Diagnostic Accuracy of Pre-Operative Breast Magnetic Resonance Imaging (MRI) In Predicting Axillary Lymph Node Metastasis: Variations In Intrinsic Subtypes, And Potential to Omit Sentinel Lymph Node Biopsy In Some Low Risk Groups of Patients With Invasive Breast Cancer.

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Abstract

Purpose: The value and utility of axillary lymph node (ALN) evaluation with MRI in breast cancer were not clear for various intrinsic subtypes. The potential of breast MRI to identify low risk groups for which is feasible to omit sentinel lymph node biopsy (SLNB) was evaluated according to the ACOSOG Z0011 trial.

Methods: Patients with primary operable breast cancer with pre-operative breast MRI and post-operative pathologic reports were retrospectively collected. The concordance of MRI and pathology of ALN status was analyzed in different intrinsic subtypes. Furthermore, our rationale to omit SLNB in the low risks group was validated in a cohort of patients from the Taiwan Cancer Registry (TCR) by comparing locoregional events, distant metastasis, and survival outcomes.

Results: A total of 1560 patients were enrolled. The overall accuracy and negative predictive value (NPV) of breast MRI to predict the ALN metastasis are 69.6% and 80.6%. Accuracy, sensitivity, specificity, NPV, and PPV of MRI in detecting metastatic ALN are all significantly different between intrinsic subtypes ($p < 0.05$). Multivariate analysis identified tumor size and histologic type as independent predictive factors of ALN metastases. Patients with a pre-operative breast MRI node-negative status along with a tumor size ≤ 2 cm and intrinsic subtype of Luminal A, Luminal B1, or TNBC were potential candidates to omit SLNB. In a cohort of 19,620 patients with clinical node-negative status and tumor size ≤ 2 cm (cT1N0M0) from the TCR database, there were not significant differences between those with or without ALN surgery in terms of locoregional recurrence, distant metastasis free survival, and overall survival after BCS and radiotherapy.

Conclusion: The diagnostic accuracy of MRI to predict ALN metastasis varied according to intrinsic subtype. Combined pre-operative clinicopathologic and MRI findings might identify some low risk groups of invasive breast cancer patients who are potentially suitable to omit SLNB.

Introduction

Axillary lymph node (ALN) staging remains critical in the management of patients with breast cancer; it helps determine the clinical stage, treatment plan, and prognosis[1]. The golden standard and the most accurate way for evaluating ALN status in breast cancer patients is surgical lymph node biopsy, either axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB)[2, 3]. SLNB, which has been associated with less morbidity, has gradually become the dominant surgical ALN evaluation procedure in patients with clinical node-negative primary operable breast cancer [4].

In most of the randomized controlled studies, the identification rate and the false negative rate (FNR) of SLNB are over 90% and under 10%, respectively[5-7]. A high FNR had been of clinical concern because of the probabilities of occult axillary metastasis, early local recurrence, and inappropriate staging until the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial[8]. For women with cT1-2N0 breast cancer and metastases to 1 or 2 sentinel lymph nodes undergoing breast-conserving surgery, whole-breast irradiation, and adjuvant systemic therapy, 10-year overall survival for patients treated with SLNB alone was not inferior to those treated with ALND (86.3% vs 83.6%, respectively)[9]. However, SLNB is not a risk-free procedure. It is associated with up to a 6% axillary lymph edema rate and a 10% morbidity rate[10, 11].

The non-invasive imaging modalities for assessing ALNs are rapidly evolving, and magnetic resonance imaging (MRI) has been one of the potentially promising tools. A meta-analysis revealed the pooled diagnostic sensitivity and specificity of MRI to detect ALN metastasis in patients with breast cancer were 0.77 (95% confidence interval [CI] 0.75–0.80) and 0.90 (95% CI 0.89–0.91), respectively[12]. Recent studies showed the negative predictive value (NPV) was around 80% and accuracy was 70%–80% for MRI to detect ALN metastasis in breast cancer patients[13-24], which is acceptable but not safe enough to omit axillary surgery based on a negative MRI result. More studies are needed to identify non-invasive lymph node evaluation methods that result in lower morbidity than surgical ALN biopsy without compromising disease control.

In the past ten years, breast cancer diagnosis and treatment have been greatly influenced by the concept of different intrinsic subtypes[25], which have different patterns of disease presentation, metastatic spread and response to treatment[26, 27].

However, there is limited information about the diagnostic accuracy of breast MRI in the prediction of ALN metastasis with regard to different intrinsic subtypes. We hypothesized that the intrinsic subtype might influence the diagnostic accuracy of MRI in prediction of ALN metastasis, and by combining pre-operative clinicopathologic factors, intrinsic subtypes and MRI findings, we might identify some low risk groups of patients with invasive breast cancer that can potentially omit SLNB.

The aim of the current study is to determine the diagnostic accuracy of breast MRI in detecting axillary metastatic lymph nodes in newly diagnosed breast cancer according to different intrinsic subtypes. The second goal is to find out the potential of using non-surgical ALN evaluation, like breast MRI, to replace SLNB in some low risk group of patients with invasive breast cancer by considering pre-operative clinicopathologic and imaging evaluation. Furthermore, we perform a validation analysis with a population-based cancer registry database to examine the effects of omitting surgical biopsy in selected groups of early breast cancer patients who were treated with breast conserving surgery (BCS) and whole breast radiotherapy.

Methods

Patients

Women with primary operable breast cancer who underwent breast surgery during the period of January 2011 to December 2019 were retrospectively recruited. Patients were systemically excluded from the study if there was no pre-operative MRI, if they received a neoadjuvant treatment (chemotherapy, hormone therapy or radiotherapy) or had a locoregional recurrence, or if the axillary status was not mentioned in the MRI report or pathology report. A flow chart of the patient selection process was shown in Fig 1. The study was approved by our Institutional Review Board (CCH IRB No. 141224).

The clinicopathologic factors gathered from the database include age, tumor location, biopsy method, pathologic tumor size, histology, tumor grade, status of estrogen receptor (ER), progesterone receptor (PR), human epithelial growth factor receptor 2 (HER-2) expression, and Ki-67 percentage.

Diagnostic accuracy of breast MRI to predict axillary lymph node (ALN) metastasis in different intrinsic subtypes

Diagnostic performance parameters (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy) were calculated for breast MRI. In the subgroup analysis, these diagnostic performance parameters were calculated for each of the intrinsic subtypes using immunohistochemistry (IHC) surrogate markers[28]. The subtypes were Luminal A (ER >1% positive, PR ≥20% positive, HER-2 negative, Ki67% ≤20%), Luminal B1 (ER >1% positive, and/or PR <20% positive, HER-2 negative, Ki67% >20%), Luminal B2 (ER >1% positive, and/or PR >1% positive, HER-2 positive, Ki67% ≤20%), HER-2 (ER and PR negative, HER-2 positive), and triple-negative breast cancer (TNBC) (ER/PR/HER-2 negative). Two definitions of measures of diagnostic accuracy were conducted in this study. One is the NPV by TMN staging, which was defined as number of TN/ initial MRI report negative ALNs. The other is the NPV by ACOSOG Z0011, which was defined as initial MRI report negative ALNs and has 0, 1, or 2 metastatic lymph nodes on surgical ALN staging/ initial MRI report negative ALNs.

Omission of sentinel lymph node biopsy (SLNB) in some low risk group?

One of the aims of our current study is to identify some potential groups of patients for which surgical lymph node biopsy can be safely omitted. We hypothesized that ALN biopsy can be safely omitted in some low risk groups of patients with pre-operative MRI node-negative findings. We predefined low risk as breast MRI having a NPV higher than 90% and the FN ALNs being limited to a low lymph node burden, defined as N1 (1-3 positive lymph nodes). Such low risk patients might be potential candidates for omitting SLNB if they received BCS followed by whole breast radiotherapy and adequate adjuvant treatment according to breast cancer treatment guidelines and ACOSOG Z0011. Fig 2 shows the rationale of our hypothesis to identify low risk groups of invasive breast cancer patients that can omit surgical lymph node biopsy.

Magnetic resonance imaging (MRI) and protocol

MR imaging was performed with a Siemens MAGNETOM Verio 3.0 Tesla MRI machine. All patients were imaged in the prone position with both breasts placed into a dedicated 16-channel breast coil. MR imaging protocols included the following: bilateral axial turbo-spin-echo fat-suppressed T2-weighted imaging (TR/TE 4630/70 ms; field of view 320 mm; slice thickness 3 mm; number of excitations 1), axial turbo-spin-echo T1 weighted imaging (TR/TE 736/9.1 ms; field of view 320 mm; slice thickness 3 mm; number of excitations 1). Dynamic contrast enhanced MR images (DCE-MRI) were obtained with a three-dimensional fat-suppressed volumetric interpolated breath-hold examination (VIBE) sequence with parallel acquisition once before and five times after a bolus injection of gadobenate dimeglumine (0.1 mmol/kg). Both breasts were examined in the transverse plane at 60 s intervals in each phase of the dynamic studies. The dynamic MRI parameters were as follows: TR/TE 4.36/1.58 ms; field of view 320 mm; slice thickness 1 mm.

Evaluation of axillary lymph nodes via MRI

Two radiologists, HKW and WPW with 35 and 10 years of breast imaging experience performed the breast MRI interpretation and made the reports. The ALNs were assessed by nodal morphology and size on T2 weighted and contrast enhanced T1 weighted sequences. Morphology criteria of pathologic nodes were considered when there were one or more of the following features: cortical thickening greater than 3 mm, abnormal lymph node shape (round or not uniform), or completely/partially effaced fatty hilum.

Validation analysis with Taiwan Cancer Registry (TCR)

To examine the hypothesis of selection criteria derived from our study, we used a cohort of patients from the Taiwan Cancer Registry (TCR), which is a population-based cancer registry database in Taiwan. The TCR was launched in 1979, and all reporting hospitals are mandated to submit cancer data to the registry. Currently, the TCR has achieved 97% completeness, and its data quality is considered excellent in Taiwan. Breast cancer patients registered in the TCR from 1 January 2007 to 31 December 2017 were searched to examine our hypothesis that some small groups of patients could safely omit surgical SLNB. The presumed groups of patients were identified according to selection criteria, and the locoregional events, distant metastasis, and survival outcomes between two groups of patients were compared.

Statistical Analyses

Data are expressed as mean $\pm$ standard deviation for continuous variables. The independent t-test was used to compare continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Significant predictors in the univariate analysis were included in a multivariate logistic-regression model to identify the most important predictors.

The incidence of metastatic ALN, the NPV of MRI, the nodal status distribution, and the average number of false negative ALNs were calculated to access the MRI efficacy after subgrouping by tumor size on pathology and imaging, as well as by intrinsic subtype. These covariates were chosen based on multivariate findings. The survival and relapse outcomes in the validation analysis were compared between patients treated with and without surgical axillary staging using Kaplan-Meier analysis and log-rank tests. Statistical analyses were performed by using Statistical Product and Service Solutions (SPSS) for Windows (Version 19.0, SPSS Inc, Chicago, IL).

Results

Study participants and MRI ALN prediction rate

A total of 1560 patients with primary operable breast cancer who underwent pre-operative breast MRI evaluations and had detailed post-operative pathologic ALN biopsy results were enrolled in the current study (Fig 1). Among them, 490 (31.2%) patients had pathologically confirmed metastatic ALNs and 1074 (68.8%) had negative ALNs. According to intrinsic subtype classifications, there were 603 (42.4%) Luminal A, 370 (26%) Luminal B1, 206 (14.5%) Luminal B2, 117 (8.2%) HER-2, and 126 (8.9%) TNBC patients. The demographic data and histological results of the 1560 patients were summarized in Table 1. The

diagnostic performance of breast MRI to predict ALN metastasis was calculated: the sensitivity was 61.4% (301/490), specificity 73.3% (784/1070), NPV 80.6% (784/973), PPV 51.3% (301/587), and the overall accuracy was 69.6% (1085/1560). The results were summarized and compared with other reported studies in Table 2.

MRI ALN prediction in different intrinsic subtypes

The accuracy of breast MRI for detecting metastatic ALNs in different intrinsic subtypes was evaluated (Table 3), and the overall accuracy in Luminal A, Luminal B1, Luminal B2, TNBC, and HER-2 was 74.1% (447/603), 66.5% (246/370), 67.5% (139/206), 67.5% (85/126), and 59.9% (70/117), respectively. The NPV was 85.6% (374/437) in Luminal A, 69.9% (146/209) in Luminal B1, 75.7% (78/103) in Luminal B2, 84.1% (58/69) in TNBC, and 71.2% (42/59) in HER-2. The sensitivity was highest in the TNBC group (71.1%, 27/38), and the highest PPV was in the Luminal B1 group (62.1%, 100/161). Accuracy, sensitivity, specificity, NPV, and PPV of MRI in detecting metastatic ALNs all significantly differed between different intrinsic subtypes (Table 3).

Prediction of ALN metastasis by clinicopathologic biomarkers

Using univariate analysis, we found that pathologic tumor size, MRI tumor size, histologic type, histologic grade, HER-2 status, and Ki-67 were statistically significant predictors of ALN metastasis. Multivariate analysis identified pathologic tumor size, MRI tumor size, and histologic type (invasive ductal carcinoma (IDC) versus non-IDC) as independent predictive factors of ALN metastasis (Table 4).

Prevalence of ALN metastasis and potential to omit SLNB based on clinicopathologic and MRI imaging factors

Based on the results of multivariate analysis, four individual risk groups of nodal involvement for each intrinsic subtype were generated, and the prevalence of ALN metastasis differed between subgroups (Table 5). According to our predefined condition of MRI lymph node prediction having a NPV $\geq 90\%$ and no FN ALN metastatic disease worse than N1, we tried to identify some low risk groups of patients with invasive breast cancer that are potential candidates to omit SLNB (Fig 2).

Two definitions of measures of diagnostic performance were conducted in this study. By the definition of TNM staging, patients with pre-operative breast MRI tumor size ≤ 2 cm, no sign of ALN metastasis and pre-operative intrinsic subtypes Luminal A (metastatic ALN prevalence rate: 7.3%, MRI NPV: 95.4%, 125/131), Luminal B1 (metastatic ALN prevalence rate: 13.1%, MRI NPV: 91.8%, 45/49), or TNBC (metastatic ALN prevalence rate: 5.9%, MRI NPV: 93.8%, 15/16) were potential candidates to omit SLNB if they planned to receive BCS followed by whole breast radiotherapy. While by the definition of ACOSOG Z0011, patients with pre-operative breast MRI tumor size ≤ 2 cm, regardless of intrinsic subtypes, all reached NPV over 90% (range 93.8-100%, Table 5, Fig 2).

Validation analysis from the population-based Taiwan Cancer Registry (TCR)

According to our evaluation, patients with pre-operative MRI tumor size ≤ 2 cm and no sign of ALN metastasis might be potential candidates to omit SLNB. To validate our hypothesis, breast cancer patients who had a clinical tumor size ≤ 2 cm at diagnosis, had no sign of ALN metastasis (cT1N0M0) breast cancer, and underwent BCS and whole breast radiotherapy were identified from the TCR.

A total of 19,620 patients were enrolled according to inclusion and exclusion criteria, and these patients were stratified by whether surgical axillary staging was performed (performed n=17,275; not performed n=2345). The 5-year local recurrence free survival, distant metastasis free survival, and overall survival were not statistically different between these two groups (Fig 3 A-C). In subgroup analysis by molecular subtype, there were also no differences between patients who received or did not receive surgical axillary staging (Fig 3 D-F).

Discussion

Our current study enrolled 1560 primary operable breast cancer patients with detailed pre-operative breast MRI evaluation and post-operative ALN pathologic results for diagnostic accuracy analysis. In patients meeting ACOSOG Z0011 criteria with pre-operative MRI showing negative ALN metastasis and a tumor size no more than 2 cm, we identified three intrinsic subtypes (Luminal A, Luminal B1, and TNBC) that have low risk of FN ALN and may not require SLNB.

Owing to more effective pre-operative evaluation and locoregional adjuvant therapies, the potential risks of axillary surgery may outweigh its actual benefits, especially in early-stage breast cancer patients treated with BCS[6, 29]. In 1994, Giuliano reported that SLNB is a highly reliable modality in axillary staging[3]. Since then, there has been a trend towards minimizing invasive staging and treatment of the axilla in clinically node-negative patients owing to increased arm morbidity and decreasing quality of life after ALND.

The ACOSOG Z0011 trial reported 5-year disease free survival to be similar between “axillary dissection” versus “no dissection” groups in SLN positive patients (82.2% vs. 83.9%; $p < 0.01$ for non-inferiority), which indicated that there is no need to perform ALND for low-burden axillary disease (1-2 positive nodes, mainly N1) identified by SLNB[8]. In the meantime, it also raised doubts on the necessity of SLNB when treatment or prognosis of breast cancer did not change depending on whether the information of surgical ALN biopsy was provided. Ideally, for physicians who follow the results of ACOSOG Z0011 trial to omit ALND, if MRI is able to accurately discern patients with no ALN metastasis or low burden ALN metastases (< 3 nodes, $\leq$ N1) from those with high burden ALN metastases (3 or more nodes, $\geq$ N2), both the prognosis of the disease and type of treatment do not change based on whether SLNB was performed. In the past decade, many studies were designed to investigate whether non-invasive imaging staging of the axilla could replace surgical ALN evaluation, and thus improve a patient’s quality of life[30, 31]. MRI is widely used on breast cancer patients for pre-operative assessment of disease extent and ALN status, screening of the contralateral breast, and evaluation of post-neoadjuvant treatment outcome [32, 33]. A literature review of studies evaluating the ability of MRI to predict ALN metastasis was summarized in Table 2, and our results are consistent with previous studies that show an overall NPV around 80% and accuracy in a range of 70%~90%.

The incorporation of breast cancer intrinsic subtype information into clinical breast cancer assessment and treatment planning is an important step toward personalized medical care[28]. Hence, examining MRI results among different breast cancer intrinsic subtypes is an emerging area of research. Our study demonstrated that all the diagnostic performance parameters (sensitivity, specificity, NPV, PPV, and accuracy) of ALN evaluation via MRI were significantly different among intrinsic subtypes (Table 3). As we are interested in omitting SLNB, the NPV of MRI needs to be non-inferior, or at least, approach to the NPV of SLNB. A meta-analysis showed a false-negative rate of 8.61 % (95 % CI: 8.05–9.2 %) of the SLNB[34], so the cutoff point in the current study was set as an NPV $\geq$ 90%..

Previous studies showed that tumor size, either from pathology reports or from MRI reports, was an important independent predictive factor of ALN metastases[35, 36], which is consistent with our results from multivariate logistic regression analysis (Table 4). Therefore, in this study, our strategy is to investigate detailed axillary MRI performance based on combinations of IHC biomarkers (intrinsic subtypes) and anatomical features (tumor size) that associate with ALN involvement (Table 5). The NPV is higher for MRI $\leq$ 2 cm than for pathology size $\leq$ 2 cm in nearly all molecular subtypes. Onesti et al. and our previous study reported that MRI tumor size correlates with pathology size but tends to overestimate[37, 38]. The reason might be attributed to a smaller actual size in the MRI group than in the pathology group, which leads to less axillary involvement. Thus, using tumor size from MRI is a more favorable criteria than using size from a pathology report, which is only available post-operation.

By the definition of ACOSOG Z0011, patients with pre-operative breast MRI tumor size $\leq$ 2 cm, regardless of intrinsic subtypes, all reached NPV over 90% (range 93.8-100%, Table 5). Our study highlights that in a population of patients meeting ACOSOG Z0011 criteria, with a negative MRI ALN metastasis, the overall risk of heavy nodal disease burden is low and the majority of women may not need SLNB. In a more stringent way by using TNM staging definition, NPV exceeded 90% in the Luminal A, Luminal B1, and TNBC subgroups when there was a small tumor burden (tumor size $\leq$ 2 cm on MRI) (Fig 2, Table 5). When there was a small tumor burden, the average number of FN lymph nodes in Luminal A and Luminal B1 was 1.33 and 1.25, respectively. For patients in the TNBC subgroup having small tumor burdens, the average number of FN ALNs was more than

2, which might be due to only 1 (5.9%) patient developing ALN metastasis. Similar to our study, Lu et al. published that the lowest probability of node metastasis was for ER- / HER2- tumors[39], and Houvenaeghel et al. also reported TNBC had the lowest probability of node metastasis[40]. Owing to a high NPV and small possibility of ALN metastasis, ALN staging by MRI is still promising in the TNBC group.

In validating our results, we used a large population-based cancer registry dataset and the 5-year local recurrence free survival, distant metastasis free survival, and overall survival were not statistically different based on whether or not cT1N0M0 breast cancer patients received axillary surgery (Fig 3). The same findings were also observed in breast cancer intrinsic subgroup analysis, though the patient number in subgroup analysis was low due to lack of ER, PR, and HER data before 2011. These population-based cancer registry findings combined with results derived from our analysis based on the ACOSOG Z0011 trial provided evidence to support our hypothesis that ALN biopsy surgery might be omitted safely in some low risk early breast cancer patients when they are treated with BCS and whole breast irradiation followed by adequate adjuvant therapy.

Our present study has some limitations. First, it is a single site study. Second, it is a retrospective study, and the validation portion is also conducted retrospectively. However, it is important to note that these results are based on a large number (N=1560) of patients, which was derived from a screen of 3256 cases, with complete pre-operative breast MRI evaluation and detailed post-operative breast cancer & lymph node pathologic information. This enabled us to perform comprehensive intrinsic subtype analysis and identify subgroups of patients that can potentially omit surgical lymph node biopsy in a safe manner. Further studies to prospectively validate our concepts of omitting SLNB in some low risk groups of patients by considering clinicopathologic factors, IHC markers and MRI ALN detection performance are needed and are now in progress.

Conclusions

According to our study, MRI prediction of axillary lymph node metastasis differed according to intrinsic subtype. Combined with pre-operative clinicopathologic factors and intrinsic subtypes, MRI could identify some groups of patients with low risks of axillary lymph node metastasis, high NPVs, and low burdens of axillary disease even in FN cases. The findings from a population-based cancer registry study and an ACOSOG Z0011 trial-based study provided support for de-escalating axillary surgery in the management of breast cancer patients.

Abbreviations

ALN
axillary lymph node
MRI
magnetic resonance imaging
SLN
sentinel lymph node
SLNB
sentinel lymph node biopsy
ALND
axillary lymph node dissection
TCR
Taiwan Cancer Registry
ACOSOG
American College of Surgeons Oncology Group
NPV
negative predict value
PPV
positive predict value

FNR
false negative rate
BCS
breast conserving surgery
IHC
immunohistochemistry
ER
estrogen receptor
PR
progesterone receptor
HER-2
human epithelial growth factor receptor 2
TNBC
triple-negative breast cancer
TP
True positive
TN
True negative
FP
False positive
FN
False negative
IDC
invasive ductal carcinoma

Declarations

-Ethics approval and consent to participate This study was approved by the institutional review board (IRB) of Changhua Christian Hospital (CCH IRB No.140404), and all patients gave written informed consent.

- Consent for publish Not applicable.

- Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

- Competing interests The authors declare that they have no competing interests.

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- Authors' Contributions HWL contributed to study conception and design, general supervision of the research group, and also critical revised the manuscript. STC involved in data interpretation and was a major contributor in writing the manuscript. TWL and HYK collected data from the Taiwan Cancer Registry, and performed the validation of the hypothesis as well. TCW contributed to English language reviewing of the manuscript. WPW and HKW contributed to imaging interpretation and annotation. STC, DRC, and SJK drafted the method part of the manuscript, and engaged in data acquisition and analysis, as well as imaging and figures processing. YJC contributed to statistical analysis. All authors read and approved the final manuscript.

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Tables

Table 1
Demographic data and tumor characteristics of the 1560 Patients

N = 1560	
Age, y	51.8 ± 10.6
Location	
Right	751(48.1)
Left	809(51.9)
Biopsy method(N/A = 45)	
US-guided Core needle biopsy	1310(86.5)
Stereotactic vacuum assisted biopsy	102(6.7)
Excisional biopsy	84(5.5)
Fine needle aspiration	5(0.3)
Stereotactic core needle biopsy	14(0.9)
Tumor size, cm	2.4 ± 1.9
Lymph node	
Positive	490(31.4)
Negative	1070(68.6)
Stage (N/A = 40)	
0	248(16.3)
I	507(33.4)
II	597(39.3)
III	164(10.8)
IV	4(0.3)
Lymph node stage(N/A = 88)	
N0	986(67.0)
N1	344(23.4)
N2	90(6.1)
N3	52(3.5)
Grade (N/A = 62)	
I	251(16.8)
II	818(54.6)
III	429(28.6)
ER(N/A:21)	
Positive	1217(79.1)
Negative	322(20.9)

N = 1560	
PR(N/A:25)	
Positive	1118(72.8)
Negative	417(27.2)
HER-2(N/A:138)	
Positive	334(23.5)
Negative	1088(76.5)
Subtype (N/A = 138)	
Luminal A	603(42.4)
Luminal B1	370(26.0)
Luminal B2	206(14.5)
HER-2(+)	117(8.2)
TNBC	126(8.9)
Pathology (N/A = 92)	
DCIS	255(17.4)
DCIS + LCIS	7(0.5)
IDC	207(14.1)
IDC + DCIS	916(62.4)
IDC + ILC	7(0.4)
IDC + LCIS	3(0.2)
ILC	19(1.3)
ILC + DCIS	1(0.1)
ILC + LCIS	47(3.2)
LCIS	6(0.4)
Ki 67 (N/A = 408)	661(57.4)
≤20	491(42.6)
>20	
N/A: not available	
ER: estrogen receptor, PR: progesterone receptor, HER-2: human epidermal growth factor receptor 2, TNBC: triple negative breast cancer, DCIS: ductal carcinoma in situ, LCIS: lobular carcinoma in situ, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma	

Table 2
Literature review of MRI diagnostic performance on axillary lymph node

Author	Journal/Year	Patient numbers	Reference standard	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Yoshimura et al ¹²	Breast Cancer/1999	202	ALND	79.0	93.0	87.0	89.0	88.0
Kvistad et al ¹³	Eur Radiol/2000	65	ALND	83.0	90.0	90.0	83.0	88.0
Orguc et al ¹⁴	Balkan Med J/2012	155	ALND	89.0	14.0	80.0*	21.4*	Not reported
He et al ¹⁵	Eur J Radiol/2012	136	ALND	33.3–86.5	95.2–98.2	1.9–16.7	66.7–82.6	18.5–96.2
Scaranelo et al ¹⁶	Radiology/2012	61	ALND/SLNB	88.4	82.4	94.7	69.4	85.0
Hwang et al ¹⁷	J Breast Cancer/2013	349	ALND/SLNB	47.8	88.7	82.6	60.2	77.9
Hieken et al ¹⁸	Surgery/2013	505	ALND/SLNB	54.2	78.2	75.7	57.7	69.7
Abe et al ¹⁹	Acad Radiol/2013	50	ALND/SLNB	60.0	79.0	81.0	59.0	74.0
An et al ²⁰	Nuklearmedizin/2014	132	ALND	67.5	78.0	79.2	65.9	74
Arslan et al ²¹	Springerplus/2016	35	SLNB	73.3	95.0	82.6	91.7	85.7
Hyun et al ²²	Eur J Radiol/2016	425	ALND/SLNB	51.3	92.2	83.3	71.4	80.9
Barco et al ²³	Clin Transl Oncol/2016	1351	ALND/SLNB	29.8	96.6	68.4	84.9	Not reported
Chen et al		1560	ALND/SLNB	61.4	73.3	80.6	51.3	69.6

Table 3
Diagnostic performance of MRI on axillary lymph node metastasis per molecular subtype

	Luminal A	Luminal B1	Luminal B2	HER-2	TNBC	p value
Sensitivity	53.7	61.3	70.9	62.2	71.1	< 0.01*
Specificity	80.1	70.5	65.0	58.3	65.9	< 0.01*
NPV	85.6	69.9	75.7	71.2	84.1	0.03*
PPV	44.0	62.1	59.2	48.3	47.4	0.03*
Accuracy	74.1	66.5	67.5	59.9	67.5	< 0.01*

Table 4
Risk factors for axillary lymph node metastasis in breast cancer patients

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
Age	1.00	0.99–1.1	0.41			
Pathologic tumor size (invasive, cm)	1.17	1.10–1.26	< 0.01*	1.42	1.28–1.58	< 0.01*
MRI tumor size (invasive, cm)	1.21	1.13–1.28	< 0.01*	1.19	1.10–1.29	< 0.01*
Pathology (Non-IDC) VS IDC	0.44	0.30–0.65	< 0.01*	0.44	0.27–0.72	< 0.01*
Histological Grade (II, III) VS I	1.86	1.35–2.56	< 0.01*	1.28	0.88–1.86	0.20
ER (positive) VS negative	1.09	0.83–1.42	0.54			
PR (positive) VS negative	0.93	0.73–1.18	0.55			
HER-2 (positive) VS negative	1.32	1.03–1.70	0.03*	1.23	0.88–1.73	0.23
Ki -67 (> 20) VS $\leq$ 20	1.73	1.36–2.20	< 0.01*	1.15	0.87–1.53	0.33

Table 5

Correlation of tumor size and negative predict value (NPV) and pathological nodal stages of the false negative patients in the molecular subtype groups

	Prevalence of LN metastasis N (%)	NPV of MRI by TNM staging %	NPV of MRI by ACOSOG z0011 % †	Average FN LN ^a	N1 N (%)	N2 N (%)	N3 N (%)
Luminal A	136/603 (22.6)	85.6	96.1*	2.1	50(79.4)	10(15.9)	1(1.6)
P size ≤ 2 cm	37/338 (10.9)	91.5*	98.1*	1.6	19(82.6)	2(8.7)	0
P size ≤ 3 cm	95/484 (19.6)	86.9	97.3*	1.7	41(85.4)	5(10.4)	0
MRI size ≤ 2 cm	12/164 (7.3)	95.4*	99.2*	1.3	6(100)	0	0
MRI size ≤ 3 cm	49/328 (14.9)	90.6*	98.0*	1.8	20(83.3)	3(12.5)	0
Luminal B1	163/370 (44.1)	69.9	90.9*	3.1	48(76.2)	11(17.5)	4(6.3)
P size ≤ 2 cm	48/162 (29.6)	80	94.5*	1.9	19(86.3)	3(13.6)	0
P size ≤ 3 cm	99/274 (36.1)	76	94.7*	1.8	36(87.8)	5(12.2)	0
MRI size ≤ 2 cm	8/61 (13.1)	91.8*	100*	1.3	4(100)	0	0
MRI size ≤ 3 cm	56/175 (32)	78.6	96.6*	1.8	23(92)	2(8)	0
Luminal B2	86/206 (41.7)	75.7	96.1*	2.2	22(88)	3(12)	0
P size ≤ 2 cm	23/92 (25)	80.3	98.4*	1.6	11(91.7)	1(8.3)	0
P size ≤ 3 cm	55/151 (36.4)	77.3	97.7*	1.5	19(95)	1(5)	0
MRI size ≤ 2 cm	4/18 (22.2)	78.6	100*	1.3	3(100)	0	0
MRI size ≤ 3 cm	23/77 (29.9)	76.9	96.2*	1.75	11(91.7)	1(8.3)	0
HER2	45/117 (38.5)	71.2	88.1	4.46	13(76.5)	2(11.8)	2(11.8)
P size ≤ 2 cm	14/56 (25)	73.7	92.1*	2.70	9(90)	0	1(10)
P size ≤ 3 cm	26/83 (31.3)	72.9	89.6	2.85	11(84.6)	1(7.7)	1(7.7)
MRI size ≤ 2 cm	2/10 (20)	85.7	100*	1.00	1(100)	0	0
MRI size ≤ 3 cm	8/26 (30.8)	73.7	94.7*	1.40	5(100)	0	0

	Prevalence of LN metastasis N (%)	NPV of MRI by TNM staging %	NPV of MRI by ACOSOG z0011 % †	Average FN LN ^a	N1 N (%)	N2 N (%)	N3 N (%)
TNBC	38/126 (30.2)	84.1	88.4	4.18	7(63.6)	3(27.3)	1(9.1)
P size ≤ 2 cm	7/52 (13.5)	92.3*	94.9*	2.33	3(100)	0	0
P size ≤ 3 cm	19/85 (22.4)	90.6*	96.2*	1.80	5(100)	0	0
MRI size ≤ 2 cm	1/17 (5.9)	93.8*	93.8*	3.00	1(100)	0	0
MRI size ≤ 3 cm	8/43 (18.6)	87.5	90.6*	4.75	3(75)	0	1(25)

Figures

Figure 1

Flowchart of patient inclusion

Figure 2

Potential workflow for axillary staging with MRI instead of surgical lymphatic mapping in selected groups

Figure 3

Validation analysis with Taiwan Cancer Registry (TCR) A. Total local recurrence free survival (LRFS). B. Total distant metastasis free survival (DMFS). C. Total overall survival (OS). D. Luminal type survival analysis. E. HER-2 type survival analysis. F. TNBC (triple negative breast cancer) type survival analysis.