CHAPTER IV

ABBREVIATED BREAST MRI PROTOCOLS IN BREAST CANCER SCREENING- REVIEW ARTICLE

Inci Kizildag Yirgin

(Asst. Prof. Dr.), Istanbul University, Istanbul, turkey, e-mail: inci.kizildag@gmail.com

0000-0003-0563-5964

1.Introduction

Breast cancer is the second fatal cancer after lung cancer in women (1). Mammography (MG) is currently the most effective method used in breast cancer screening (2). However, breast cancer is still one of the most important health problems, despite mammographic screening programs and technical advances in mammography for more than 30 years. Studies have shown lower sensitivity of mammography which is about 70-85% (2,3). The most important reasons of the low sensitivity of mammography are dense breast structure, and inability to detect biologically aggressive tumors (4). A screening program should have as much as possible contributing to the patient survival and ability to detecting biologically important tumors. Most of the criticisms made about mammography on breast cancer screening are on these topics (5). Several imaging modalities used in detecting the breast cancer in daily practice sech as digital breast tomosynthesis (DBT), ultrasound (US), and magnetic resonance imaging (MRI). DBT was predicted to be beneficial particularly in dense breasts however, the contribution was less than expected with an average 1.2 per 1000 patients (6). Ultrasonography, and fully automatic breast US are useful in the diagnosis of breast cancer in women with dense breast structure, however the limitations are longer examination time, lower sensitivity, and higher rates of unnecessary biopsies (7). Moreover, the detection rate of additional cancer is moderate as many published studies have shown the rate as approximately 2–4.4/1000 in examined women (7-9). Breast MRI has been shown to be the most sensitive imaging modality for the detection of breast cancer (both invasive, and ductal carcinoma in situ) (10-12). MRI is not effected by breast density as MG, and relies on contrast enhancement, so can detect more biologically relevant cancers due to angiogenic activity (4). Due to these advantages, MRI is used as a standard method with MG in screening high-risk patients.

The standard full diagnostic protocol (FDP) of breast MRI consists of multiple sequences before and after contrast enhancement with and without fat suppression with examination time ranging from 20-60 minutes. The abbreviated protocols (AP) reduce the interpretation time of the images, and the cost due to shorter imaging time (11). Therefore, AP breast MRI has recently been investigated as a supplemental screening method for women in high and average risk groups.

In the present review the different AP breast MRI protocols used for screening in high and average risk of breast cancer, and the superiority and limitations of the procedure will be studied, and future possible application areas will be discussed.

2.Literature Review

Kuhl and colleagues were the first group who explored the use of AP breast MRI in 2014 (12). They investigated whether AP was suitable for breast MRI screening, and compared the procedure with FDP. 443 women at mild to moderately increased risk of breast cancer, and 606 screening MRI examinations were evaluated in the study. AP consisted of a single pre-contrast, first post-contrast T1 weighted sequence with the substracted and a single maximum-intensity projection (MIP) images. First, the MIP images were evaluated for significant contrast enhancement by two experienced and blinded radiologists. Then, the substracted images, and FDP were evaluated, and the evaluation time of each section was separately noted. Similar rate of cancer detection, similar sensitivity, specificity and PPV were found with the AP for screening of women with dense breast. This study showed that MRI acquisition time (3 min versus 17 min), and interpretation time (28 sec versus 2-4 min) might be substantially reduced with the AP without affecting the cancer yield, and the diagnostic accuracy.

In 2015, Mango et al. published a study which investigated whether so many sequences were needed to detect breast cancer (13). MRI images of 100 breast cancer patients were retrospectively evaluated by four radiologists. The AP consisted of only one pre-contrast and one post-contrast T1 weighted sequence. Post-processed subtracted first post-contrast and subtraction maximum intensity projection images were also obtained. They found no significant difference between the sensitivities within each sequence among four readers.

Heacock et al. evaluated the efficacy of the T2-weighted sequence added to AP in a study published in 2016 that included 107 patients who were retrospectively diagnosed with breast cancer (14). AP included the pre-contrast, and post-contrast T1 weighted sequences with subtracted images. Three breast radiologists separately evaluated the images. Protocols designed into 3 groups as AP1; T1-weighted non-contrast, post-

contrast and post-contrast subtracted images, AP2; T1-weighted images with clinical history and prior imaging, and AP3; T1-weighted images and T2-weighted images with clinical history and prior imaging. Cancer detection percentages were 97.8%, 99.4%, and 99.4%, respectively. This study showed that the addition of T2 sequence provided no statistically significant difference however, increased the lesion visibility.

Grimm et al. published another feasibility study to compare the performance of two different AP (AP-1 and AP-2), and FDP for breast cancer screening in the high-risk group (15). They retrospectively evaluated forty-eight breast MRIs [24 normal, 12 benign, and 12 malignant (8 IDC, 1 ILC, and 3 DCIS)]. The period between the short and long protocol evaluation was one month, and 3 experienced radiologists performed the evaluation. AP-1 included fat saturated pre-contrast T2-weighted, pre-contrast T1-weighted, and first pass T1-weighted post-contrast sequences and AP-2 included the abbreviated 1 protocol plus the second pass T1-weighted post-contrast sequence. There was no statistically significant difference between sensitivity, and specificity of FDP, AP-1, and AP-2. Overall sensitivity was 86% for AP 1, 89% for AP 2, and 95% for FDP. The specificity of AP 1 was 52%, AP 2 was 45%, and FDP was 52%. This study showed the average image interpretation time for AP 1 was 2.98±1.86 for FDP, and 2.95 ± 1.5 minutes. The results of this study demonstrated that the use of AP breast MRI for breast cancer screening can be a cost-effective method due to shorter examination and interpretation time (15).

In 2016, Harvey and colleagues published a study in which 568 high-risk patients were screened (16). In this study, they evaluated the AP and FDP. AP consisted of only pre-contrast and first post-contrast fat-suppressed T1 sequences subsequently, and the MIP and subtraction images were obtained. The mean scan time for AP was 4.4 minutes, and 23.2 minutes for FDP. Interpretation times were 1.55 for AP, and 6.43 minutes for FDP. Only 12 (2.1%) cases required additional MRI evaluation. Seven cancers were detected in this study (5 were invasive, and 2 were in situ ductal carcinoma), all diagnosed cancers were identified in both protocols. Their study showed statistically significant differences between scanning, and the interpretation times. The study also showed that AP was equally effective as FDP in cancer detection in high risk patients (16).

In 2017, Panigrahi and colleagues published a prospective cohort study including 1052 high-risk MRI cases (17). This study investigated the effectiveness of AP in breast cancer screening and its concordance with the Breast Imaging Reporting and Data System (BI-RADS) classification. The abbreviated protocol included a pre-contrast T1-weighted sequence with fat saturation, and a single post-contrast T1-weighted sequence with

fat saturation. Fourteen cancers were detected, and all cancers were diagnosed with both AP, and FDP. Changes in BI-RADS category were detected in only 3.4% of cases after FDP assessment.

Chen et al. included 356 women who had dense breast tissue with negative mammography findings into their study published in Korea in 2017 (18). MRI images were retrospectively divided into 3 groups (AP-1, AP-2, and FDP). As in previous studies, AP-1 consisted of a pre-contrast and a post-contrast T1-weighted series with subtracted and MIP images while AP-2 consisted of diffusion weighted imaging (DWI) series in addition to AP-1. Average interpretation times with the AP-1, AP-2, FDP were 37 seconds, 54 seconds and 3 minutes respectively, and there was a statistically significant difference between AP, and FDP. Fourteen cancers were detected. There were no significant differences in sensitivity among AP-1, AP-2, and FDP in the diagnosis of breast cancer. However, the specificity of AP-1 was significantly lower than that of AP-2 and FDP and there was no difference between AP-2, and FDP. Researchers in that study found that adding DWI to AP in screening of dense breast structure was as effective as FDP in detecting cancer, and at the same time effective in reducing the cost (18).

Petrillo et al. published a retrospective study evaluating 508 patients with MR images in 2017 (19). Abbreviated protocol included one pre-contrast, and the first post-contrast T1-weighted series. Full protocol consisted of four post-contrast, and one pre-contrast T1-weighted series. 206 out of 207 cancers were diagnosed by both FDP, and AP. There was not statistically significant difference between the performances of these two protocols (19).

Dogan and her colleagues evaluated 23 high-risk women by AP and FDP breast MRI in a feasibility study published by the American College of Radiology in 2018 (20). The AP included a single T2W fast spin-echo, triple echo Dixon T2 sequence, and a 3D dual-echo fast spoiled gradient-echo two-point Dixon sequence for volumetric T1W imaging prior to and after contrast as the dynamic sequence. FDP included unenhanced T1-weighted axial and sagittal, dynamic contrast-enhanced T1-weighted gradient-echo sequence, iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) and DWI sequences. The mean acquisition time for AP was 9.42 minutes, and 22.09 minutes for FDP. These results showed that AP consisting of high resolution T2-weighted imaging, unenhanced T1-weighted imaging, and four phases of contrast-enhanced T1-weighted imaging had significantly shorter acquisition time compared with the time in FDP. In addition, they found no statistical differences on image quality, and in detecting anatomical details between two protocols.

Oldrini et al. aimed to compare the diagnostic performance, and interpretation time of two protocols in 2018 (21). They retrospectively evaluated 90 breast MR examinations (30 were BI-RADS 1-2, 30 were BI-RADS 3, 30 were BI-RADS 4-5). Their study showed that using the abbreviated protocol decreased the interpretation time with no difference in sensitivity, and specificity. There was a high degree of consortium between AP, and FDP.

Choi et al. investigated the effectiveness of AP including fat-suppressed T2-weighted imaging, pre- and post-contrast T1-weighted, and subtracted MIP images for the screening of women with a history of breast cancer surgery in a study published in 2018 (22). They prospectively included 725 women who had a previous history of breast cancer history into the study. They found twelve cancers (7 cancers could not be diagnosed with second look US, and MG while 5 cancers could be diagnosed with second look US, and MG). This study has shown that AP is an effective method in screening of patients with a history of breast cancer in terms of both early detection of cancer, and diagnosis of possible cancer in the contralateral breast.

Yamada et al. investigated the detectability of breast cancer with unenhanced, and enhanced AP MRI in their study published in Japan in 2018 (23). Unenhanced AP (AP1) included fat-supressed T2 weighted images, DWI and MIP which were derived from DWI. Enhanced AP (AP2) included fat-supressed T2 weighted images, second post contrast T1-weighted squences and MIP derived from post-contrast images. Eighty-seven patients with 89 breast cancer lesions $\leq$ 2 cm in diameter were included into the study. The images were retrospectively evaluated by two radiologists. The sensitivity/specificity for AP1 and AP2 for reader 1 was 89.9/97.6% and 95.5/90.6%, for reader 2 was 95.5/94.1% and 98.9/94.1%, respectively. In this study, researchers concluded that the unenhanced AP with DWI may compete with the enhanced AP in the evaluation of cases known to have breast cancer below 2 cm in diameter.

3.Considerations

The initiation of breast cancer screening in 1970s enabled a great deal of knowledge on breast cancer. Currently, breast cancer is known to have a heterogeneous genetic background, and the radiological appearance of each cancer with different genetic characteristics is different from each other. To give an example, the spiculations are a typical feature of luminal-A cancers (24,25). The cause of architectural distortion is desmoplastic reaction due to hypoxia of tumoral area (26). Necrosis resulted with microcalcifications (27,28). The investigation of the tumors that could be detected by mammography showed that approximately 90% are less aggressive tumors (29). Unfortunately, these characteristics are not usually

detected in rapidly growing and biologically important interval cancers. The examination of the breast structure characteristics of the screened population showed that almost half of the population has dense breast structure, which reduced the sensitivity of mammography to 30% (30). Besides, interval cancer rate should be equal to zero in an ideal screening method. However, the interval screening was reported to be 30-50% in mammography studies in Europe based screening studies (31).

Breast cancer is a type of cancer that can be screened because the patient can be diagnosed in the asymptomatic period, and the target population is specific. The starting of the routine mammographic screening of the target population is at age 40 in the United States, and at age 50 in Europe, and screening is performed in every 1-2 years (4). The most important features of the screening method are being easily accessible, fast and reliable. Today MG is used in screening because it is easily accessible, cost-effective and fast. However, the modern clinical approach requires the high sensitivity in screening method, in biologically aggressive tumors and low rate of interval cancer. Scientists who have struggled to find a solution to this problem have performed considerable studies particularly on AP breast MRI in recent years. Breast MRI is a diagnostic method which was used in the early 1990s (32-34). Multiple studies have shown that breast MRI had high diagnostic efficacy in various benign and malignant breast diseases regardless of breast density, tumor stage, and histopathological background (4). At present, screening breast MRI is used only in patients with a lifetime risk greater than 20% in accordance with the ACR guideline (35). This group especially includes BRCA positive patients. The investigation of the tumor characteristics of these patients showed that they were more aggressive, and mostly interval and was difficult to detect with mammography. Although the interval cancer rates decreased to zero by MRI, and MG screening has many disadvantages, the use of screening breast MRI is still unclear in the low, and average risk group in the literature (4,36).

The abbreviated protocol which is defined for further introduction of screening into daily practice, does not contain as many sequences as conventional MRI. The commonly used sequences in the studies in the literature were fat sat pre-contrast T1, and first post-contrast T1 sequences. The subtracted, and MIP examinations performed by post-processing were also added to these sequences (Table-1).

Table 1. Abbreviated Breast MRI Protocols Used in Twelve Studies

Study	T1 Pre-CE	T1 Post-CE First Pass	Substraction	MIP	T1 Post-CE Second Pass	T1 Post-CE Third Pass	T2	STIR	DWI
Kuhl et al., 2014	×	×	×	×					
Mango et al. 2015	×	×	×	×					
Heacock et al. 2016 AP 1	×	×	×	×					
Heacock et al. 2016 AP 2	×	×	×	×			×		
Grimm et al. 2015 AP 1	×	×	×				×		
Grimm et al. 2015 AP 2	×	×	×		×		×		
Harvey et al. 2016	×	×	×	×					
Dogan et al. 2018							Dixon T2 sequence and 3D dual-echo, fast spoiled gradient-echo two-point dixon sequence		

Chen et al. 2017 AP 1	×	×	×	×					
Chen et al. 2017 AP 2	×	×	×	×					×
Oldrini et al. 2018	×	×	×						
Choi et al. 2017	×	×	×	×			×		
Yamada et al. 2018 AP1				×					×
Yamada et al. 2018 AP2				×	×		×		
Panigrahi et al 2017	×	×	×	×					
Petrillo et al. 2017	×	×	×						

Different than FDP, kinetic examination cannot be performed, and only the early contrast enhancement of the lesion can be evaluated. In fact, the researchers demonstrated that a rapid wash-in is correlated with tumor grade, and invasive disease because the contrast between the angiogenic tumor, and the adjacent fibroglandular tissue was in the highest level at that moment (37). Grimm and colleagues added a second post-contrast sequence to AP while investigating the contribution of kinetic analysis and found no differences in reader sensitivity or specificity (15). Moreover, early contrast enhanced series were the eliminating background parenchymal enhancement (BPE) of normal fibroglandular tissue that can be seen in further contrast enhanced images.

Studies have shown that MRI acquisition time, and evaluation time of the images are significantly reduced with AP when compared with FDP owing to the decreased number of sequences to review. The shortest times

were reported as 3 minutes for acquisition time, and as 2.8 seconds for evaluation time (with MIP images only) in the study of Kuhl (12). The duration was only 4.4 minutes in the study of Dogan et al. in the full protocol implemented with fast sequences (20). (Table-2).

Table 2. Studies and pathology information.

References	**Number of patients**	**MRI examinations**	**Number of invasive carcinomas**	**Number of DCIS**	**Duration (FDP/AP/ minutes)**
Kuhl et al.	443	606	7	4	3
Mango et al.	100	100	79	21	15
Heacock et al.	107	107	94	13	12
Grimm et al.	48	48	9	3	11/13
Harvey et al.	505	568	5	2	4.4
Dogan et al.	23	23	0	0	9.42/22.09
Chen et al.	356	356	14		3
Oldrini et al.	90	90	25	1	-
Choi et al.	725	799	7	5	8.38
Yamada et al.	87	87	67	12	-
Panigrahi et al.	746	1056	14	2	3
Petrillo et al.	508	508	183	24	-

Figure 1, 2 and 3 show three cases in which the first, and second post-contrast images, DWI, MIP images were evaluated (Figure 1,2,3).

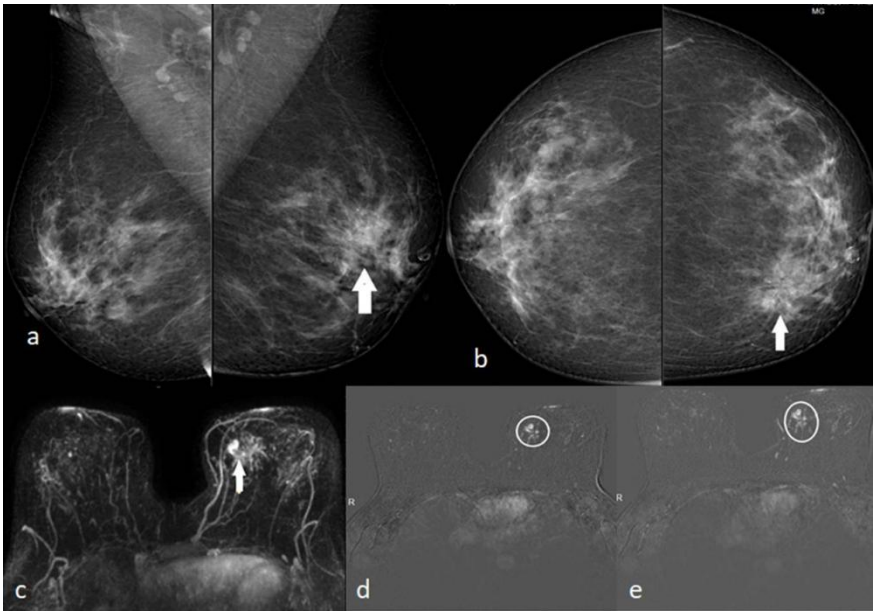

Figure 1. The patient aged 41 years diagnosed with invasive lobular carcinoma presented by mammography, and abbreviated MRI images. **a-b)** CC (craniocaudal) and MLO (medio-lateral-oblique) mammograms show parenchymal distortion with pleomorphic microcalcifications (arrows). **c)** MIP(Maximum Intesity Projection) image shows malignant lesion with greater contrast enhancement than adjacent normal parenchyma in the same area (arrow head) **d-e)** First and second post-contrast T1-weighted sequences with fat saturation show malignant lesion with irregular margins showing contrast enhancement, respectively (circles)**.**

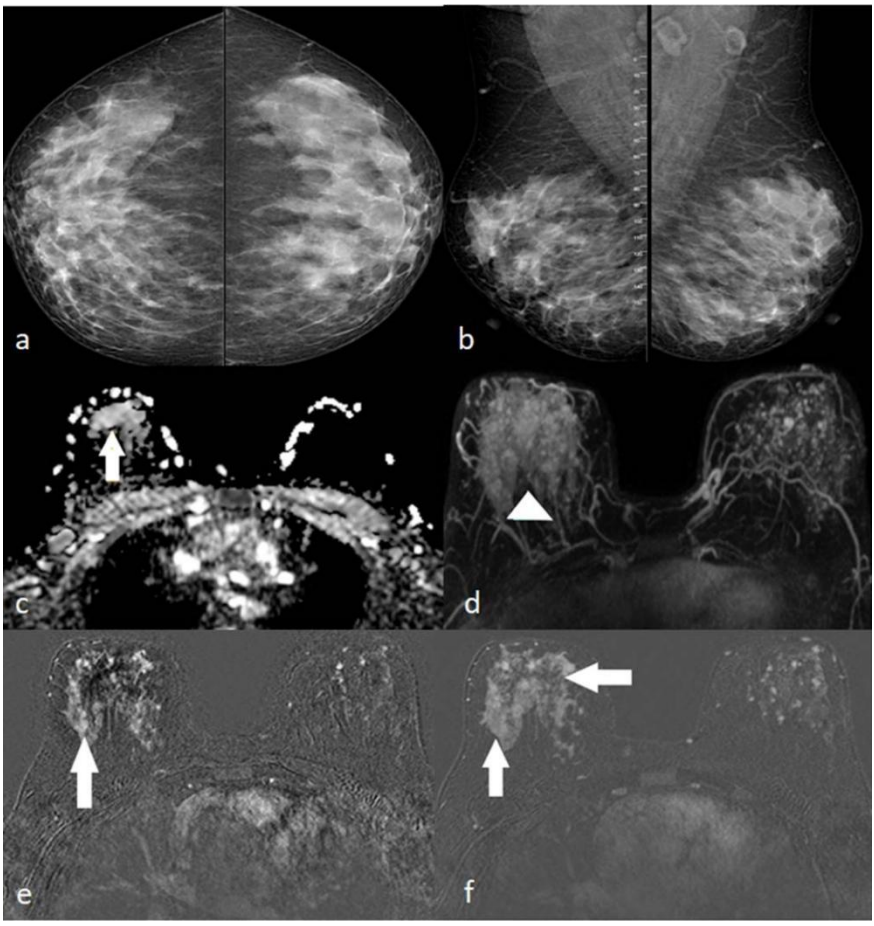

Figure 2. The patient aged 39 years presented with a palpaple mass in her right breast that was diagnosed with invasive tubular, and micropapillary carcinoma assosiated with in situ component. **a-b)** CC (craniocaudal) and MLO (medio-lateral-oblique) mammograms cannot show the lesion due to dense breast parenchyma structure**. c)** ADC (Apparent Diffusion Correlation) map image shows hypointensity due to the hypercellularity of the lesion (arrows). **d)** MIP (Maximum Intesity Projection) image shows infiltrative lesion with a wide area of contrast enhancement, without a clear mass configuration. **e-f)** First and second post-contrast T1-weighted sequences with fat saturation show the same infiltrative lesion with a wide area of contrast enhancement, without a clear mass configuration, respectively (arrows).

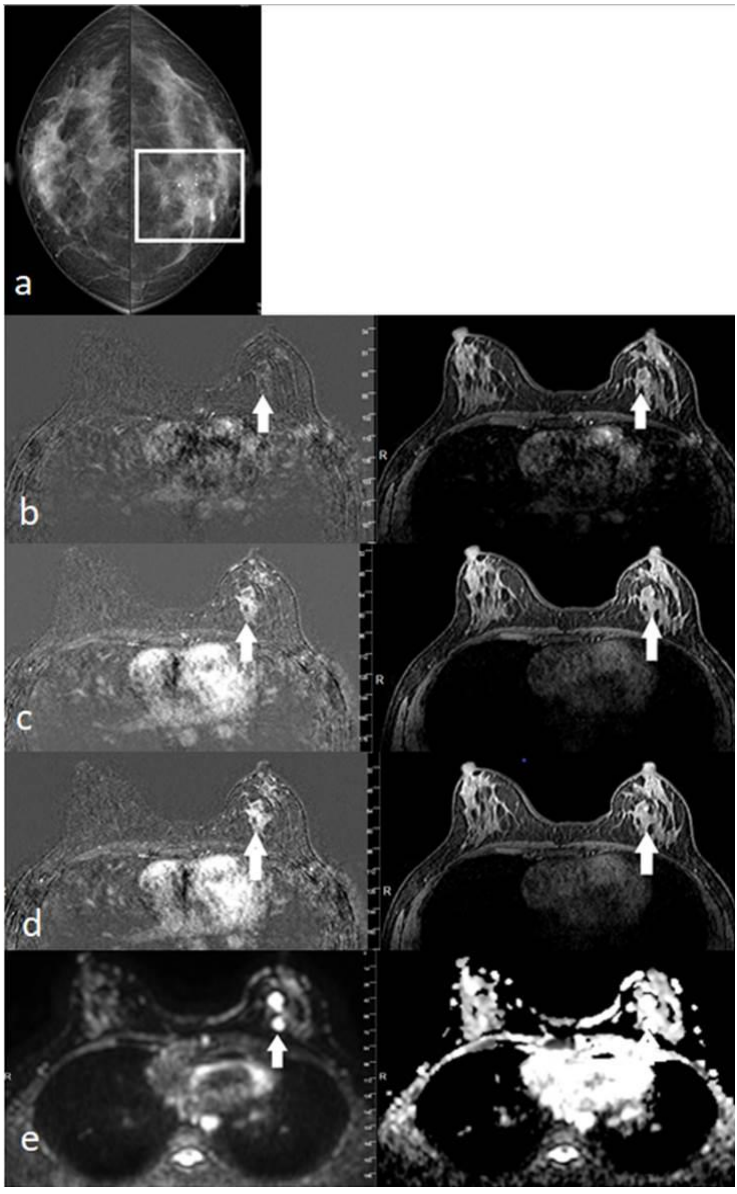

Figure 3. The patient aged 37 years diagnosed with a palpable mass in her left breast which was confirmed as mucinous carcinoma presented by mammography, and abbreviated MRI images. **a)** CC (craniocaudal) mammograms show malignant lesion with spiculated margins and amorphous microcalcifications in the inner quadrant of the left breast (square). **b-c-d)** The first, second and last post contrast subtracted, and nonsubtracted T1-weighted sequences images show a malignant lesion with peripherally contrast enhancement assosiated partly necrotic component (circles). **e)** DWI, and ADC (Apparent Diffusion Correlation) maps both show hyperintense lesion due to its hypocellularity, a general feature of mucinous carcinomas.

Although the use of different sequences, different patient numbers and populations, AP had the same cancer detection rates and diagnostic efficacy as FDP in nearly all published studies (Table-3). Dogan et al. used T2W fast spin-echo, triple echo Dixon T2 sequence, and a 3D dual-echo fast spoiled gradient-echo two-point Dixon sequence for volumetric T1W imaging before and after the contrast as the dynamic sequence in AP (20). The aim of their study was to determine anatomic detail as well as FDP, and to perform the kinetic analysis. Therefore, the MRI acquisition time could be reduced from 22 minutes to only 9.42 minutes. The difference of this study from other studies was the ability to perform the similar kinetic analysis.

Table 3. Sensitivity and Specificity of FDP vs. AP

	Sensitivity (%)		Specificity (%)	
Studies	**FDP**	**AP**	**FDP**	**AP**
Kuhl et al.	100	100, 90.9[a]	93.9	94.3
Mango et al.	n/a	96, 93[a]	n/a	n/a
Heacock et al.	n/a	97.8[b],99.4[c],99.4[d]	n/a	n /a
Grimm et al AP 1	95	86	52	52
Grimm et al.AP 2	95	89	52	45
Harvey et al.	n/a	100	n/a	n/a
Dogan et al.	n/a	n/a	n/a	n/a
Chen et al. AP 1	100	92.9	96.8	86.5
Chen et al. AP 2	100	100	96.8	95
Oldrini et al.	100[e] 100[f]	100[e] 100[f]	91.5[e] 94.4[f]	91.5[e] 95.1[f]
Choi et al.	n/a	100	n/a	89.2
Yamada et al.AP1	n/a	89.9[g]/95.5[h]	n/a	97.6[g]/94.1[h]
Yamada et al.AP2	n/a	95.5[g]/98.9[h]	n/a	90.6[g]/94.1[h]
Panigrahi et al.	81.8	81.8	97.4	97.2
Petrillo et al.	99.5	99.5	77.1	75.4

n/a=not/applicable or information not provided.

a. **MIP only.**
b. **Protocol 1**
c. **Protocol 2**
d. **Protocol 3**
e. **Junior reader**
f. **Senior reader**
g. **Reader 1**
h. **Reader 2**

Different than the others, Chen et al. showed that the specificity of the method increased from 86.5% to 95% by adding DWI to AP (18). Moreover, using the diffusion sequence instead of the use of IV contrast has also been investigated due to the current published side effects, and complications of the use of IV contrast (38,39). Yamada et al. conducted the most way out study in the literature because they used no intravenous contrast material which is an indispensable part of breast MR. Their results showed that DWI based MIP images would be promising if supported by more comprehensive studies in the future (23). However, the addition of DWI sequences to the AP or using of IV contrast media is still highly controversial due to the absence of a standardized protocol.

4.Conclusion

AP breast MRI protocols or fast sequences, along with the shortening of the imaging time, can reduce the interpretation time of the images, and reduce the cost by maintaining a high diagnostic accuracy of full diagnostic protocol. However, reliability and application of abbreviated protocol and short sequences should be proven and standardized in larger and prospective series.

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