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The value of MRI in the detection of axillary lymph node metastases in breast cancer: a systematic review

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Summary

Staging of the axillary lymph nodes is an essential step to determine the appropriate treatment for breast cancer. Sentinel lymph node biopsy (SLNB) is currently the first step in staging and the gold standard. However, if the sentinel node is positive, a full dissection of the axillary lymph nodes should be performed (axillary lymph node dissection or ALND). This technique used to be the gold standard but had considerable sequelae which diminished quality of life. SLNB still has sequelae but the incidence is much lower. The goal of this systematic review is to assess whether MRI can replace or assist the current gold standard for axillary lymph node staging in breast cancer. With the use of these non-invasive techniques, the risk of morbidity could be reduced even more. A comprehensive search and an additional brief search in several databases has been performed using PRISMA. Studies were selected based on titles and abstracts and were included or excluded using predetermined criteria. The studies were assessed for validity and applicability using the QUADAS-2 tool by two readers. Data of three studies using diffusion-weighted imaging (DWI) were pooled and statistical analysis was performed. A total of seven studies were included for review. Three studies used DWI, others used T2-weighted imaging, contrast-enhanced imaging, T1-weighted imaging or an MRI scoring system. Due to the heterogeneously divided MRI modalities, a small meta-analysis of DWI was performed. Other studies were evaluated qualitatively. DWI reached a sensitivity of 87.67% (95% CI 77.88-94.20) and a specificity of 59.31% (95% CI 50.85-67.38), a positive predictive value (PPV) of 52.03% (95 CI 42.84-61.12), and a negative predictive value (NPV) of 90.53% (95% CI 82.78-95.58). MRI can aid in the detection of axillary lymph node metastasis, but it cannot replace the current gold standard (SLNB/ALND).

Key words: Sentinel node; Axillary; Staging; MRI; Breast cancer.

Introduction

Breast cancer is with 1.7 million new cases worldwide in 2012, the most prevalent cancer in women. In 2012, 10,531 women and 79 men were diagnosed with primary breast cancer in Belgium. Belgium is ranked number 1 worldwide for breast cancer incidence (111.9 new cases per 100,000 person years in 2012). Belgium is, however, also the leader in five-year survival of breast cancer from a proportional view. For patients with breast cancer, staging of the axillary lymph nodes is an important step in determining the appropriate treatment and prognosis.

The current diagnostic pathway, according to the NICE guidelines [1], involves a clinical examination followed by an ultrasound. Patients with negative lymph nodes on ultrasound and ultrasound-guided biopsy undergo sentinel lymph node biopsy (SLNB) if the primary tumor is < 3 cm (< T2) [2]. Patients with positive lymph nodes undergo axillary lymph node dissection (ALND). The largest disadvantages of SLNB and ALND are the possibility to develop considerable sequelae that can diminish quality of life. Possible sequelae after these operations are: reduced range of motion from the shoulder, seroma, edema in the limb, numbness in either limb or fingers, etc. [3]. Although SLNB has reduced the occurrence of these sequelae in comparison to ALND, they still are prevalent. In general, SLNB has long-term complications in 3% of patients and ALND in 35% [4]. It is therefore necessary to further research non-invasive methods that can detect axillary lymph nodes and that can differentiate between benign and malignant invaded lymph nodes. MRI has been proposed as a valid alternative. For MRI to completely replace SLNB in the detection of metastatic axillary lymph nodes, it requires a sensitivity that is high enough to miss as little invaded lymph nodes as possible. The specificity will affect the false positive patients who will wrongly undergo axillary surgery, which in turn will raise the morbidity. The present authors wrote this review and meta-analysis to assess the diagnostic accuracy of MRI in patients with metastatic axillary lymph nodes.

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Materials and Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed. Four different databases were searched including: TRIP (Turning Research Into Practice) database, SUMsearch, MEDLINE, and Cochrane library. Search terms were chosen using the PICO method and translated into MeSH-terms. It included: "(Breast Cancer) AND (MRI) AND (Axilla) AND (Lymph node)". All studies between 1/1/2008 to 30/6/2016 were evaluated for inclusion.

Studies were selected for inclusion by two reviewers. This occurred in three stages. Firstly, irrelevant titles were excluded. Secondly, abstracts of articles with eligible titles were evaluated for inclusion, if they were eligible for inclusion after this stage, the full text was read and evaluated.

All cohort studies that met the following criteria were included: 1) a newly confirmed diagnosis of breast cancer in TNM Stage I, II or IIIA, 2) an MRI mammography/axilla performed by an MRI apparatus with a magnetic field of at least 1.5 T must have been performed, and 3) anatomopathologic results of an ALND/SLNB must be available.

If any of the following criteria were met, the study was excluded: 1) case-control studies, 2) patients with ductal or lobular carcinoma in situ (DCIS or LCIS), 3) MRI-mammography was performed after neoadjuvant chemotherapy was administered, 4) ultrasmall superparamagnetic iron oxide (USPIO)-enhanced MRI-mammography, and 5) no sensitivity and specificity results available

The quality assessment was performed by two readers using the Quality Assessment of Diagnostic Accuracy (QUADAS-2) checklist. The included articles were assessed in four domains: patient selection, index test, reference standard, and flow and timing. Data were extracted by one reader and checked by the second reader. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were extracted from the articles. Wherever values were not mentioned in the article, they were calculated with either the available data about the assessed lymph nodes or by creating a 2×2 table with the given sensitivity and specificity.

Results

After excluding irrelevant titles, evaluating abstracts, and reading the full texts, seven articles met the inclusion criteria for this review and were included. Two studies used contrast-enhanced MRI [5 ,6], three examined diffusion-weighted MRI images solely [7-9] (of which one compared it to unenhanced T1), one combined T2 and diffusion-weighted images [10], and one used an MRI scoring system based on different parameters [11]. The authors grouped the studies by imaging modality and compared the data in these groups. This was done to enhance the value of the data comparison. One study [12] was divided in two because data was available for both imaging modalities (DWI and T1), as is shown in Table 1.

After assessment with the QUADAS-2 checklist, two primary studies were found to be at high risk for bias [6, 7], four studies were found to be at unclear risk for bias [5, 8, 9, 11], and only one study was classified at low risk for bias [10]; all of them scored well in terms of applicability (Figure 1). The most common problem the authors encountered performing the assessment was a lack of information regarding the domain. Flow and timing were often assessed as unclear because no time interval between the index test and the reference standard was specified. This is a quite important parameter in this review's case, since the longer the interval between the index test and the reference test is, the higher the chance is a metastasis occurred during that interval.

Table 1.— *All included MRI studies with their respective methods and sensitivity, specificity, PPV, and NPV values.*

Article	Year	Method	Sens	Spec	PPV	NPV
Schipper *et al.*	2015	T2+DW	69	95	83	90
Hwang *et al.*	2013	cMRI 1.5T	47.8	88.7	60.2	82.6
Lu *et al.*	2013	cMRI 3T	86	95	88.3	97.6
Kamitani *et al.*	2013	DW	53.8	86.9	56	85.9
Fornasa *et al.*	2012	DW	94.7	91.7	90.0	95.7
Scaranelo *et al.*	2012	DW	83.9	77	78.5	82.7
Scaranelo *et al.*	2012	T1	88.4	82.4	83.4	87.7
Ni *et al.*	2012	MRI scoring	93	91	92	92

Table 2. — *2×2 contingency table with pooled data from studies using diffusion weighted imaging*

	Histopathology +	Histopathology -	Total
DWI +	64	59	123
DWI -	9	86	95
	73	145	218

Legend: Histopathology +: lymph nodes found to contain malignant cells.
Histopathology -: lymph nodes found to be free of malignant cells.
DWI +: lymph nodes assessed as being metastasized on diffusion weighted magnetic resonance imaging.
DWI -: lymph nodes assessed as being free of metastasis on diffusion weighted magnetic resonance imaging.

The sensitivity, specificity, PPV, NPV values, and MRI modality used per included study are shown in Table 1. The included studies are quite heterogeneously divided concerning MRI modality [5-10, 12] . DWI was the most prevalent modality among the included studies. Therefore, the authors decided to perform a small meta-analysis of these studies. The remaining studies will be reviewed descriptively. All three DWI MRI studies used a 1.5T magnet and two studies provided a cut-off value for the apparent diffusion coefficient they handled. One study had no preceding literature on apparent diffusion coefficient (ADC) values and correlated the ADC values with T1 findings [9]. They found that malignant lymph nodes had significantly lower ADC-values. A 2×2 contingency table was created using raw data extracted from the article or after being acquired by contacting the original author. These data were pooled in a new 2×2 contingency table (Table 2) and sensitivity, specificity, NPV, and PPV were calculated from the pooled data.

The authors found a sensitivity of 87.67% (95% CI 77.88-94.20), a specificity of 59.31% (95% CI 50.85-67.38), a PPV of 52.03% (95 CI 42.84-61.12), and a NPV of 90.53% (95% CI 82.78-95.58).

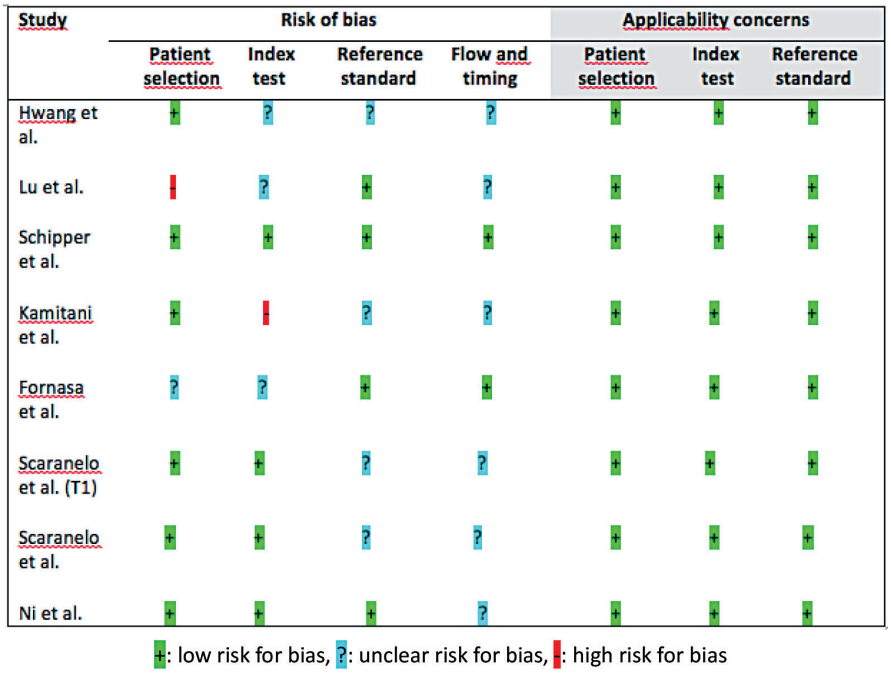

Figure 1. — Quality of the included studies scored with the QUADAS-2 criteria.

Discussion

The meta-analysis we performed concerning the three studies about DWI showed a reasonable sensitivity, but a more than suboptimal specificity. SLNB has a reported sensitivity and specificity of, respectively, 93-95% and 100% [13]. Comparing the results of the present meta-analysis with SLNB shows that replacing SLNB with DWI would increase the number of false positives, which in turn will cause more ALNDs to be performed when not needed, causing more patients to have morbidities postoperatively. The number of false negatives will increase as well. Evaluating the results from included studies, it seems that the most accurate way to evaluate lymph nodes is through an MRI scoring system based on different parameters of the lymph node, possibly combining different MRI modalities (or other) for this. However, more studies with combined MRI modalities and standardized cut-off values are needed to determine the most accurate MRI protocol for the detection of metastatic axillary lymph nodes.

Previous research into MRI for breast cancer and metastases sometimes included studies with USPIO-enhanced MRI, which showed to be very promising with high sensitivity (ranging from 61-100%), specificity (ranging from 72-100%), and NPV ranging from 78-98% [13-18]. The problem with USPIO lies within the few studies that selectively investigated possible adverse effects in contrast to the larger number of studies that have investigated its values and diagnostic accuracy over the years of its existence. One recent study discovered USPIO contrast agents to be thrombogenic after being administered intravenously (thus in vivo) and in vitro as well [19]. Another study proved these contrast agents to have an anticoagulant effect [20]. USPIO contrast has not been approved yet by the FDA in the United States of America, which makes it unavailable to be used in the general population. Studies performed with these contrast agents are thus only possible when pharmaceutical companies provide them to the researcher. This in turn may or may not introduce a bias. An application requesting the approval from the European Medicines Agency for an USPIO contrast agent was withdrawn in 2007. No other or new applications are ongoing.

Gadofosveset, a recently developed gadolinium-based contrast in the form of a trisodium salt, was originally designed as a blood pool agent for use in MRI angiographies. It binds to serum albumin, and due to high molecular weight and larger size, it does not travel to the interstitial space as easily. Given that lymphatic fluid contains high albumin levels as well, it gave incentive to research gadofosveset as a lymphatic contrast. A study using gadofosveset to evaluate axillary lymph node status in breast cancer patients was performed after promising results were achieved using it in the staging of rectal carcinomas. The study proved that the usage for axillary lymph node evaluation was feasible with peak enhancement times of lymph nodes ranging between 11 and 21 minutes after bolus injection. Synchronously, ten patients with mammary carcinoma classified no higher than T2 were evaluated using gadofosveset. Although this is a small study population, the results seemed promising with a sensitivity, specificity, PPV (calculated) and NPV (calculated) of, respectively, 86%, 94%, 75%, and 97% for macrometastases [21].

A high interstudy difference occurs in the case of the dif-

fusion-weighted image studies. This is because they all have a different protocol for their study. For example: Kamitani *et al.* [7] acquired diffusion weighted images along with ADC-maps and assessed them as is with a preset cut-off value for the ADC . Fornasa *et al.*[8] on the other hand, first acquire unenhanced T1 images and assessed the axillae to see if there were any lymph nodes larger than 6 mm in size. Only if they found lymph nodes of these sizes, they acquired DWIs and ADC-maps to assess these larger nodes.

Another factor that may account for variability is the MRI-machine itself, a 3T machine can acquire higher resolution images in shorter periods of scanning. Different criteria used in the protocol to define a metastasized lymph node also accounts for interstudy variation in sensitivity and specificity. To counter this, a consensus should be reached over what criteria should be used to deem a lymph node malignant. Lastly, only one study used a node by node comparison between the MRIs and the anatomical pathology reports [10]. This allowed for a more accurate assessment of the value of MRI in assessing lymph nodes. The therapeutic consequences are important. Recent studies and reviews like the AMAROS Trial have shown evidence that performing ALND as standard after a positive SLNB showed no benefit in overall and disease-free survival. One must note that this is only the case in early stage breast cancer [T1-2]. One or two metastasized sentinel nodes (be it micro- or macrometastasis) in these patients can be treated conservatively with adjuvant radiotherapy [22, 23].

A SWOT-analysis (strengths, weaknesses, opportunities, threats) of MRI can teach us why the usage of this imaging modality could be (dis)advantageous compared to the gold standard (SLNB/ALND).

One of the strengths of MRI is that it is non-invasive. To perform dynamic contrast enhanced images (DCE), contrast needs to be administered. Inherently this contains a risk for side-effects, although this risk is quite low. With recent advancements in technology, speed and quality have greatly improved and patients can obtain imaging achieving the same quality as before or better with less time spent in the scanner.

The downside or weakness to MRI is that the scanner itself is very large, and because of the nature of the imaging, the detectors need to be positioned close to the body to detect the changes in the magnetic field. This leaves only little room for the patient to reside in which makes it less suitable for claustrophobic or obese patients. The infrastructure needed to house the MRI machine and its associated electronics can be quite expensive to purchase and install as well (e.g.: a cage of Faraday must be installed in the room and the machinery is heavy). Maintenance costs should not be underestimated as well. The noise MRI scanners make when acquiring is quite loud and repetitive, adjusted hearing protection is needed, although the sounds can still be heard with the necessary precautions. These sounds can cause discomfort in the patient which in term can lead to agitation and movement of the patient. Another weakness of this examination is the proneness to imaging artefacts. This is due to movement of the patient. The longer acquisition times make this scanner a less suitable imaging form for lungs and heart, although there have been strides of advancements on this part of the technology.

Due to the longer scanning times and restricted availability compared to CT, there usually is a long waiting time to obtain an appointment, which can be frustrating for both doctor and patient. Patients with pacemakers or implants cannot always undergo MRI examinations due to interference with the operation of the device. Recent pacemaker models, however, do have the ability to be programmed for MRI examinations. Lastly contrast-allergy makes DCE imaging impossible and renal insufficient patients are at risk for developing nephrogenic systemic sclerosis.

There is still much advancement or opportunities to be made with MRI; even quicker image acquiring times, higher quality imaging, new imaging protocols or new contrast fluids to enhance structures that are difficult to visualize, etc. A higher availability or shorter scanning time will lower the waiting times for an examination. Also, advancements in technology will allow the price of the scanners to decrease, which will allow it to be adopted more widely.

In Belgium, legislation regulates the amount of MRI scanners that can be available. This is because of subsidies that the government allocates for this imaging modality. Further growth and use of this scanner could possibly be held back by this legislation.

In conclusion, MRI can be used to aid in axillary lymph node metastasis detection, but it cannot replace the current gold standard (SLNB). The preferred modality after reviewing the included evidence in MRI, seems to be a scoring system based on multiple parameters to assess whether a lymph node is benign or malignant. However, there still is much fragmentation regarding MRI research for lymph node assessment in breast cancer. To achieve more accurate results for reviewing, a consensus about or standardisation of how to perform studies should be achieved. There is a need for larger homogenous studies with standardized MRI protocols and criteria to determine the most accurate combination of these methods. Furthermore, a consensus between manufacturers of MRI-scanners and their console counterparts should use standardized methods of applying values to signals (e.g.: apparent diffusion coefficient values will be different for the same localization in the same patient on different scanners).

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