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Analysis of Prognoses according to Breast MRI Results in Patients with Axillary Lymph Node Metastases from an Unknown Primary Origin

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Purpose: To compare the prognosis of patients with axillary adenocarcinoma from an unknown primary (ACUPax) origin with negative MRI results and those with MRI-detected primary breast cancers.

Materials and Methods: The breast MRI images of 32 patients with ACUPax without signs of primary breast cancer on mammography and ultrasound (US) were analyzed. Spot compression-magnification mammography and second-look US were performed for the area of MRI abnormality in patients with positive results; any positive findings corresponding to the MRI abnormality were confirmed by biopsy. If suspicious MRI lesions could not be localized on mammography or US, MR-guided biopsy or excision biopsy after MR-guided localization was performed. We compared the prognosis of patients with negative breast MRI with that for patients with MRI-detected primary breast cancers.

Results: Primary breast cancers were confirmed in 8 (25%) patients after breast MRI. Primary breast cancers were not detected on MRI in 24 (75%) patients, including five cases of false-positive MRI results. Twenty-three patients underwent axillary lymph node dissection (ALND) followed by whole breast radiation therapy (WBRT) and chemotherapy (n=17) or subsequent chemotherapy only (n=2). Recurrence or distant metastasis did not occur during follow up in 7/8 patients with MRI-detected primary breast cancers and 22/24 patients with negative MRI results. Regional recurrence or distant metastasis did not occur in any MR-negative patient who received adjuvant chemotherapy after ALND and WBRT.

Conclusion: The prognoses of MR-negative patients with ACUPax who received ALND and WBRT followed by chemotherapy were as good as those of patients with MRI-detected primary breast cancers.

Key Words: Axilla, lymph nodes, magnetic resonance imaging, metastases, unknown primary

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INTRODUCTION

Axillary adenocarcinoma from an unknown primary (ACUPax) tumor source can be defined as isolated metastatic axillary lymphadenopathy without an established primary origin.[1] It is necessary to evaluate the breasts of women with ACUPax because the ipsilateral breast is the most common site of origin of metastatic lymphadenopathy in the axilla.[2,3]

Since breast magnetic resonance imaging (MRI) shows greater sensitivity for the detection of breast cancer, compared to mammography or ultrasound (US),[4-8] breast MRI has become the standard of care when other diagnostic modalities fail to

locate the primary tumor source in the breasts of patients with ACUPax.[8,9] A few studies have reported that breast surgery could be avoided in the absence of suspicious lesions on breast MRI images of patients with ACUPax.[10-12] However, the follow-up results of true positive and false positive findings on MRI and the clinical courses of patients with negative MRI are not well known, owing to the rarity of this disease. One study[13] reported the imaging findings of MRI-detected lesions in patients with ACUPax; however, the study included MRI scans obtained between 1995 and 2001 and defined cases of ACUPax as patients with negative mammographic and clinical findings without US evaluation. Recent advances in breast imaging, including digital mammography, high-resolution breast US, and breast MRI with three-dimensional (3D) dynamic contrast enhancement (DCE-MRI) with or without diffusion-weighted imaging (DWI), may lead to differences between the results obtained with these new modalities and those acquired during the 1990s. Hence, in this study, we aimed to evaluate the outcomes of patients with ACUPax based on the results of breast MRI and review the prognosis of MRI negative-cases, compared to those with MRI-detected occult breast cancers.

MATERIALS AND METHODS

Patients

This study was approved by our Institutional Review Board (IRB No.: 2018-05-045), which waived the need for informed consent, owing to the retrospective nature of the study.

We reviewed the medical records and radiologic reports of consecutive patients who presented with ACUPax between January 2001 and January 2015. Patients with systemic metastases involving multiple organs from unknown primary cancers were excluded at the outset. Thirty-four patients with ACUPax alone, without any clinical evidence of other malignancies, were identified. We excluded two patients with a past history of contralateral breast cancers. Finally, 32 patients who exhibited no evidence of primary breast cancer upon clinical examination, mammography, and US were included in our study. All patients had malignant axillary lymph nodes that were proven with pathological examination after US-guided core needle biopsy (n=23) and excision biopsy (n=9) and had undergone DCE-MRI with DWI to ascertain the presence of occult breast cancer. All patients were women, whose ages ranged from 34 to 78 years (mean age: 51 years).

Breast MRI examination

Breast MRI was performed using a 1.5-T (Signa CV/I; General Electric Medical System, Milwaukee, WI, USA or Interna; Philips Medical Systems, Best, the Netherlands) (n=8) or 3.0-T system (Interna) (n=24). All patients were imaged in the prone position using a dedicated bilateral phased-array breast coil. The MRI protocol comprised axial turbo spine-echo T1-weighted and fat-suppressed T2-weighted sequences, a 3D-DCE sequence, and DWI. The delayed phase of contrast-enhanced T1 axial turbo spin-echo with fat suppression covering the region between the lower neck and the axilla was obtained to evaluate the lymph nodes after breast scanning. Axial DCE-MRI images were obtained with one pre-contrast and six post-contrast scans after bolus injection of gadobutrol 0.1 mmol/kg (Gadovist; Bayer Healthcare, Berlin, Germany) or gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ, USA), followed by flushing with 20 mL of saline. Images were acquired from 30 s after contrast injection, six times per 60 s, with a gradient echo sequence (eTHRIVE) and an acquisition time for each scan of approximately 60 s. DWI was performed before DCE-MRI for both breasts in the axial plane with two b values (0 and 750 s/mm^2 on the 1.5-T device; 0 and 1000 s/mm^2 on the 3-T device). Reformatted bilateral sagittal images and reformatted 3-dimensional maximum intensity projection images were also obtained.

Interpretation of breast MRI

All MR images were interpreted by one of seven dedicated breast radiologists who were aware of the clinical history and findings of mammography and breast US. MRI findings were reported as per the Breast Imaging Reporting and Data System (BI-RADS) lexicon.[14]

The following lesions were considered as primary breast cancer: 1) a mass with irregular shape and irregular or spiculated margin or a mass with rim enhancement, 2) non-mass enhancement with linear or segmental distribution or with a heterogeneous internal enhancement pattern, and 3) mass or non-mass enhancement with washout kinetics or architectural distortion. Any abnormal enhancement that was not correlated with typical benign lesions was also considered as potential primary breast cancer. We conducted a consensus meeting for problematic cases in terms of the interpretation and management of MRI-detected lesions in ACUPax patients once a week.

Management after breast MRI

Previous mammography and breast US scans with negative radiological findings were re-evaluated in patients with positive MRI findings. Mammography with spot compression on the magnification view and second-look US were also performed for the area of MRI abnormality. Any positive findings on mammography or US corresponding to the MRI abnormality, such as benign-appearing lesions, were confirmed using US-guided or mammography-guided biopsy. If the suspicious MRI lesions were not associated with any corresponding abnormality on mammography or US, MR-guided biopsy or MR-guided localization and excision biopsy were performed. Benign lesions with discordant results after percutaneous biopsy (i.e., those with suspicious findings on MRI, but benign biopsy results) underwent excision biopsy after localization.

Patients with confirmed primary breast cancer on breast MRI

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underwent surgery followed by adjuvant chemotherapy and/or whole breast radiation therapy (WBRT). Patients with negative findings on breast MRI underwent either blind total mastectomy with axillary lymph node dissection (ALND) alone or ALND followed by ipsilateral WBRT and/or adjuvant chemotherapy. We reviewed medical records to evaluate the patient outcomes, including the occurrence of ipsilateral or contralateral breast lesions and regional or distant metastases, and compared the outcomes of patients with negative breast MRI with those of patients with MRI-detected primary breast cancers.

RESULTS

Results of breast MRI

Positive findings were detected on MRI in 13 (40.6%) of 32 patients (Table 1). Five patients had probably benign lesions on MRI, and eight patients had suspicious lesions. Second-look US examinations detected abnormal findings corresponding to MRI abnormalities in 11 of 13 patients. One of the two patients who lacked corresponding lesions on second-look US showed faint suspicious microcalcifications on spot compression with magnification mammography in the area with MR abnormality, while no corresponding abnormality was found on either mammography or second-look US in the other patient.

The results of second-look US examination and spot compression with magnification mammography for the positive MRI findings were as follows: five patients had BI-RADS category four lesions, seven patients had BI-RADS category three lesions, and one patient had a negative finding. All eight BI-RADS four lesions on MRI were confirmed to be malignant, except one intraductal papilloma (IDP), even though three lesions showed probably benign findings on second-look US. One of the five probably benign lesions on MRI were confirmed to be ductal carcinoma in situ (DCIS), while the remaining lesions were benign. PET-CT was performed in 24 patients to detect primary malignancy; however, PET-CT revealed no occult breast cancers, including four of eight cases in which occult breast

Table 2. Final Pathology of ACUPax with and without Primary Breast Cancer Detected on Breast MRI after Surgery

	Primary cancer on MRI (n=8)	No cancer on MRI (n=23)
Tumor size		
Mean size, cm	0.8 (0.3–2.3)	N/A
T stage		
Tis	2	N/A
T1	5	
T2	1	
N stage		
Mean No. of node removed	26 (9–52)	24 (8–62)
Mean No. of positive node	7 (1–40)	9 (1–38)
1–3	6	11
4–10	1	6
> 10	1	6
Molecular subtype		
Luminal A	2	9
Luminal B	1	3
$HER2^+$	2	3
Triple negative	3	8

$HER2^+$, human epidermal growth factor receptor 2; N/A, not applicable.
Numbers in parentheses: range.

Table 1. Characteristics of Patients with ACUPax according to Breast MR Findings (n=32)

Results of MRI	MR BIRADS category	2nd look US/ MG BIRADS category	Method of biopsy	Results of biopsy		Surgery	Final surgical pathology
Positive (n=13)	3 (n=5)	3 (n=4)	US guided CNB (n=2)	Benign (n=2)	Fibrocystic change	ALND	-
					Fibroadenoma	ALND+WBRT+CTx	
			US guided localization (n=2)			BCS+ALND (n=2)	DCIS
							Fibrocystic change
			MR guided localization (n=1)			BCS+ALND	Usual ductal hyperplasia
	4A (n=5)	3 (n=2)	US guided CNB (n=2)	Benign (n=1)	Stromal fibrosis	BCS+ALND	IDC
				Malignant (n=1)	IDC	BCS+ALND	IDC
		4A (n=2)	US guided VAB (n=1)	Benign (n=2)	IDP	BCS+ALND	Tubular carcinoma
			US guided CNB (n=1)		IDP	Mastectomy+ALND	Multiple IDPs
		4B (n=1)	US guided CNB	Malignant	IDC	BCS+ALND	IDC
	4B (n=1)	4A (n=1)	MG guided localization			BCS+ALND	IDC
	4C (n=2)	3 (n=1)	US guided localization			Mastectomy+ALND	DCIS
		4C (n=1)	US guided CNB	Malignant	DCIS	Mastectomy+ALND	IDC
Negative (n=19)			-			ALND (n=18)	
						No surgery (n=1)	

CNB, core needle biopsy; FNA, fine needle aspiration; MG, mammography; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; IDP, intraductal papilloma; BCS, breast conserving surgery; ALND, axillary lymph node dissection; WBRT, whole breast radiation therapy; CTx, adjuvant chemotherapy.

cancer was detected with breast MRI. Three out of 24 PET-CT showed breast lesions with mildly increased uptake; however, all of them were revealed as benign lesions after biopsy (n=2) and follow-up (n=1).

Patients with MRI-detected breast cancers

Finally, primary breast cancers were confirmed after surgery in 8 (25.0%) of the 32 patients with ACUPax. The details of the final pathology after surgery for the primary breast cancers detected on MRI are presented in Table 2. Five of the eight primary breast cancers were invasive ductal carcinoma (IDC), two were DCIS, and one was tubular carcinoma. The size of invasive cancers was very small (median, 0.5 cm; range, 0.3–0.7 cm), except for one case with a mass measuring 2.3 cm with a surrounding non-mass lesion, which exhibited highly suspicious findings on MRI and second-look US.

The imaging findings of eight primary breast cancers detected on MRI included segmental or linear non-mass enhancement (n=5), a focal area of non-mass enhancement (n=1), and an oval enhancing mass (n=2). The US features of primary breast cancers on second-look US included a small circumscribed benign-looking mass in three patients (Fig. 1), clustered cysts in one patient, heterogeneous hypoechoic parenchyma in one patient, and a small but suspicious mass in two patients. Half of the eight primary breast cancers showed probably benign features and were categorized as BI-RADS 3 on second-look US.

Patients with no primary breast cancer on MRI

Primary breast cancers were not detected on MRI in 24 (75.0%) of 32 patients, including five false positive cases. Four of the five false positive cases on MRI were BI-RADS category three le-

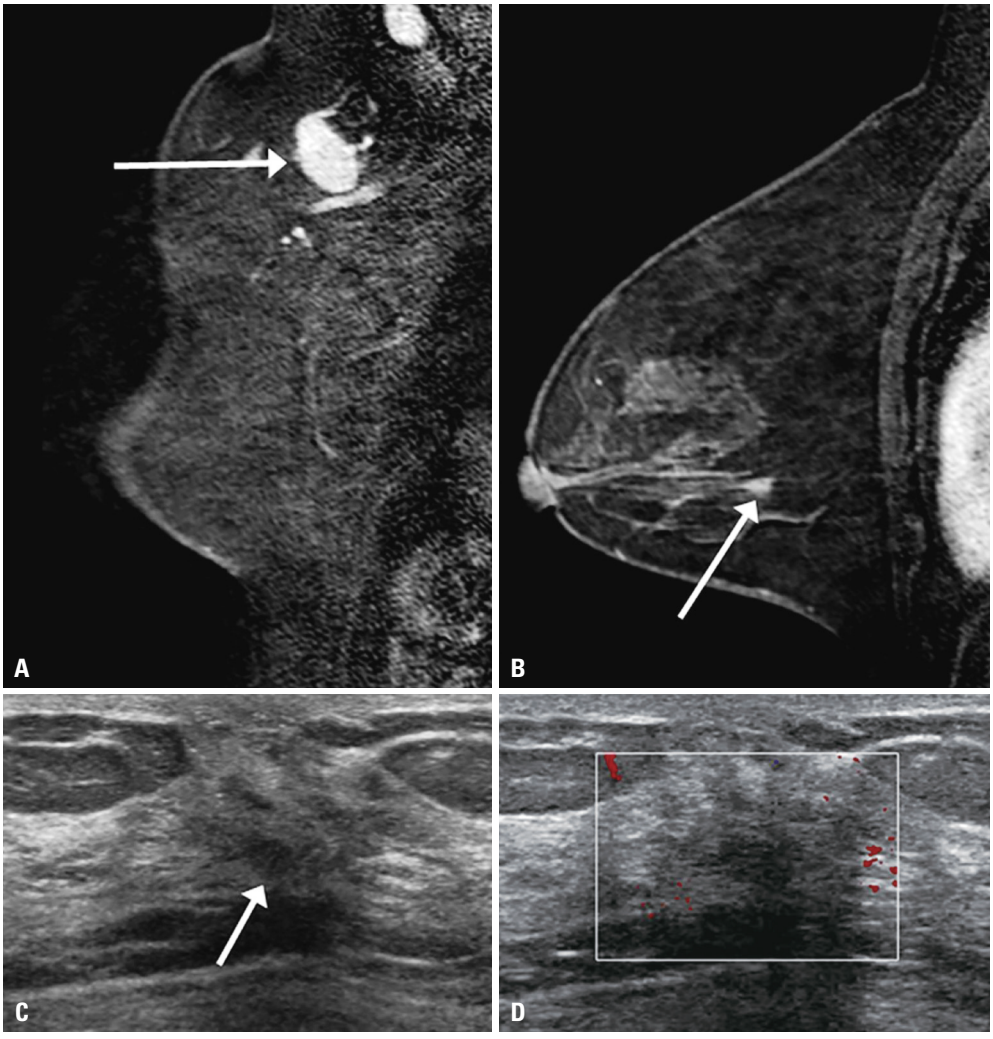

Fig. 1. A 57-year-old woman with a palpable left axillary lymph node identified as metastatic adenocarcinoma. (A) Contrast enhanced sagittal T1-weighted fat suppressed MR images show a 3-cm enlarged lymph node with strong enhancement (arrow) in the left axilla and (B) a 0.6-cm oval shape mass with mild enhancement in the left breast central portion (arrow). (C) Second-look ultrasound (US) targeting the area of MRI abnormality shows an ill-defined small circumscribed isoechoic mass (arrow) without vascularity on color Doppler US (D). The mass was confirmed as ductal carcinoma in situ after US-guided localization and breast conserving surgery.

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sions and one lesion was BI-RADS category 4. The latter showed multiple small suspicious masses on MRI, which were finally diagnosed as IDPs. All patients who underwent ALND underwent subsequent WBRT and chemotherapy (n=17) or chemotherapy alone (n=2), except one patient who had ALND alone and refused additional treatment. Table 2 shows the pathologic results after surgery. In 23/24 patients without primary breast cancer on MRI showed N1 stage in 45.8% of the patients. The mean number of positive axillary nodes was nine. The most common molecular subtype of nodal metastasis was luminal A (39.1%), followed by triple-negative cancer (34.8%). Three patients without primary breast cancer detected on MRI also underwent breast surgery. One patient with multiple intraductal papillomas underwent mastectomy to reduce the possibility of hidden malignant foci, and the other two patients with probably benign lesions on MRI underwent excision biopsy. One patient who undergone previous excisional biopsy for a palpable metastatic axillary lymph node underwent chemotherapy with WBRT without additional ALND. The mean follow-up period of the patients in whom primary cancer was not detected on breast MRI was 7 years (range, 2–12 years).

Prognosis

The management and clinical outcomes of patients with ACUPax are summarized in Table 3. Overall, recurrent cancer was found in 3 (9.4%) patients during the follow-up period. The mean follow-up period of the patients with and without primary cancer on MRI was 9 years (range, 4–15 years) and 7 years (range, 2–12 years). One of the 24 patients without primary breast cancer detection on MRI who underwent chemotherapy and WBRT without additional ALND developed ipsilateral breast cancer 2 years after the initial diagnosis of ACUPax. The lesion measured 1 cm and was a triple-negative IDC, which was detected on follow-up breast US (Fig. 2). Another one of the 24 patients without primary breast cancer detected on MRI who received ALND alone and refused chemotherapy and WBRT experienced regional node recurrence in the ipsilateral axilla after 6 years. One patient with MRI-detected breast cancer and T2N3 disease during the initial diagnosis died due to distant metastasis; this patient developed ipsilateral axillary lymph node metastasis and lung metastasis 3 years after primary breast cancer surgery. No regional recurrence or distant metastasis occurred in any patient who underwent ALND and WBRT followed by adjuvant chemotherapy during the mean follow-up period of 7 years.

Table 3. Management and Clinical Outcomes of ACUPax Patients with and without Primary Breast Cancer Detected on Breast MRI

	Primary cancer on MRI (n=8)	No cancer on MRI (n=24)
Follow-up years		
Mean (range)	9 (4–15)	7 (2–12)
Management		
Surgery		
Adjuvant treatment		
BCS+ALND		
WBRT+CTx+HTx	3	1*
WBRT+CTx	3	1*
Mastectomy+ALND		
WBRT+CTx	1	
CTx+HTx		1*
CTx	1	
ALND		1†
WBRT+CTx+HTx		7
WBRT+CTx		10
CTx+HTx		1
CTx		1
No additional surgery		
WBRT+CTx		1
Outcome		
Alive and disease-free	7	22
Breast cancer		1
Regional node recurrence		1
Distant metastasis	1	

BCS, breast conserving surgery; ALND, axillary lymph node dissection; WBRT, whole breast radiation therapy; CTx, adjuvant chemotherapy; HTx, hormonal therapy.
*Patients with false positive MRI findings; †Patient refused chemotherapy and radiation therapy.

DISCUSSION

Malignant axillary lymphadenopathy can be caused by secondary findings of various primary tumors. Breast cancer is the most common cause of malignant axillary lymphadenopathy in women presenting with isolated axillary lymph node metastasis.[3,15-17] Breast MRI examination is a routine step in the evaluation of patients in whom mammography and breast US cannot localize the primary breast cancer and can undoubtedly decrease the frequency of women with occult breast cancer.[9,10] Experience with applying MRI in the setting of occult breast cancer indicates that MRI will identify a lesion suspected for a primary breast cancer in 36%–86% of cases with negative physical examination and mammography.[4] In our study, breast MRI identified primary breast cancer in 25.0% of 34 patients with ACUPax, which was lower than the rate reported by a recent meta-analysis.[4] This could be attributed to differences in previous studies,[8,13,18-20] which included patients with negative mammography results, although breast US was not routinely performed. However, we performed both mammography and breast US to evaluate primary breast cancer in all patients with ACUPax. Therefore, previous studies could have included breast cancer that was detected by US before MRI examination, unlike our study.

In the past, the conventional approach for the treatment of

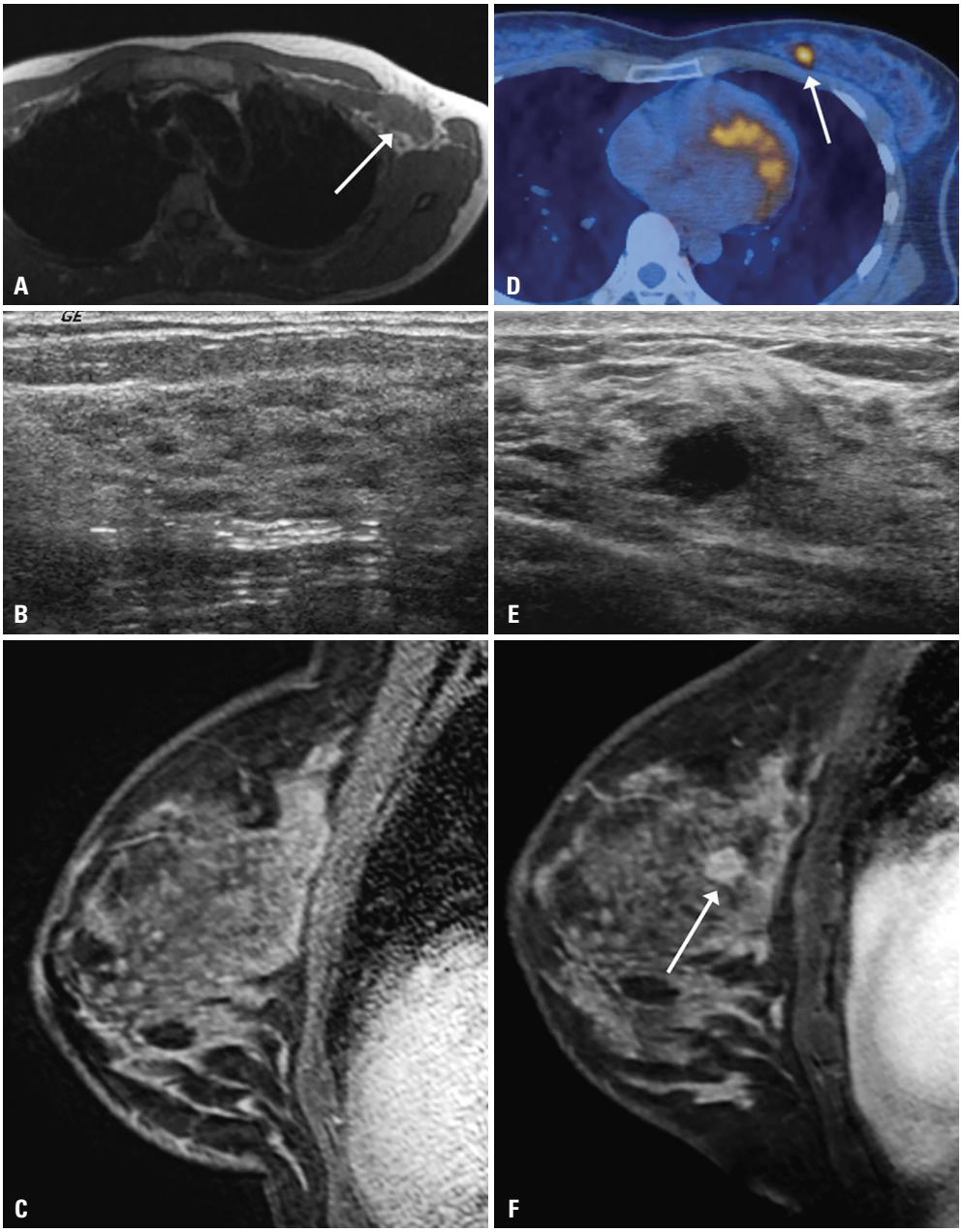

Fig. 2. A 36-year-old woman with a palpable left axillary lymph node was confirmed with metastatic adenocarcinoma of unknown primary (ACUPax). (A) An axial T1-weighted MR image shows a 3.1-cm enlarged lymph node with an irregular margin (arrow). (B) Ultrasound and (C) contrast enhanced sagittal T1-weighted fat suppressed MR images show no in-breast lesion in the left upper inner breast. (D) On PET-CT, 2 years after the diagnosis of ACUPax by excision biopsy of the axillary lymph node, new abnormal focal FDG uptake (arrow) is apparent in the left breast upper inner quadrant (p-SUV= 4.7). (E) US for the PET-CT detected lesion reveals a 0.8-cm microlobulated, low echoic mass, and (F) contrast enhanced MRI shows a 1-cm irregular mass (arrow) in the same area of FDG uptake. The mass was diagnosed as invasive ductal carcinoma of triple negative type, same as the subtype of the previous axillary lymph node.

ACUPax involved mastectomy.[2] The frequency of primary tumors in mastectomy specimens ranged from 35% to 82%.[2,21] The application of MRI for the identification of primary breast cancer in patients with ACUPax may lead to the selection of breast conserving surgery instead of unnecessary mastectomy, with a concomitant decrease in the rate of true occult breast cancer. In our study, proper treatment was possible in 25% of patients with ACUPax whose primary breast cancer was detected on MRI. The primary breast cancers detected on MRI did not often exhibit typical malignant findings and half of these lesions exhibited benign features on second-look US or mammography. Therefore, once a visible MRI finding is localized on second-look US or mammography, confirmation is necessary with biopsy, even if the US or mammographic findings appear slightly favorable or resemble cysts.

ALND with WBRT has recently become the treatment of

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choice for ACUPax in the absence of indications of primary breast cancer on breast MRI following MG and US.[22] In our study, there was no significant difference between the clinical outcomes of patients who underwent breast surgery for MRI-detected breast cancers and those with negative MRI findings who underwent only WBRT. Rueth, et al.[11] showed similar rates of locoregional control, distant metastasis, and mortality between patients who underwent modified radical mastectomy and those who underwent ALND with WBRT. Moreover, a recent study reported good outcomes in patients with ACUPax who were treated with ALND and WBRT without mastectomy.[22] In-breast recurrences were observed in 8% of patients whose breast was preserved and treated with WBRT.[12] None of the patients in our study with negative MRI findings who underwent ALND with WBRT experienced in-breast recurrence or distant metastases. Our results support the findings of previous studies that demonstrated the safety of WBRT for patients with true occult breast cancer, with low rates of local and regional recurrence without distant metastases. The role of additional WBRT for local control after breast conserving surgery has been well established by several studies.[23-25] Masinghe, et al.[25] found that WBRT may reduce ipsilateral breast tumor recurrence and increase survival in patients with ACUPax. Barton, et al.[23] also found that patients who had undergone WBRT had better local and distant control than those who only underwent observation. The omission of additional WBRT resulted in a significantly higher rate of locoregional recurrence caused by the failure to excise or irradiate the primary breast lesion and perhaps worsened long-term survival.[23-25]

Our study has some limitations. First, the small sample size was the chief limitation of this study. The study was mainly a descriptive analysis of available variables, owing to the small study population. Therefore, it is difficult to establish specific associations between the study variables and patient outcomes. The other limitation is that we did not review all MRI images again, but conducted the study based on the radiologic reports of MRI at the time of diagnosis. However, we think the results of MRI interpretation would be homogeneous because radiologists in breast imaging conduct regular consensus meetings to reach a homogeneous diagnosis. Lastly, this study was designed as a single-institution retrospective review.

In conclusion, breast MRI appears to play an excellent role in detecting otherwise occult breast cancers in patients with ACUPax, thereby ensuring proper surgical treatment. Among the patients in this study, the prognoses of patients who did not have occult breast cancer on MRI were as excellent as those for patients whose occult cancers were detected by MRI, if they were treated with ipsilateral ALND and WBRT followed by chemotherapy.

DATA AVAILABILITY STATEMENT

The data are not available for public access because of patient privacy concerns, but are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: Eun Young Ko and E-Ryung Choi. Data curation: Haejung Kim and Jeong Eon Lee. Formal analysis: E-Ryung Choi, Ok Hee Woo, Eun Young Ko, Ji Soo Choi, and Eun Sook Ko. Investigation: E-Ryung Choi, Ok Hee Woo, Eun Young Ko, Ji Soo Choi, and Eun Sook Ko. Methodology: Eun Young Ko and E-Ryung Choi. Project administration: Eun Young Ko. Resources: E-Ryung Choi, Boo-Kyung Han, Ji Soo Choi, Eun Sook Ko, and Jeong Eon Lee. Supervision: Eun Young Ko and Boo-Kyung Han. Validation: Haejung Kim and Myoung Kyoung Kim. Visualization: Ok Hee Woo and Myoung Kyoung Kim. Writing—original draft: E-Ryung Choi and Ok Hee Woo. Writing—review & editing: Ok Hee Woo, Eun Young Ko, Haejung Kim, and Myoung Kyoung Kim. Approval of final manuscript: all authors.

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