International Research Journal of Oncology

2(1): 1-10, 2019; Article no.IRJO.47345

Evaluate the ADC Values in Probably Benign and Suspicious Malignant Breast Lesions

Chugh Asmita[1], Saini Manju[1*], M. Goel[1], A. Kusum[2], M. Pattanayak[3] and S. Raghuvanshi[1]

[1]Department of Radiodiagnosis, Himalayan Institute of Medical Sciences, SRH University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.
[2]Department of Pathology, Himalayan Institute of Medical Sciences, SRH University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.
[3]Department of Surgery, Himalayan Institute of Medical Sciences, SRH University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand, India.

Authors' contributions

This work was carried out in collaboration between all authors. Authors SM and CA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MG, AK and MP managed the analyses of the study. Authors CA and SR managed the literature searches. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Guy-Armel Bounda, Department of Clinical Pharmacy, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, China.
Reviewers:
(1) Heba Gamal Abd El-Aziz Nasr, Al-Azhar University, Cairo, Egypt.
(2) Chhanda Das, India.
Complete Peer review History: http://www.sdiarticle3.com/review-history/47345

Original Research Article

Received 26 October 2018
Accepted 14 February 2019
Published 07 March 2019

ABSTRACT

Background: Breast carcinoma is at increasing trend in India. The young age has been found to be a major risk factor for breast carcinoma in Indian females. The age adjusted rate of carcinoma breast is found as high as 41/100,000 in different registries. The conventional imaging for breast have their own limitations. MRI is a promising tool. The diffusion weighted imaging (DWI) is influenced by histologic structure and is an indirect evidence of histology.
Aim: To characterize probably benign and suspicious breast lesions with non invasive MRI techniques of diffusion weighted imaging (DWI) using apparent diffusion coefficient (ADC) values and to correlate the values of apparent diffusion coefficient (ADC) with histopathological findings of breast lesions.
Study Design: Observational study.
Place and Duration of Study: The study was conducted in Department of Radiology of Himalayan

**Corresponding author: E-mail: drmanjusaini@gmail.com;*

Institute of Medical Sciences, SRH University, Dehradun from September 2016 to June 2018.
Methods: In this observational study, 54 patients were included with diagnosis of BIRADS III and BIRADS IV on X ray mammography and sonomammography. The diffusion weighted imaging **(**DWI) MRI was done and apparent diffusion coefficient (ADC) values were calculated and results were correlated with histopathological outcome.
Results: Comparison between the diffusion weighted imaging **(**DWI) analysis and histopathological findings reveals that the majority of the lesions 58.7% with apparent diffusion coefficient (ADC) value≤1.03 x10-^{3} mm^{2}/s (*P* <.005). Diffusion weighted imaging (DWI) analysis showed a sensitivity of 73.68%, a specificity of 88.88%, a PPV of 83.25%, an NPV of 82.75% and an accuracy of 82.60%.
Conclusion: Diffusion weighted imaging (DWI) MRI is a non invasive technique used to discriminate benign and malignant lesions and helps in reducing unnecessary interventions.

Keywords: ADC value; BIRADS; DWI.

1. INTRODUCTION

Breast is a modified sweat gland, comprising of fibrous, fatty and glandular tissue. It can be a site for various lesions ranging from mastitis to invasive carcinoma, over a wide range of age. It becomes essential to differentiate between inflammatory and benign lesions from early carcinoma, especially in women predisposed to breast carcinoma.

One of the leading causes of cancer death in women is breast carcinoma [1]. It has been ranked number one cancer in Indian females with age adjusted rate of 25.8 per 100,000 with mortality rate of 12.7 /100,000 women [2]. The increasing rate of breast carcinoma is an alarming area in the field of clinicians and researchers [3]. Breast imaging has proven to detect breast cancer in its early stage. However, in females under 40 years of age with dense breast, other technologies pertaining to early detection such as sonomammography and MRI breast may also contribute to the early detection of breast carcinoma, for whom the X-ray mammography is less sensitive [4]. Magnetic resonance technique have shown great potential to enhance the sensitivity and specificity in diagnosing breast malignancy. Dynamic contrast enhance (DCE) MRI is a important imaging tool in diagnosis and management of breast masses. It gives detail information about the extent of the lesion and precise information about the multifocal or multicenteric disease which influences the treatment decisions [5]. MRI was established as an imaging technique in medicine over 20 years but only in the last few years it is being used consistently to image the breast [3]. Using routine MRI sequences there is difficulty in ascertaining the benign lesions from malignant lesions, as these two categories may share certain morphology and contrast enhancement characteristics. In the era of fast improving technology the MRI techniques have also sequences with excellent spatial resolution and soft tissue contrast which contribute in differentiating the nature of the masses. Diffusion weighted MRI (DWI) imaging might be of value in assessment as it has the ability to provide tissue contrast based on molecular diffusion [6]. Diffusion weighted MRI is highly sensitive for breast malignancy allowing its detection that is occult on physical examination, X-ray mammography and sonomammography [7]. DWI can easily be embraced as an adjunction for standard clinical imaging protocols and has been reported to achieve higher pick-up rates than X-ray mammography.

Breast MRI with special sequences may be used to discriminate benign and malignant lesions which may minimize the number of breast biopsies performed in probably benign lesions [8]. The patient is always concerned with such lesions.

DW-MRI generates images that are sensitive to water displacement at the diffusion scale and quantifies such diffusion according to a quantitative index reflecting the apparent freedom of diffusion (apparent diffusion coefficient (ADC) [9]. This sequence appears to be an effective tool for tumor detection and characterization as well as for monitoring and speculating treatment response [10]. DWI is a non-contrast sequence that has shown potential for discriminating the nature of breast lesions. In our study we will be using this single MRI sequence in the probably benign and suspicious breast masses on routine investigations and validate its usefulness in terms of its non

invasiveness in discriminating the nature of the breast lesions.

2. MATERIALS AND METHODS

The study was conducted in the Department of Radiology, Himalayan Institute of Medical Sciences (HIMS), Swami Ram Nagar, Dehradun from September 2016 to June 2018. Patients who were clinically diagnosed with breast masses were recruited from department of Surgery (cancer centre), Himalayan institute of medical sciences, Dehradun. Clearance from ethical committee of the institute and informed consent from the patient were taken. The study included 54 patients. The inclusion criteria were female patients above 30 years and who were diagnosed with BIRADS III and BIRADS IV on X ray mammography and sonomammography. Exclusion criteria were patients with ferromagnetic implants and pacemaker and all post operative patients who underwent surgery for breast mass.

2.1 The Study Tools Included

1. Conventional mammography machine SIEMENS 3000 NOVA.
2. Ultrasound machine Philips EPIQ 7G with high frequency (5-18 MHz) Linear transducer.
3. Magnetic resonance imaging machine AVANTO, SIEMENS (Germany), 1.5 Tesla with dedicated breast coil.
4. FNAC / Biopsy reports.

2.2 Study Protocol Included

1. Informed consent.
2. Conventional X ray mammographic examination (mediolateral oblique and craniocaudal views).
3. Sonomammography.
4. On the basis of combined X ray mammography and sonomammography lesions were assessed and higher category was assigned using fifth edition of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon.
5. Further diffusion weighted MR images were obtained and ADC values were calculated by manually placing the ROI within lesion on the ADC map and recorded the mean value in that ROI.
6. FNAC / Biopsy reports were analyzed.

The outcome of histopathology was considered as final diagnosis and compared with DWI ADC findings. All data was analyzed with SPSS software version 22.0. The data was presented as mean±SD for continuous variables and as frequency or percentage for categorical variables. Categorical data has been represented as frequency (number) and proportions (percentages). Continuous data has been presented as mean ± standard deviation (SD). The chi-square test and student's test were used for statistical comparison of qualitative and quantitative variables. *P* values <.005 was considered statistically significant.

3. RESULTS AND DISCUSSION

Breast carcinoma is at increasing trend in India with increase in morbidity and mortality in Indian females. The basic modalities for the detection of the breast lesions are X ray mammography, sonomammography and the breast MRI. Each of these modalities have their strengths and weakness The sensitivity and specificity of picking the breast lesions alone by the single modality is less. However when used in combination increases the detection rate.

There have been improvement in the detection of breast carcinoma with wide spread application of X ray mammography and sonomammography. However it still remains difficult to diagnose and characterize the lesion specially in dense fibroglandular breast. The limitation of the mammography is the overlapping of tissue which hides the lesions mainly in dense breast. However the sensitivity of picking microcalcification, the early sign of malignancy is markedly reduced on sonomammography. The strength of the sonomammography lies in characterization of the solid or cystic masses. Advancement in the MRI Breast specially the DWI sequence which do not require intra venous (IV) contrast, is an important tool in differentiating the benign and malignant lesions, as proved by the various studies.

In the present study we included 54 patients with 56 breast lesions. Film screen mammography and sonomammography were done on clinically palpable breast masses. The lesions were categorized on basis of BIRADS classification (ACR V edition). A combination of mammographic and sonomammographic BIRADS category III, IVA, IVB, IVC were included in our study and higher category was

assigned. DWI was done for these lesions and ADC values were calculated.

In our study all the patients were female with the mean age group of (48.81± 9.53). The majority 46.3% of patients evaluated were between 41-50 years, 22.2% in 51-60 years, 20.4% in 31-40 years and 11.1% in 61-70 years of age group. Fernanda Philadelpho and Arantes and Pereira et al. conducted a study which also showed that mean age group of female patients were 46.1 [11].

Analysis of data from more than 150,000 women who participated in 54 epidemiological studies (National cancer institute in United states) showed that overall women who had ever used oral contraceptive had a 7% increase in the relative risk of breast cancer as compared with women who had never used oral contraceptives [12]. In the present study 68.5% of patients had history of oral contraception, there was increase in the percentage of carcinoma in females who had history of oral contraception (57.1%).

It is a well known fact that the carcinoma present with breast pain in the later stages [13]. The same was not found true in our study where 81.48% patients had no pain while 18.52% had pain. As we have included BIRADS category III and BIRADS category IV and there were no advanced cases.

Most of the breast cancers are unilateral and are found in upper outer quadrant. The favored site because of increase fibroglandular tissue in this quadrant.Siwa Chan and Jeon-Hor Chen et al. in their study also reported that upper outer quadrant is the most favored site [14]. Our study also favored this fact as 96.3% of lesions were unilateral and 3.7% were bilateral, 48.21% were present in upper outer quadrant, followed by upper inner quadrant (26.79%), lower inner (10.71%), lower outer quadrant (7.14%), retroareolar region (3.57%) and the large masses acquiring upper inner and outer quadrant (3.57%).

Most of the benign lesions were well defined on film screen mammography with a peripheral halo while the malignant lesions have irregular margins as stated by Haixia Li and Xianjing Meng et al. in their study [15]. In our study most of the lesions have indistinct margins (73.21%) followed by circumscribed margins (26.79%). Majority of the lesions with indistinct margins were histologically malignant.

The clinically palpable masses may be seen as mass or asymmetry. In our study 49 mammograms showed masses while 7 mammograms showed asymmetry. This asymmetry was further seen as mass lesions on sonomammography, thus favoring the fact that combined imaging increases the detection rate.

In the malignancy the cells are compactly packed than in the benign lesions thus casting high density. In our study the mammogram showed increased density in 98.21% lesions. It is because our study comprise of lesions mainly of the BIRADS category IV.

The malignant calcifications is the hallmark of malignancy on the lesions as stated by Yojana V Nalawade in his study [16]. In our study 8.93% had suspicious calcification while 3.57% had benign calcification. The pick up rate of calcification was less because the study was conducted using film screen mammography which is less sensitive than digital mammography.

Architectural distortion may be seen in the malignant and the inflammatory lesions, we encountered 1.8% cases showing architectural distortion. This could be because of the film screen mammography used for imaging.

Sonomammography plays an important role in further characterization of the X ray mammographic masses. It acts as an adjuvant and increases the confidence rate of reporting. The malignant lesions are usually taller than wider and the benign are wider than taller. SudheerGhokhale also stated the same fact in his study [17]. In our study it was observed that 32 (57.15%) had oval shape, followed by irregular 18(32.14%) and round in 6(10.71%). Since we had not included BIRADS category V, so most of the lesions maintained their shape.

Sonomammography has a strength to discriminate cystic, solid and mixed echotexture masses. Most of the lesions in our study were hypoechoic (83.9%) followed by mixed echotexture(12.5%) and isoechoic lesions (3.6%). The purely cystic lesions were not included in our study.

The margins are better appreciated on Ultrasound than the mammography, which further helps in characterization of the masses. In our study it was observed that 44.64% of the lesions had indistinct margins, 39.3% circumcised margins, 5.4% indistinct with

spiculated margins, 5.4% microlobulated margins, 3.6% angular and 1.8% had indistinct and angulated margins. Most of these margins suggested malignancy. It is in concordance with the findings as majority of the study cases (57.1%) are malignant.

Sonomammography is a good modality to evaluate the infiltration of the mas in the surrounding tissue. This is helpful to label the mass as malignant, however one has to be cautious in differentiating from inflammation. We observed that adjacent Parenchyma was hyperechoic in 58.93% and normal in 41.07% as our lesions spectrum mainly included BIRADS category IV masses.

Evaluation of the skin over the breast mass is important in characterizing the masses. The pure benign masses do not produce any change in the skin, however usually the advanced malignant and inflammatory masses do so. We found in our study on the basis of combined mammography and sonomammography the overlying skin was seen normal in (89.3%) and affected in (10.7%). This was because the masses included in the study are BIRADS III and IV. It was found that nipple was also retracted in (10.7%) because of the same reason.

All the lesions were categorized on the combined mammography and sonomammography findings and the higher category was awarded. Of the BIRADS IV category lesions, 55.4% of the patients had Category IVC, 8.9% category IVA and 8.9% category IVB. While 26.8% had BIRADS Category III lesions.

As the histopathology was the gold standard investigation in our study. It was found that on the basis of histopathology 57.14% of the lesions were malignant and 42.86% were benign.

A study conducted by I Trop and Lalonde et al., in 2009, concluded that the sensitivity and specificity of CBE alone was 17% and 95.9%, that of mammography was 58% and 95.4%, and that of ultrasonography was 42% and 93.8%. Combined sensitivity and specificity of CBE, mammography and US was 67% and 90.3% [18].

In our study we included the clinical breast examination, mammography and sonommamo-graphy to increase the sensitivity and specificity of the lesions.

The main objective of study was to evaluate the ADC values of breast masses by the diffusion weighted sequence. DWI is a technique where no IV contrast is used. The various studies conducted by Fernanadaphiladelpho and Arantes Pereira et al. in 2007 [11], RichaBansal and Viral Shah et al. in 2013 [19], Wasan Ismail AL Saadi et al. in 2014 [20], HongminCai and Lizhi Liu et al. [21] and Uma Sharma and Rani G. Sah et al. [22] showed the efficacy of DWI in characterizing the benign or malignant lesion. In our study, out of the 56 lesions, 81.6% lesions showed restricted diffusion and 17.86% showed no restriction.Majority of the masses showing restriction were the solid masses. The ADC value was calculated by using the ROC curve, the cut off value came out to be $1.03x10^{-3}$ mm^2/s (Fig 1), In our study comparison between the DWI analysis and histopathological findings reveals that the majority of the lesions (58.7%) with ADC value≤$1.03\ x10^{-3}$ mm^2/s were found to be malignant (P<.005) and 41.3% with ADC value >$1.03\ x10^{-3}$ mm^2/s were found to be benign (Table 1). The ADC values of malignant lesions were lower with a range of 0.6 to $1.0\ x\ 10^{-3}$ mm^2/s and the ADC value of benign lesions were higher with range of 1.1 to $2\ x10^{-3}$ mm^2/s. In our study in order to distinguish benign and malignant lesions, DWI analysis shows sensitivity of 73.68%, a specificity of 88.88%, a PPV of 83.25%, an NPV of 82.75% and an accuracy of 82.60%.

The cut off ADC value was taken as $1.03x10^{-3}$ mm^2/s. 27(48.21%) showed ADC values ≤$1.03\ x10^{-3}$ mm^2/s and 19 (33.39%) showed ADC value >$1.03\ x10^{-3}$ mm^2/s and 10(17.86%) showed no restricted diffusion.

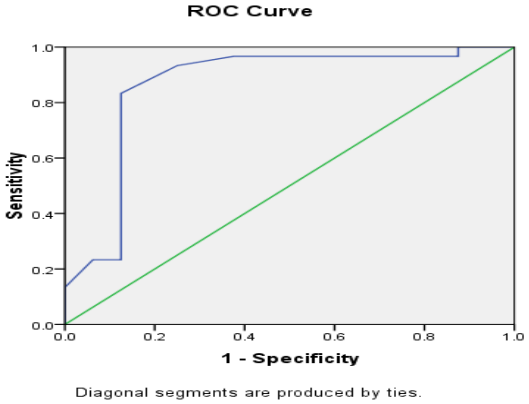

Fig. 1. Receiver operating curve showing the cut off value of ADC

Table 1. Shows correlation between the ADC values and histopathology results

		ADC		Total	*P* value
		Benign	Malignant		
HISTO	**Benign**	14	3	17	0.005
		82.4%	17.6%	100.0%	
	Malignant	5	24	29	
		17.2%	82.8%	100.0%	
Total		19	27	46	
		41.3%	58.7%	100.0%	

The considerable variation was explained by the different protocols used in the studies. The cut off ADC values obtained in the differentiation between benign and malignant lesions were dependent upon the respective b value chosen. In our study we use b value of 800 s/mm^2, in terms of the ADC values, cut off value, sensitivity and specificity, were in agreement with those found in literature.

Despite the promising capacity of ADC values to differentiate between benign and malignant lesions, the ADC values for benign and malignant lesions can overlap leading to false positive and false negative results. In our study false negative cases i.e 5 out of 32 lesions showed the ADC values >1.03x10-^{3} mm^2/s came out to be malignant on histopathology and all were ductal carcinomas and there was only 1 of 32 lesion that shows no restriction but diagnosed as ductal carcinoma on histopathology. 2 out of 24 benign lesions show ADC <1.03x10-^{3} mm^2/s, however came out to be chronic abscess on histopathology.

The results of the present study should be considered in the context of certain limitations. Firstly our patient population comprised of individuals referred mainly from our surgery department (cancer centre) in the institute, featured a predominance of malignant pathological findings. Secondly, the clinically suspected benign lesion usually undergosonomammography, thereby limiting the cases.

The single sequence of DWI is a non invasive technique and has high sensitivity and specificity and is a great tool that helps us in discriminating benign from malignant breast lesions and can reduce the intervention.

4. CONCLUSION

In present day scenario breast carcinoma is the most common cause of cancer related death in females. Early detection of malignancy is essential to decrease the morbidity and mortality. Various imaging modalities are used to detect breast lesions, which includes Mammography, sonomammography and breast MRI. However mammography is the basic modality for screening and ultrasound (US) is an adjuvant to it. These modalities are known to have high false positive rates because of their own limitations. DWI MRI is a technique based on diffusivity of water molecules and is quantified by ADC value. High cell proliferation in malignant tumors increases cellular density, creating more barriers to the extracellular water diffusion, reducing the ADC, and resulting in signal loss and vice a versa occurs in benign lesions and shows high value. This parameter is used in our study to discriminate between benign and malignant lesions and helps in reducing unnecessary interventions.

CONSENT

All the authors declare that 'written informed consent was obtained from the patient for publication of this paper and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

ACKNOWLEDGEMENT

We gratefully acknowledge Dr. Vijay Dhasmana, the Honorable Vice Chancellor of Swami Rama Himalayan University, Dehradun, India, for his support and for providing the necessary facilities. We are thankful to Prof (Dr) Samuel Doraisamy and Prof. (Dr) Shailender Raghuvanshi, Deparment of Radiodiagnosis, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun for encouraging and facilitating the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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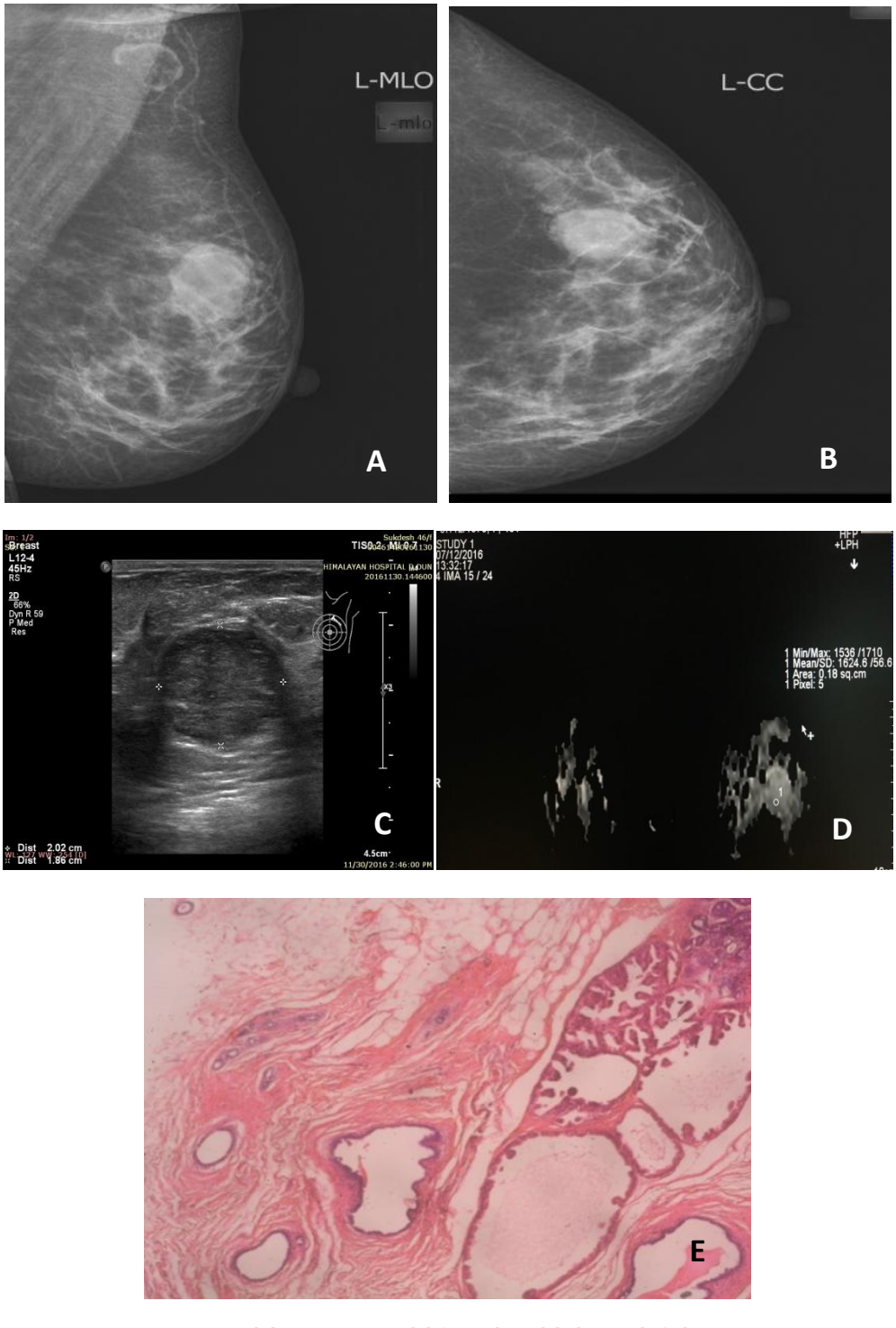
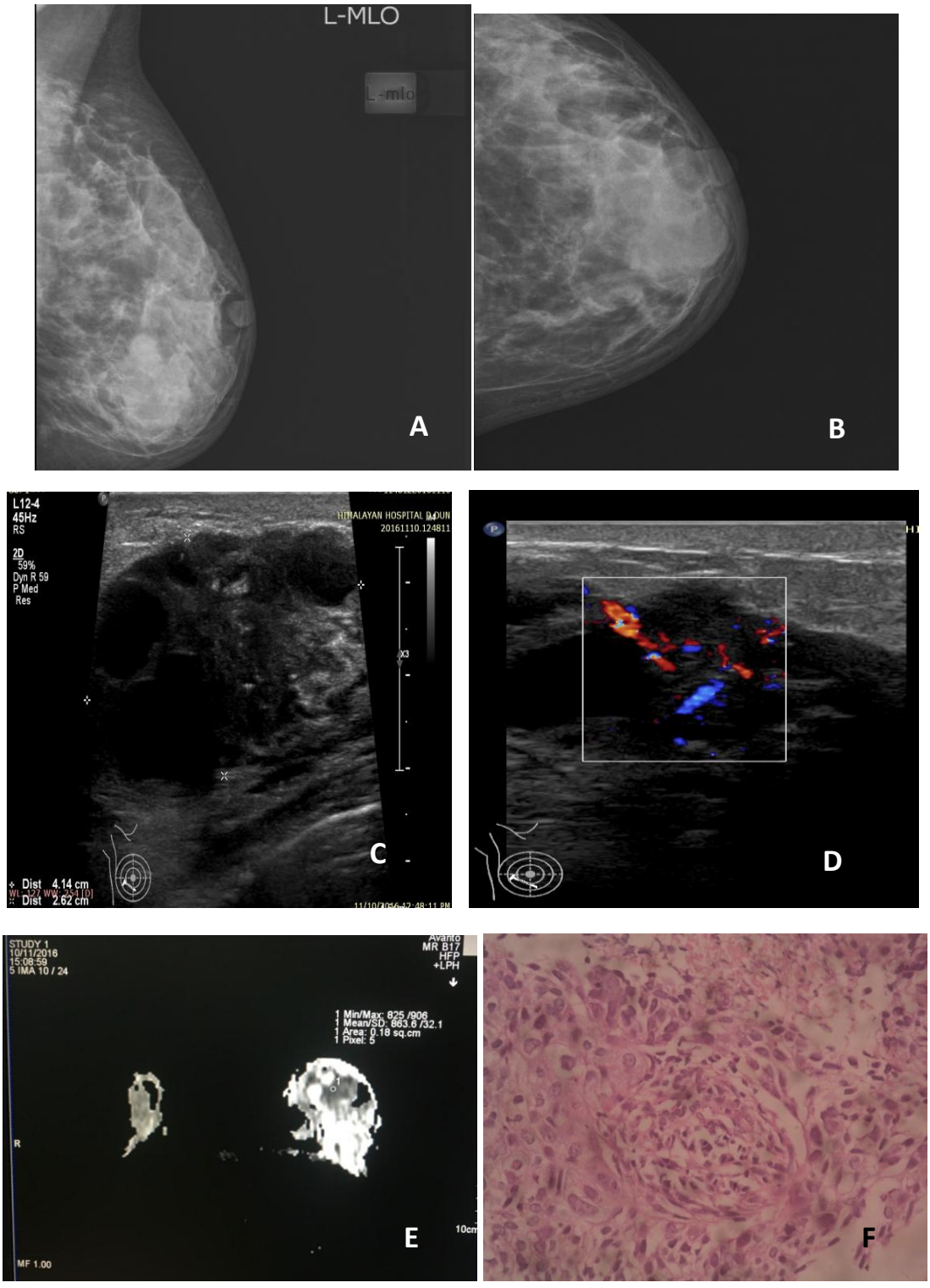
Appendix A. Cases



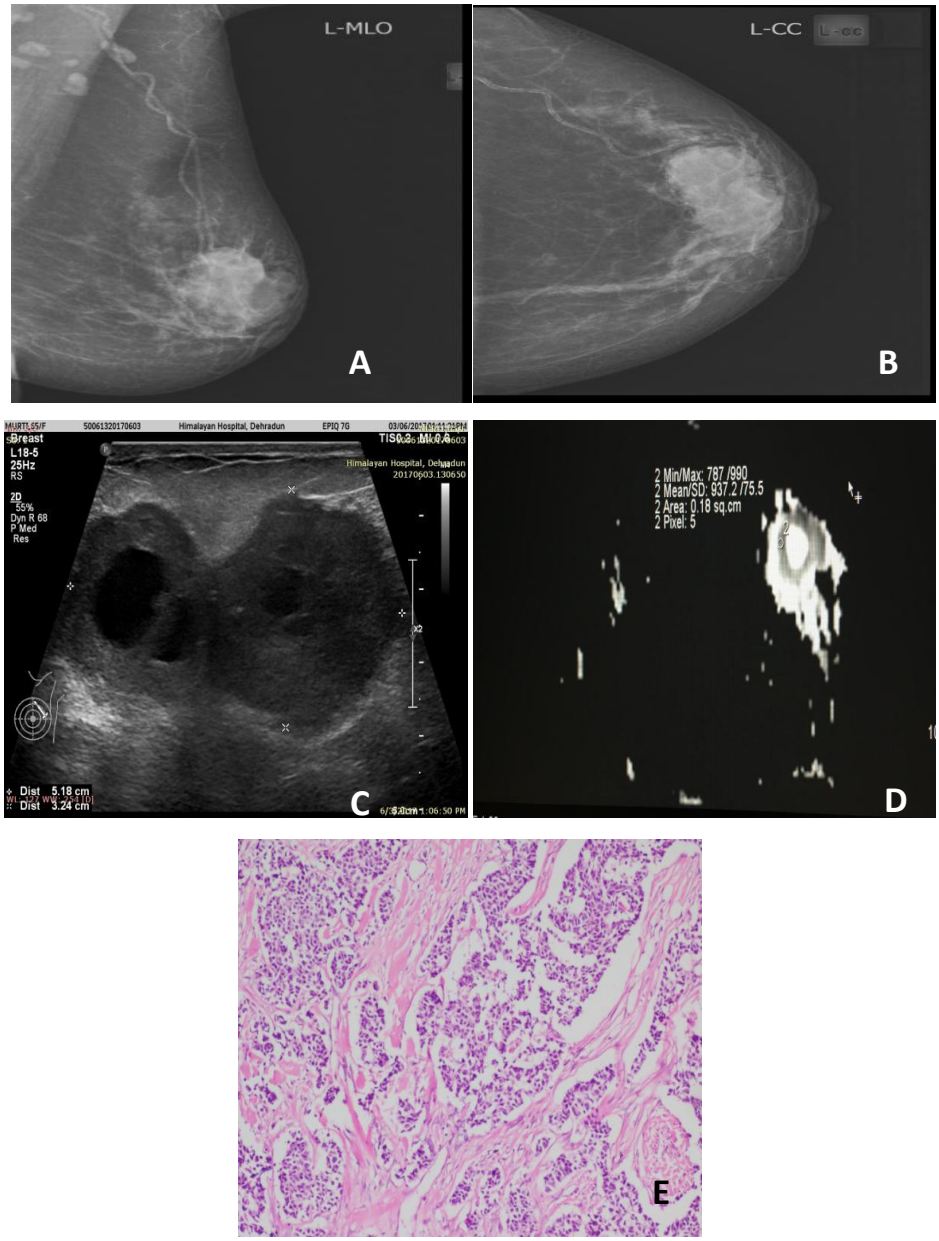
A.1. Case (1). 46 years old female with lump left breast

Mammography, (A) MLO and (B) CC show soft tissue density mass in upper outer quadrant with smooth margins. (C)Ultrasound shows hypoechoic mass with posterior wall enhancement in upper outer quadrant, categorised as BIRADS category III on combined mammography and sonomammography. (D) DWI MRI with ADC mapping at b= 800 and ADC value of 1.6x 10-3. (E) Histopathology H and E section reveals fibroadenoma (10X).



Case 2. 35 years old female with lump left breast breast

Mammography, (A) MLO and (B) CC show soft tissue density mass in lower inner quadrant with ill defined margins. (C) and (D)Ultrasound shows complex mass with solid and cystic areas, solid component shows vascularity on color doppler and calcification, categorised as BIRADS category IVC on combined mammography and sonomammography. (E) DWI MRI with ADC mapping at b= 800 and ADC value of 0.8x 10-3. (F) Histopathology H and E section reveals infiltrating ductal carcinoma (40 X).



Case 3. 65 years old female with painless lump left breast.

Mammography, (A) MLO and (B) CC show soft tissue density mass in upper outer quadrant with irregular margins. (C) Ultrasound shows hypoechoic mass with anechoic areas within and smooth lobulated margins in upper outer quadrant, categorised as BIRADS category IVC on combined mammography and sonomammography. (D) DWI MRI with ADC mapping at b= 800 and ADC value of 0.9x 10-3. (E) Histopathology H and E section reveals infiltrating ductal carcinoma (40X).

Peer-review history:
The peer review history for this paper can be accessed here:
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