rcr.ac.uk/index.asp?PageID=310&PublicationID=184

22 Rissanen TJ, Makarainen HP, Mattila SI, Lindholm EL, Heikkinen MI, Kiviniemi HO. Breast cancer recurrence after mastectomy: diagnosis with mammography and US. Radiology 1993; 188:463-467

23 Bartella L, Smith CS, Dershaw DD, Liberman L. Imaging Breast Cancer. Radiologic Clinics of North America 2007; 45 (1) 45-67.

24 Crystal P, Strano SD, Scharynski S, Koretz MJ. Using sonography to screen women with mammographically dense breasts. AJR 2003; 181:177-182

25 Kaplan SS. Clinical utility of bilateral whole-breast US in the evaluation of women with dense breast tissue. Radiology 2001; 221:641-649

26 Buchberger W, DeKoekkoek-Doll P, Springer P, Obrist P, Dunser M. Incidental findings on sonography of the breast: clinical significance and diagnostic workup. AJR Am J Roentgenol 1999; 173:921-927

27 Jung Hee Shin et al. Ultrasonographic detection of occult cancer in patients after surgical therapy for breast cancer. J Ultrasound Med 2005; 24:643-649

28 Grunfeld E, Mant D, Yudkin P, Adewuyi-Dalton R, Cole D, Stewart J, et al. Routine follow up of breast cancer in primary care: randomised trial. *BMJ* 1996;313:665-9

29 Bossuyt PM, Leeflang MM. Chapter 6: Developing Criteria for Including Studies. In: *CochraneHandbook for Systematic Reviews of Diagnostic Test Accuracy* Version 0.4 [updated September2008]. The Cochrane Collaboration, 2008.

Appendices

Appendix 1 Prelimary search strategy for Medline/Embase multifile search

1 exp *breast neoplasms/ use mesz
2 exp *breast tumor/ use emez
3 breast.ti.
4 or/1-3
5 neoplasm recurrence, local/ use mesz
6 tumor recurrence/ use emez
7 cancer recurrence/ use emez
8 neoplasms, second primary/ use mesz
9 second cancer/ use emez
10 (recur$ or second or secondary or contralateral or ipsilateral or ibtr or mbcb).tw.
11 or/5-10
12 exp mammography/
13 (mammograph$ or mammogram$).tw
14 physical examination/
15 breast self-examination/
16 breast examination/ use emez
17 ((physical or clinical or self) adj1 (exam? or examin$)).tw.
18 surveillance.hw,tw.
19 follow up.ti.
20 (routine adj3 (visit or follow up)).tw.
21 Magnetic resonance imaging/ use mesz
22 Nuclear Magnetic resonance imaging/ use emez
23 (magnetic resonance imag$ or mri).tw.
24 ultrasonography, mammary/ use mesz
25 echomammography/ use emez
26 (ultrasound or ultrasonograph$ or echo mammogra$ or echomammogra$).tw.
27 or/12-26
28 neoplasm recurrence, local/di use mesz
29 tumor recurrence/di use emez
30 cancer recurrence/di use emez
31 neoplasms, second primary/di use mesz
32 second cancer/di use emez
33 or/28-32
34 4 and 33
35 "sensitivity and specificity"
36 roc curve/
37 receiver operating characteristic/ use emez
38 predictive value of tests/
39 diagnostic errors/ use emez
40 false positive reactions/ use mesz
41 false negative reactions/ use mesz
42 diagnostic accuracy/ use emez
43 diagnostic value/ use emez
44 du.fs. use mesz
45 sensitivity.tw.
46 distinguish$.tw.
47 differentiat$.tw.
48 identif$.tw.
49 detect$.tw.
50 diagnos$.tw.
51 (predictive adj4 value$).tw
52 accura$.tw.
53 comparison.tw.
54 or/35-53

55 27 and 11 and 4 and 54
56 34 or 55
57 remove duplicates from 56
58 limit 57 to yr="1990 - 2009"
59 limit 58 to la=english

Appendix 2 Study Eligibility Screening Form - Version 1, March 2009

Assessor initials:	**Date:**
Study identifier **(Surname of first author + year of publication)**	
Participants in the study Q1. Are some or all of the participants in the study adult women who have been treated for primary breast cancer without detectable metastatic disease?	Yes Unclear No
Tests used Q2a. Does the study assess film or digital mammography performance for detecting IBTR or MCBC?	Yes Unclear No
Q2b. Does the study assess performance for detecting IBTR or MCBC in one or more of the following comparators: - Unstructured primary care follow up: *GP led follow up*, *Self examination*, *Self presentation* - MRI - Ultrasound - Specialist led clinical exam *Hospital clinician led*, *Hospital nurse led*	Yes Unclear No
Reference standard Q3a. Is the reference standard histopathological examination of biopsied tissue or cytology for positive index or comparator test results?	Yes Unclear No
Q3b. Have negative index or comparator test results been verified within a 3 year follow up period?	Yes Unclear No
Type of study Q4a. Is the study an RCT in which people are randomised to the index and comparator test(s) and all receive the reference standard test, and have been enrolled in the study from 1990 onwards?	Yes Unclear No
Q4b. Is the study a consecutive cohort study in which the index test and comparator test and reference standard are done in the same study population and participants have been enrolled from 1990 onwards?	Yes Unclear No
Q4c. Is the study a consecutive cohort study with at least 100 participants included in the analysis and enrolled from 1990 onwards?	Yes Unclear No
Outcomes reported Q5a. Does the study report true positives, false positives, false negatives and true negatives for the detection of IBTR or MCBC?	Yes Unclear No
Q5b. Does the study allow calculation of true positives, false positives, false negatives and true negatives for the detection of IBTR or MCBC?	Yes Unclear No
Decision	**Include Unclear Exclude**

Appendix 3 Data Extraction Form - Version 4, May 2009

Study id: **Extractor initials:** **Date:**

Study ids of linked reports:

Aim of study:

Types of participants:

- ☐ Women without detectable metastatic disease who have received breast conserving surgery for primary breast cancer
- ☐ Women without detectable metastatic disease who have received mastectomy for primary breast cancer

Test(s):

- ☐ Mammography
- ☐ GP follow up
- ☐ Self examination
- ☐ Self presentation (of symptoms)
- ☐ MRI
- ☐ Ultrasound
- ☐ Hospital clinician led examination
- ☐ Hospital nurse led examination

Outcomes reported:

- ☐ IBTR
- ☐ Test performance
- ☐ Adverse effects
- ☐ Radiological or other operator expertise
- ☐ Interpretability/readability of tests
- ☐ Acceptability of tests

- ☐ MCBC
- ☐ Test performance
- ☐ Adverse effects
- ☐ Radiological or other operator expertise
- ☐ Interpretability/readability of tests
- ☐ Acceptability of tests

Study design:

- ☐ RCT
- ☐ Non-randomised comparative study with some participants receiving the index test, some receiving the comparator test and all receiving the reference standard
- ☐ Direct head-to-head with all participants receiving index test, comparator test and reference standard
- ☐ Cohort with all participants receiving either the index test or comparator and reference standard

Multicentre study? ☐ Yes If yes, number of centres:

Study start/end dates: Duration of study:

Country:

Source of funding:

Additional information on study design:

Inclusion criteria:

Exclusion criteria:

Characteristics of the participants

	Group 1	Group 2	All
Enrolled			
[For RCTs – number randomised]			
Received tests			
Received reference standard			
[Post randomisation exclusions]			
Analysed			
Lost to follow-up			
No Age: Mean			

Median SD Range No. <50 No. 50 and over			
Menopausal status: No. premenopausal No. postmenopausal			
HRT Status: No. currently receiving HRT No. previously received HRT No. never received HRT			
Primary Treatment:			
No. received primary breast conserving surgery (WLE)			
No. received primary mastectomy			
No. reconstructed breast			
No. receiving treatment for primary breast cancer: Neoadjuvant radiotherapy Neoadjuvant chemotherapy Adjuvant radiotherapy Adjuvant chemotherapy Adjuvant tamoxifen /Endocrine Oopherectomy or ovarian ablation			
Additional patient information:			

Characteristics of the tests

Index Test - Mammography

Film ☐
Digital ☐

Scoring system and positive test result defined as:

Details of interpreter/reader experience if reported:

Additional information on test (e.g. radiation dose, time taken, etc):

Comparator test:

- ☐ MRI
- ☐ Ultrasound

For the following comparators, a positive test result (e.g. lump identified by palpation) will initiate an imaging test prior to biopsy or Fine Needle Aspiration Cytology (FNAC). Please indicate whether a mammogram or other imaging test was conducted prior to biopsy/ FNAC for people with positive test results. Reported test performance (sensitivity/specificity) should reflect the comparator test and not the imaging test alone.

	Mammo/Other prior to biopsy/FNAC
☐ GP follow up	☐
☐ Self Examination	☐
☐ Self presentation (of symptoms)	☐
☐ Hospital Clinician led examination	☐
☐ Hospital Nurse led examination	☐

Positive test result defined as:

Details of operator experience if reported:

Additional information on comparator test:

Reference standard:

Positive Index/Comparator test results verified by:

- ☐ Histopathological assessment of biopsied tissue
- ☐ Fine Needle Aspiration Cytology

Negative Index/Comparator test results verified by:

- ☐ Subsequent testing within a 3 year follow up period

Length of follow-up time for verifying negative index/comparator test results:

How was tumour size determined?

How was tumour grade determined?

Additional information on reference standard:

Results

IBTR/MCBC Tumour Type

Please record the number of women with IBTR and/or MCBC

No of women with:	**No of women with:**
IBTR	MCBC

Please record the associated the number of women with the following for IBTR and/or MCBC:

IBTR – No of women with:	**MCBC – No of women with:**
DCIS	DCIS
LCIS	LCIS
Invasive	Invasive
Grade 1	Grade 1
Grade 2	Grade 2
Grade 3	Grade 3

If reported, please record the number of women with the following:

IBTR	MCBC
<u>Size</u>	<u>Size</u>
Not measurable	Not measurable
Invasive tumor in mm (largest dimension of dominant invasive tumour focus)	Invasive tumor in mm (largest dimension of Dominant invasive tumour focus)
Whole size of tumor (invasive plus surrounding DCIS if DCIS extends > 1 mm beyond invasive)	Whole size of tumor (invasive plus surrounding DCIS if DCIS extends > 1 mm beyond invasive)
<u>Morphologic type</u>	<u>Morphologic type</u>
a. Ductal/no specific (ductal NST)	a. Ductal/no specific (ductal NST)
b. Lobular	b. Lobular
c. Other	c. Other

Test performance (true and false positives and negatives)

Record data for each level of analysis e.g. patient, all biopsies, e.g. Size, grade, DCIS, Invasive, etc on separate sheet(s) containing 2x2 tables

General information on IBTR/MCBC:

Adverse events associated with tests

General information on adverse events:

Adverse events reported	Group 1 no. of women with event and % of total women in group	Group 2 no. of women with event and % of total women in group	All no. of women with event and % of total women in study

Inter-observer agreement

Scale used e.g. Kappa			Notes

Additional study information:

Appendix 4 Data Extraction (2x2 Table) - Version 2, March 2009

Study id: **Extractor initials:**

Date:

Study ids of linked reports:

Please record the unit of analysis as reported by the study authors – e.g. women level, biopsy level.

If given, please record unit of analysis by our considered sub-groups: Age, menopausal status, HRT status, primary treatment, second tumour type.

Test: **IBTR/MCBC**

	Unit of analysis:		
	With disease	**Without disease**	
Positive test	TP	FP	**Total testing positive**
Negative test	FN	TN	**Total testing negative**
	Total with disease	**Total without disease**	

Sensitivity: **LR+:**

Specificity: **LR-:**

Appendix 5 Quality Assessment Form – Version 3, March 2009

Study id: Extractor initials:

Date:

Study ids of linked reports:

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice? (women previously treated for primary breast cancer)			
2.	Is the reference standard likely to correctly classify the target condition?			
3a	For positive test results, is the time period between reference standard and index/comparator test short enough to be reasonably sure that the target condition did not change between the two tests? (biopsy or FNAC within 3 months, histopathology within 6 months)			
3b	For negative test results, is the time period between the index/comparator test and the reference standard short enough to be reasonably sure that the target condition did not change between the two tests? (follow up within 3 years)			
4.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?			
5a	Did patients testing positively on the index/comparator test receive the same reference standard (i.e. FNAC or biopsy)?			
5b	Did patients testing negatively on the index/comparator test receive the same reference standard (i.e. follow up)?			
6.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
7.	Were the index test results interpreted without knowledge of the results of the reference standard?			
8.	Were the reference standard results interpreted without knowledge of the results of the index test?			
9.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?			
10.	Were uninterpretable/ intermediate test results reported?			
11.	Were withdrawals from the study explained?			

Appendix 6 Quality assessment checklist (RCTs) – Version 1 Sept 2008

Study id: Assessor initials:

Date assessed:

Criteria	Yes	No	Unclear
1. Was the assignment to the treatment groups really random? Adequate approaches to sequence generation • computer-generated random tables • random number tables Inadequate approaches to sequence generation • use of alternation, case record numbers, birth dates or week days			
2. Was the treatment allocation concealed? Adequate approaches to concealment of randomisation • centralised or pharmacy-controlled randomisation • serially-numbered identical containers • on-site computer based system with a randomisation sequence that is not readable until allocation • other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients Inadequate approaches to concealment of randomisation • use of alternation, case record numbers, birth dates or week days • open random numbers lists • serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)			
3. Were the groups similar at baseline in terms of prognostic factors?			
4. Were the eligibility criteria specified?			
5. Was the intervention (and comparison) clearly defined?			
6. Were the groups treated in the same way apart from the intervention received?			
7. Was follow-up long enough to detect important effects on outcomes of interest?			
8. Was the outcome assessor blinded to the treatment allocation?			
9. Was the care provider blinded?			
10. Were the patients blinded?			
11. Were the point estimates and measures of variability presented for the primary outcome measures?			
12. Was the withdrawal/drop-out rate likely to cause bias?			
13. Did the analyses include an intention-to-treat analysis?			
14. Was the mammogram undertaken by somebody experienced in performing the procedure?			