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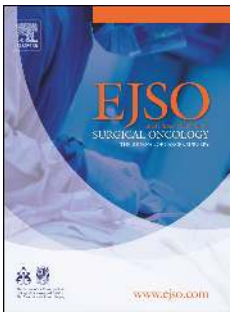

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Breast MRI in clinically and mammographically occult breast cancer presenting with an axillary metastasis: a systematic review

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Abstract

Background: Axillary metastatic lymphadenopathy with no primary tumour identified in the breast on physical examination, mammography or ultrasound is referred to as occult breast cancer. The goal of this systematic review is to give an overview of the value and additional considerations of using breast MRI in occult breast cancer.

Methods: The databases of Pubmed, Embase, CINAHL and the Cochrane library were searched for studies addressing the use of breast MRI in occult breast cancer. Cross-referencing was used to find additional articles.

Results: 8 retrospective studies were included. Breast MRI can detect an otherwise occult breast cancer in more than two thirds of patients with a high sensitivity but lower specificity. In 80% of patients MRI detected lesions could be localized again by using ultrasound. Furthermore the size and localization of the lesions found on MRI most often correlated closely with findings at pathology. Breast MRI also provided the possibility of breast conserving surgery in one thirds of patients.

Conclusion: Breast MRI can result in additional detection of otherwise occult lesions in occult breast cancer. Because of low specificity of malignant lesion detection by breast MRI, lesions should be histologically confirmed. This can be achieved either by MRI or ultrasound guided biopsy, as long as all MRI detected lesions are histologically checked. Routine application of breast MRI in occult breast cancer may also alter locoregional treatment by offering the possibility of breast conserving surgery in one thirds of patients.

Keywords

Occult breast cancer, axillary metastasis, magnetic resonance imaging, breast cancer, unknown primary

Introduction

The most likely source of metastatic lymphadenopathy in the axilla is the ipsilateral breast [1-4]. In 0.3-1.0% of all women with breast cancer metastatic lymphadenopathy is the first presenting symptom [5-7]. Consequently when no other primary source becomes evident during workup or physical examination, and mammography or ultrasound of the breast shows no abnormalities, this is called occult breast cancer.

With the introduction of more advanced diagnostic techniques in the past century, like mammography and ultrasound of the breast, the incidence of occult breast cancer has decreased [8]. In recent years other diagnostic modalities, like CT, positron emission tomography (PET) and other types of scintigraphy have also been used to find the primary source, but none of these techniques are applied routinely and evidence for routine use in occult breast cancer is insufficient [9-14].

Nowadays MRI of the breast is frequently applied when other diagnostic modalities fail to find a primary source in the breast. Although the sensitivity of MRI for detection of breast cancer is high, the specificity is much lower [15]. Hence the correlation of detected MRI lesions to findings at pathology and the implications for treatment are important issues. Because of the low incidence of occult breast cancer, published studies usually consist of small numbers of patients which prevents addressing these matters adequately.

The goal of this systematic review is to give an overview of the value and additional considerations of using breast MRI in occult breast cancer. The questions that will be addressed are the following:

1. What is the sensitivity and specificity of a breast MRI in case of an occult breast cancer?

2. Is MRI guided biopsy preferred over MRI guided sonographic biopsy?
3. Are the breast MRI findings correlated to the pathological findings?
4. What percentage of patients with occult breast cancer and MRI detected lesions can be treated by breast conserving surgery?

Methods

Search strategy

In this systematic review the database of Pubmed, Embase, CINAHL and the Cochrane library were searched for patient studies (≤2009) using the MeSH terms: "axilla", "neoplasms", "unknown primary", "breast neoplasms" and "magnetic resonance imaging" and using the free terms: "breast", "cancer" or "carcinoma", "occult", "unknown primary", "axilla" and "MRI". Limits were set for languages; only English, German, Spanish, French and Dutch articles were included. Cross-references were used to find additional relevant articles covering the use of MRI in occult breast cancer. Studies were selected independently by two of the authors (J. de Bresser and B. de Vos) first by screening of the abstracts, and if necessary selected articles were retrieved in full text and analysed.

Definition of occult breast cancer

With the introduction of MRI the incidence of occult breast cancer is decreasing. Although more commonly used, ultrasound (US) in occult breast cancer has a high false-positive and a high false-negative rate [16]. Therefore, the results of US are not routinely used to define occult breast cancer.

For the purpose of this review occult breast cancer is defined as isolated metastatic axillary lymphadenopathy with no palpable mass in the breast and no signs of primary breast cancer on mammography and no detected primary tumour outside the breast.

Exclusion criteria

Studies were excluded if included patients fulfilled the definition of occult breast cancer. Furthermore, case reports and small patient series (<10 patients) were also excluded, because

these studies often present highly heterogeneous patient groups and critical appraisal of these studies is not reliable.

Critical appraisal

All included studies were critically appraised independently by two of the authors (J. de Bresser and B. de Vos) using the 14 item QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool [17-19]. This included appraisal of: covered patient spectrum, reference standard, disease progression bias, verification bias, review bias, clinical review bias, incorporation bias, test execution, study withdrawals and indeterminate results. QUADAS is the best tool for critical appraisal of diagnostic studies described to date. It is widely used to give an overview of the different aspects of the studies and is not used to assess the individual studies on validity, because of lack of evidence [20].

Analysis

Outcome measures (sensitivity, specificity, success rate of sonographic biopsies, identified tumours at pathology and success rate of breast conserving surgery) are described as ranges of data found in the studies and means of pooled patient data. If pooling was not possible, only ranges of values found in the studies are reported. No statistical tests were done because of heterogeneity of the study groups.

Results

Inclusion of studies

A total of 21 studies were selected that seemed relevant on screening of the abstract. On reading the full text articles another 6 studies were excluded because not all included patients fulfilled the definition of occult breast cancer. The remaining 15 studies were all retrospective studies, no prospective studies or randomized controlled trials were found and no male patients with occult breast cancer were described in these studies. A further 4 studies were excluded because it were case reports and 3 studies were excluded because less than 10 patients were included. After the exclusion process, 8 studies were included in this review [21-28]. Differences between the two authors in the independent selection and exclusion of the studies were discussed, and agreement could be made on all differences.

Description of included studies

Eight retrospective studies were found which included 12 to 55 patients, describing a cumulative total of 220 patients with occult breast cancer. All studies described the results of strategies to obtain histopathological diagnosis in case of positive MRI findings. In 5 of these studies the use of (wire) localization or biopsy by MRI guided ultrasound was described [23-27]. In 3 studies the use of MRI guided wire localization or biopsy was reported [21,22,28]. In contrast to the other studies, the study of Chen et al. only included patients with occult breast cancer and suspicious lesions on breast MRI [22]. In table 1 the included studies are shown.

Critical appraisal

Differences in the critical appraisal by independently using the QUADAS tool by two of the authors were discussed on and consensus was reached in all cases. In table 2 the critical

appraisal of the studies using the QUADAS tool is shown. All studies used physical examination and mammography in the assessment of the primary tumour. Most studies also performed a breast ultrasound. A problem in these studies is that the outcome of the MRI is often incorporated in the decision for treatment. In some patients without MRI detected lesions the breast was not surgically treated. In these cases follow-up was done to detect primary breast cancer occurrence.

The diagnostic strategy to find a non breast primary was variable between studies and even within studies. The extensiveness of this approach varied with clinical probability of a possible alternate primary. Because of the follow-up period of the studies the missed other primaries were detected at a later stage and excluded from analysis.

Sensitivity and specificity of breast MRI

In the 7 studies describing the results of MRI in diagnosing the breast primary in occult breast cancer, in 36 to 86% (pooled mean: 72%) of patients a lesion suspect for primary breast cancer was visualized [21,23-28]. If a suspect lesion was detected on MRI, in 85 to 100% of cases this indeed was a malignant breast tumour. Pooling the individual patient data results in a sensitivity of 90% [25,28]. The specificity of occult breast cancer detection is however considerably lower en more variable, ranging from 22 to 50% (31% if data are pooled) [25,28]. For the calculation of sensitivity and specificity only the studies which reported histological or pathological confirmation were used. Hereby excluding studies in which some of the patients without a lesion found on MRI got follow-up as a check for occurrence of primary breast cancer. In table 3 the extracted data from the individual studies is shown.

MRI guided biopsy versus MRI guided sonographic biopsy

In 5 studies results of MRI guided ultrasound localization were reported. The MRI detected lesions could be localized again by ultrasound in 60 to 100% (pooled mean: 80%) of patients [23-26]. One study used MRI guided ultrasound localization in a subgroup of patients (16 of 28), but they could only redetect 6 lesions (38%) with ultrasound [27]. The studies reporting the results of MRI guided biopsy all fail to consequently biopsy all patients with abnormal findings but apply this only in subgroups which were not clearly defined [21,22,28]. Therefore no comparison between both biopsy methods could be made.

Correlation of MRI lesions and pathology findings

The size of lesions detected by MRI varied from 5 to 30 mm with a mean size varying between the studies from 13 to 17 mm [25,27,28]. Size on pathologic examination ranged from 1 to 50 mm with a mean size varying from 5 to 16 mm [21-23,26-28]. The size and localization of the enhancing lesion(s) on MRI most often correlated closely with found lesions at pathology [27,28]. Of the identified tumours at pathology 70 to 90% (pooled mean: 82%) were infiltrating ductal carcinoma, 8 to 20% (pooled mean: 11%) infiltrating lobular carcinoma, 8 to 11% (pooled mean: 4%) ductal carcinoma in situ, 2% mixed type and 1% tubular carcinoma [21-28].

Breast MRI and the possibility of breast conserving surgery

The studies of Morris et al. and McMahon et al. identified 60 and 78% of occult lesions and were able to perform an MRI guided sonographic wire localization in 30 and 55% of patients with a lesion detected on MRI [24,25]. Thus, in 20 and 43% of all patients in these studies sonographic wire localization with MRI guidance was achieved. In all of the patients with localized lesions breast conserving surgery was performed.

With MRI guided wire localization 37% of breast lesions were successfully localized [22,28]. These wire localizations also resulted in breast conserving surgical procedures.

In total, 21 to 60% (pooled mean: 35%) of all patients, with suspect lesions on MRI and without systemic breast cancer, underwent breast conserving surgery [21-25,27,28]. Buchanan et al. even concluded that 58% of patients with a suspect lesion on MRI could potentially be treated by breast conserving surgery [21]. However, 8% of patients opted for mastectomy and 15% had positive margins after breast conserving surgery. Effectively 35% of patients with a suspect lesion on MRI were successfully treated with breast conserving surgery.

McMahon et al. reached a similar conclusion, showing that 56% of patients with malignancy confirmed preoperatively were suitable for breast conserving surgery, but 22% opted for a mastectomy [24].

Discussion

Sensitivity and specificity of breast MRI

Breast MRI is often the first choice in attempting to find the breast primary in occult breast cancer. As a result, in approximately two thirds of the population the primary tumour can be detected [21,23-28]. In line with studies on breast MRI for other indications, sensitivity for detection of occult breast cancer is high, but specificity is much lower [15,25,28]. Thus, every lesion detected by MRI should be histologically confirmed either by MRI guided biopsy or by MRI guided sonographic biopsy.

MRI guided biopsy versus MRI guided sonographic biopsy

Because of methodological flaws in the original studies, no comparison between results of MRI guided biopsy/localization versus MRI guided sonographic biopsy/localization could be made. This is due to heterogeneity of study groups and application of procedures to non (pre)specified subgroups. Obviously, with MRI guided biopsy/localization it is probably easier to localize the lesion. However, success rates in localizing the tumour with ultrasound after identification by MRI in the included studies were relatively good. Results from a larger cohort of patients with nonpalpable, mammographically occult MRI detected lesions indicates otherwise [29]. In this cohort only 46% of lesions could be localized again by using ultrasound and sonographically occult lesions had a 22% probability of malignancy.
With the limited availability of MRI guided localization or biopsy systems, ultrasound guided localization or biopsy based on MRI findings can be a reasonable alternative. However, only if all MRI detected lesions can be redetected and biopsied. CT-guided wire localization of MRI-detected breast lesions has been reported, but also suffers from underdetection of MRI detected lesions [30].

Correlation of MRI lesions and pathology findings

Although specificity of breast MRI is low, the size and localization of the enhancing lesion(s) on MRI most often correlated closely with found lesions at pathology [27,28]. The finding of axillary metastasis in the presence of only ductal carcinoma in situ on histopathological examination may be explained by failure to identify micro invasion of this tumour [21]. The alternative explanation is of course the presence of another, "truly" occult tumour.

Breast MRI and the possibility of breast conserving surgery

Wire localization can be performed for breast conserving surgery. In the described studies a pooled mean of 35% of patients with a suspect lesion on breast MRI were treated by breast conserving surgery [21-25,27,28]. Although it was reported that breast conserving surgery was possible in more patients, some opted for ablative therapy or had positive margins after breast conserving surgery [21,24].

Limitations

A methodological problem of the described studies is the incorporation of the results of the MRI in the decision for treatment, making it part of the reference standard instead of comparing it with a reference standard.

A number of studies included patients with no lesions found on breast MRI and no surgical treatment of the breast [21,23,24]. These patients underwent follow-up to confirm negative breast cancer status. Because no pathological information was obtained from these patients, the sensitivity and specificity of breast MRI could not be calculated from these studies in a valid way. However, the studies used in the calculation of sensitivity and specificity did not systematically use a mastectomy for pathologic confirmation. Although an overestimation

could have occurred, the high sensitivity and lower specificity are in line with studies on breast MRI for other indications [15].

The conclusions of this review are limited by the small and heterogeneous patient groups and the retrospective design of the studies included. This lack of high quality studies can be explained by the low incidence of occult breast cancer.

Conclusion

Occult breast cancer incidence is decreasing, because more primary breast cancers can be detected with the introduction of more advanced techniques. However, this clinical problem is still encountered regularly. Breast MRI can identify the primary tumour in approximately two thirds of this population, but because of the low specificity lesions need to be histologically confirmed. This can be achieved either by MRI or ultrasound, as long as all MRI detected lesions are histologically checked. Additionally, a breast MRI may alter locoregional treatment of occult breast cancer, resulting in breast conserving surgery in one thirds of patients. Therefore breast MRI should routinely be performed in patients with occult breast cancer.

Authors' contributions

KH and FE conceived and designed the study. JB and BV were responsible for the data search and critical appraisal. JB produced the tables and wrote the manuscript. All other authors contributed to writing of the manuscript and approved the final version.

Conflicts of interest

The authors declare no conflicts of interest.

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Table 1: Included studies.

MRI combined with US guided localization or biopsy

Author	**N**	**Diagnostic means (n)**
Morris EA, et al	12	Suspect lesion on MRI (10) US guided localization (9) US guided wire localization (3)
Obdeijn IM, et al	31	Suspect lesion on MRI (11) US guided localization (11) US guided biopsy (11)
Olson JA, et al	40	Suspect lesion on MRI (28) US guided localization (16) US guided wire localization (3)
McMahon K, et al	18	Suspect lesion on MRI (14) US guided localization (14) US guided biopsy (11)
Ko EY et al	12	Suspect lesion on MRI (10) US guided localization (10) US guided biopsy (6) US guided wire localization (2)

MRI combined with MRI guided localization or biopsy

Author	**N**	**Diagnostic means (n)**
Orel SG, et al	22	Suspect lesion on MRI (19) MRI guided wire localization (7)
Buchanan CL, et al	69	Suspect lesion on MRI (54) US guided or MRI guided biopsy (42) US guided wire localization (3) MRI guided wire localization (2)
Chen C, et al	16	Suspect lesion on MRI (16) MRI guided wire localization (6)

Table 2: Critical appraisal of the studies using the QUADAS tool [18].

Author	Years of inclusion	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Morris EA, et al.	1995-1996	Y	Y	Y	Y	Y	N	N	Y	?	N	Y	Y	Y	Y
Obdeijn IM, et al.	1995-1998	Y	Y	Y	?	Y	N	N	Y	Y	N	Y	Y	N	Y
Olson JA, et al.	1994-1998	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Y
McMahon K, et al.	2000-2004	Y	Y	Y	?	Y	N	N	Y	N	N	Y	Y	Y	Y
Ko EY, et al.	2001-2006	Y	Y	Y	?	Y	N	N	Y	N	N	Y	Y	Y	Y
Orel SG, et al.	1993-1997	Y	Y	Y	Y	Y	N	N	Y	?	N	Y	Y	Y	Y
Buchanan CL, et al.	1995-2001	Y	Y	Y	?	Y	N	N	Y	N	?	Y	Y	Y	Y
Chen C, et al.	1995-2001	N	Y	Y	?	Y	N	N	Y	N	?	Y	Y	Y	Y

Items:

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterpretable/intermediate test results reported?
14. Were withdrawals from the study explained?

Y: Yes, N: No, ?: Unclear

Table 3: Extracted data from the studies.

		MRI							**Pathology**				**Treatment**
Author	**N**	**Patients with a suspect lesion(s) on MRI** (n)	**Successful MRI guided US localization** (n)	**Loss to follow-up** (n)	**TP** (nl)	**FP** (nl)	**TN** (nl)	**FN** (nl)	**InfD** (nl)	**InfL** (nl)	**DCIS** (nl)	**Other** (nl)	**BCS** (n)
Morris EA, et al.	12	10 of 12	6 of 10	-	9	2	2	0	7	1	1	-	3 of 10
Obdeijn IM, et al.	31	11 of 31	11 of 11	-	-	-	-	-	9	2	-	-	-
Olson JA, et al.	40	28 of 40	-	-	-	-	-	-	19	3	-	-	9 of 28
McMahon K, et al.	18	14 of 18	11 of 14	-	-	-	-	-	7	2	1	-	3 of 14
Ko EY, et al.	12	10 of 12	8 of 10	-	-	-	-	-	8	-	1	1 Tubular	6 of 10
Orel SG, et al.	22	19 of 22	-	4	17	7	2	3	18	2	-	-	7 of 19
Buchanan CL, et al.	69	54 of 69	-	12	-	-	-	-	20	2	2	2 Mixed type	9 of 26
Chen C, et al.	16	-	-	-	-	-	-	-	12	2	-	-	6 of 16
Pooled data	220	146 of 204	36 of 45	-	26	9	4	3	100	14	5	3	43 of 123

Legends

Table 1

Included patients are shown for all studies. Patients with suspect lesions on MRI are shown, and patients who had undergone a (wire) localization or biopsy are depicted.
US: Ultrasound, N: Number of patients with occult breast cancer included in study, n: Number of patients in subgroups of applied diagnostic procedures

Table 3:

All extracted data from the individual studies is shown. This information is subdivided in data associated with MRI, pathology and treatment. Data were pooled only for the studies in which it could be extracted. Information on pathology was not available for all patients in all studies.
US: Ultrasound, N: Number of patients with occult breast cancer included in study, n: Number of patients in subgroups, nl: Number of lesions in subgroups, TP: True positives, FP: False positives, TN: True negatives, FN: False negatives, InfD: Infiltrating ductal carcinoma, InfL: Infiltrating lobular carcinoma, DCIS: Ductal carcinoma in situ, BCS: Breast conserving surgery, FU: Follow-up