의학석사 학위논문

Quantification of Volumetric Breast Density using MRI Data: Comparison between 3 Representative Slice Method and Whole Breast Density Measurement

MRI 데이터에서 체적 유방 밀도의 측정: 3 대표 슬라이스 방법 및 전체 유방 밀도 측정의 비교

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서울대학교 대학원
의학과 (영상의학)
사비어

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Quantification of Volumetric Breast Density using MRI data: Comparison between 3 Representative Slice Method and Whole Breast Density Measurement

by
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A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Philosophy in Medicine at Seoul National University College of Medicine

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Approved by Thesis Committee:

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Abstract

Introduction: Volumetric breast density measured from breast MRI is more suitable for density analysis than mammographic density. However, measure ment of volumetric percentage density (VPD) from MRI of the whole breast is time consuming and impractical to apply for large breast MRI databases. The purpose of this study was to determine whether VPDs measured from 3 representative slices of MRI correlates with the VPDs measured from the whole breast.

Methods: A total of 151 breast cancer patients who underwent bilateral breast MRI were included. Pre-contrast, T1 weighted, fat suppresse d, sagittal images were used for VPD measurement. VPD of the contralateral normal breast was measured using MIPAV software (Version 5.3.3, NIH, USA). The borders of the breasts were outlined manually and fibroglandular tissue was segmented from the fat tissue using Fuzzy C-Means algorithm. The number of slices ranged from 30 to 72 on measuring VPD from the whole breast. The 3 representative slices selected for density measurements were the middle (n), (n+15)th and (n-15)th slices. VPD was measured from the whole breast as well as from 3 representative

slices for each patient and the results compared using t-test, intra-class correlation coefficient (ICC) and coefficient of variation (CV). The average time taken to measure each breast by each method was calculated.

Results: Mean VPD measured from 3 representative slices was not different from that measured from the whole breast (24.32% vs. 24.55%, p = 0.39; mean absolute difference = 2.72). The CV was 9.74%. VPDs measured by the two methods showed excellent agreement (ICC = 0.96; 95% CI = 0.95-0.97). Average time taken to measure VPD by 3-slice method was significantly lower than that by the whole breast measurement (133 sec vs. 572 sec; $p < .0001$). The mean absolute difference in VPD between the two methods was not significantly different for fatty (<20% VPD) and dense (>40% VPD) breasts (2.37% vs. 2.62%; p = 0.67). CV was higher for fatty breasts (15.33%) than dense breasts (5.11%).

Conclusions: The 3 slice MRI VPD is in excellent agreement with the VPD measured from the whole breast MRI and is less time consuming.

Keywords: breast, density, MRI, volumetric

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List of Abbreviations

TBV : Total Breast Volume

FGV : Fibro-glandular Volume

VPD : Volume Percentage Density

PD : Percentage Density

ROI : Region Of Interest

FCM : Fuzzy C-Means

MIPAV : Medical Image Processing And Visualization

ICC : Intra-Class Coefficient

CV : Coefficient of Variation

Quantification of Volumetric Breast Density Using MRI data: Comparison between 3 Representative Slice Method and Whole Breast Density Measurement

INTRODUCTION

Breast density measured from mammograms is an established and important risk factor for development of breast cancer [1-8]. High mammographic breast density (>50%) has been associated with a two- to six-fold increase in breast cancer risk [9]. Only two other factors, namely the age of the patient and mutations in genes BRCA1 and BRCA2 are associated with a higher risk for breast cancer [10]. Changes in breast density over time have been correlated to changes in cancer risk [8, 11, 12]. So it is becoming increasingly important to measure the breast density of women.

Since a mammogram is a projection image, different body position, level of compression, and the x-ray intensity may lead to a large variability in the density measurement. Breast MRI provides strong soft tissue contrast between fibro-glandular and fatty tissues, and three-dimensional coverage of the entire breast, thus making it suitable for density analysis, as demonstrated in previous studies [13-20].

Volumetric breast density measured from breast MRI is more suitable for density analysis than mammographic density. But such measurement has a few drawbacks [20] such as (1) Requirement of a certain level of user interaction to demarcate the breast boundaries and apply threshold values (2) the long duration of time it takes to make the measurements for a single case, making it extremely time consuming and impractical to apply for large breast MRI databases.

One of the ways to reduce the time taken for measurement is to make the measurements from a limited number of slices. But previous studies which aimed at measuring the VPD from a limited number of slices [17] have not been successful and were not suitable for analysis of density changes over time. Measurement of breast density from limited slices from the center of the breast led to overestimation of breast density owing to the normal distribution of fibro-glandular tissue within the breast, which is concentrated more in the middle of the breast than at the peripheries. Taking this into account, we aimed to select a limited number of slices which would provide a better representation of the entire volume and the distribution of fibro-glandular tissue in the entire breast.

MATERIALS AND METHODS

Subjects

From the breast MRI database of our institute, we selected a total of 151 breast cancer patients who had undergone routine pre-operative bilateral breast MRI during December 2011 to May 2012. The age of these patients ranged between 29 to 78 years (Mean = 47.65, Median = 48). Only the MRI data from the contralateral normal breasts were used for VPD measurements. Hence we measured the breast density from only one breast of each patient. Pre-contrast, T1 weighted, fat suppressed, sagittal images were used for our study.

MRI Protocol

The MRI images used for the study were pre-contrast, T1 weighted, fat suppressed, sagittal section images. MR imaging was performed with the patients placed in a prone position. MR examinations were performed using a 1.5-T scanner (Signa; General Electric Medical Systems, Milwaukee, WI) with a dedicated breast coil (8-channel HD breast array, General Electric Medical Systems). Dynamic contrast-enhanced examinations were performed which included one pre-contrast and five post-contrast bilateral sagittal image acquisitions using a fat-suppressed T1-weighted three-dimensional (3D) fast

spoiled gradient echo sequence (TR/TE, 6.2 sec/2.2 sec; 320mm x 256mm matrix; flip angle, 10˚; field of view, 200mm x 200mm; 1.5-mm slice thickness, no gap). Only the images from the contra-lateral normal breast of each patient were used for the analysis.

Software

The Total Breast Volume (TBV) and the Volume Percentage Density (VPD) of the contralateral normal breast was measured using the MIPAV (Medical Image Processing, Analysis and Visualization) software package (Version 5.3.3, NIH, USA). MIPAV is a freely available semi-automated image segmentation software package. It uses the Fuzzy C-Means (FCM) algorithm for segmentation of the breast tissue into fatty and fibro-glandular tissues [17, 21, 22]. The borders of the breast were outlined manually and then segmentation of the two tissue types was performed using FCM algorithm.

MEASUREMENT

The measurement of Breast VPD is a two-step process. The total breast volume and volume of the fibro-glandular tissue are measured separately and the VPD is then derived from the two values. The overall method is similar to that described in previously published articles using different software packages [20, 23, 24]. The measurements were done by a single researcher

with more than a year's experience in measuring VPD using the MIPAV software.

Whole Breast VPD measurement

Sagittal, pre-contrast, fat suppressed, T1 weighted images were used for measurement. First, the outline of the breast (ROI) was drawn manually in the MRI slice showing the highest projection [25]. The ROI was then copied to all the slices of interest in the sagittal stack of images. Since the shape of the breast does not change considerably between contiguous slices, minor manual adjustments were made as necessary so as to separate the breast from the chest wall. The total volume of the breast was then measured from the ROIs in all the slices of interest.

The number of the slices of interest ranged from 32-72 for each breast.

To measure the fibro-glandular tissue volume, the same ROIs were used. Fuzzy C-Means Algorithm was applied to segment the fibro-glandular tissue from the surrounding tissue. Usually, three breast tissue regions or classes were defined for each breast under study depending on the MRI volume and its content when applying FCM algorithm, to segment the whole breast volume into three tissue groups. A suitable threshold was then applied and the

fibro-glandular tissue volume was calculated. The VPD was then calculated as the ratio of the FGV to the TBV.

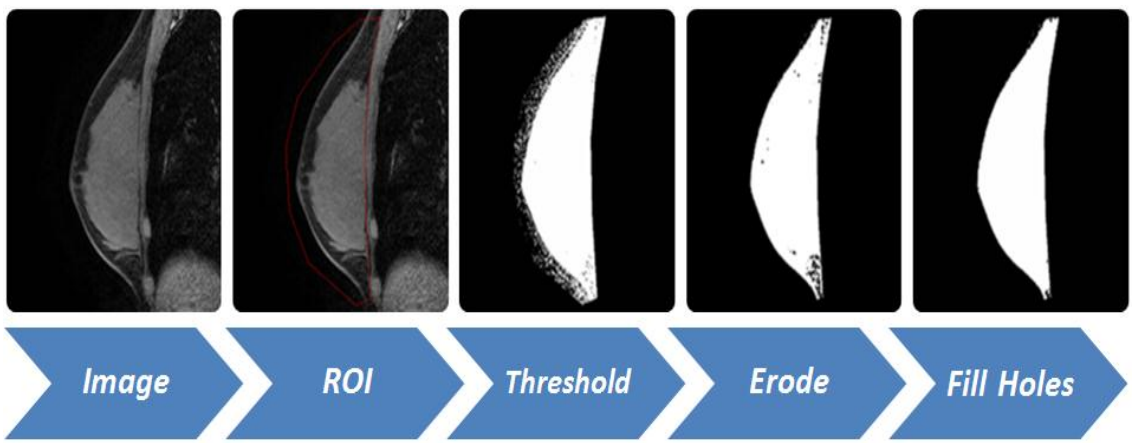

Figure 1. Total Breast Volume measurement. TV = White Pixel Count X Pixel Size X Slice thickness, of all ROIs in all Slices of Interest

3 Slice VPD measurement

The normal pattern of distribution of fibro-glandular tissue within the breast is such that it is concentrated more in the middle of the breast than at the peripheries. Taking this into account, we aimed to select three representative slices which would provide a better representation of the distribution of fibro-glandular tissue in the entire breast.

Selection of the 3 representative slices

For the 3 slice method, VPD was calculated from three representative slices for each breast. The slice in the middle in the sagittal stack of images in a MRI study of one breast was considered as the middle slice (n). We did not select the middle slice in relation to the nipple as the slice through the nipple is not always the middle slice in MRI studies.

For the selection of the suitable slices on either side of the middle slice, we considered the 5^{th} ($n\pm5^{th}$), 10^{th} ($n\pm10^{th}$) and 15^{th} ($n\pm15^{th}$) slices on either side of the middle slice. We measured the breast density values from 10 selected cases with different parenchymal patterns and a broad range of breast densities. From our measurements, the VPD values measured from the n^{th}, (n+15) and (n-15) slices were more closely correlated with the whole breast density values, than the measurements done with the ($n\pm5^{th}$) and n($\pm10^{th}$) slices.

The 3 slices selected for each breast were the middle slice (n^{th} slice) and the 15^{th} slice medial to and lateral to the middle slice ($n+15^{th}$ and $n-15^{th}$ slices).

Table 1. Comparison of Measurements with different representative slices

	N ±5th Slice	N ±10th Slice	N ±15th Slice
Correlation Coefficient (***r***)	0.9321 (0.7323-0.9842)	0.9532 (0.8094-0.9892)	0.9777 (0.9056-0.9949)
Two-tailed probability (***p***)	0.0169	0.0353	0.1959
Coefficient of Variation	18.02%	14.40%	8.81%
ICC	0.8854 (0.3770-0.9741)	0.9309 (0.6393-0.9840)	0.9756 (0.9080-0.9938)

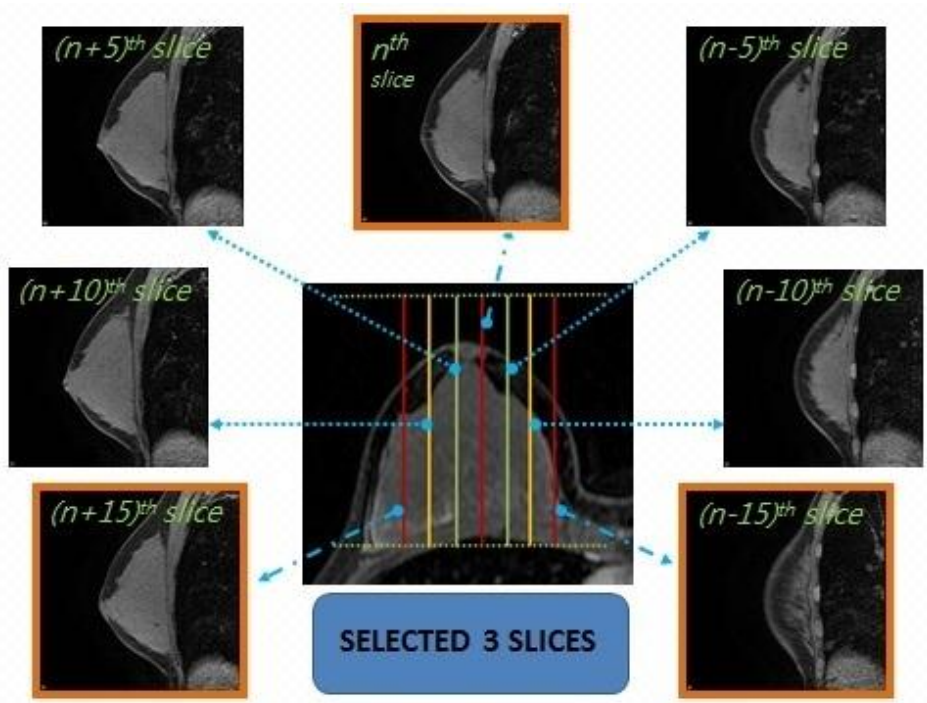

Figure 2. Selection of the 3 slices of interest

The measurement of breast density was done in the same way as the whole breast VPD measurement using the same ROIs but only for the three selected slices.

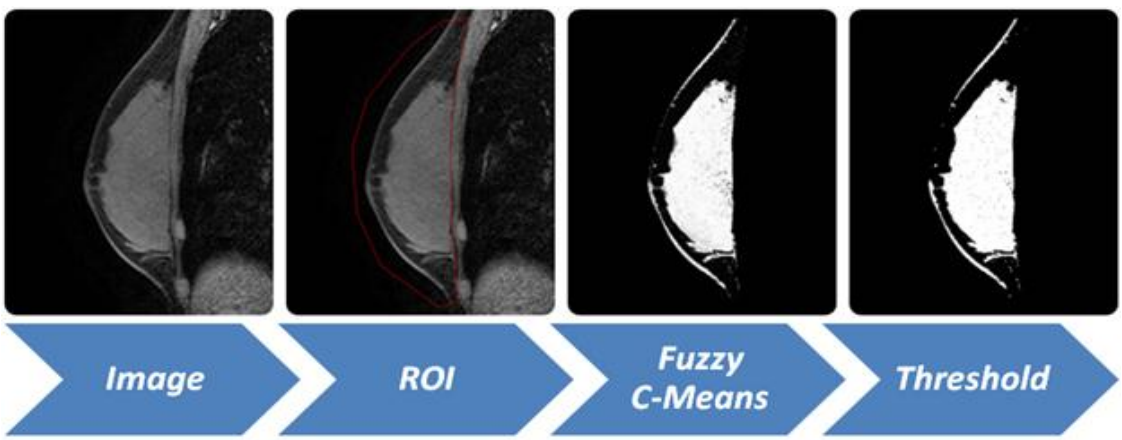

Figure 3. Fibroglandular tissue volume measurement. FGV = White Pixel Count X Pixel Size X Slice thickness, of all ROIs in all Slices of Interest

Selection of threshold value:

The selection of appropriate threshold value during the measurement of fibro-glandular volume is highly subjective and is a probable cause for significant intra and inter-observer variation. In our analysis, we found a threshold value of 0.4 to be suitable for most images with adequate fat suppression. For images with poor fat suppression, we altered the threshold values according to the quality of each set of MRIs.

Figure 4. Samples of MRI images with poor fat suppression

Calculation of total breast volume from 3-slice volume:

We tried to assess whether any linear correlation existed between the total breast volume and the volume of the 3 selected slices in the 3-slice method and whether it was possible, by regression analysis, to derive a formula to calculate the total volume of the breast from the 3-slice volume.

Comparison of 3-slice VPD (with middle slice '*n*') with 3-slice VPD with the middle slice containing the nipple

We selected 50 cases at random and measured the 3-slice VPD by selecting the middle slice as that showing the nipple, to determine whether measurements made by selecting the middle slice showing the nipple showed stronger or weaker correlation with the 3-slice VPD measurements with the middle slice as '*n*'.

STATISTICAL ANALYSIS

To assess the performance of the 3 slice method, we analyzed the obtained results statistically. The level of agreement between the measurements from the 3-slice method and the whole breast VPD measurement was assessed by performing the Intra-class correlation test to assess the correlation between the measurements, and also by measuring the Coefficient of Variation (CV), to analyze the degree of variation between the two methods.

The patients were further classified in to three groups based on the obtained VPD values into three categories, <20%, 20-40% and >40% and the correlation between the two methods was assessed to assess whether the agreement between the two methods varied depending on the VPD of the breast. We grouped the VPD results in this way as very few patients have VPD of more than 40% from breast MRI measurements.

To assess the inter-observer reproducibility of the VPD measurements by the 3-slice method, a random sample of 30 cases was selected and the 3-slice VPD measurements done by two other trained radiologists with prior experience in measuring VPD using the MIPAV software. From their measurements, the inter-observer reproducibility was assessed by calculating

the Intra-class correlation coefficients, coefficients of variation (CV) and the Inter-observer kappa (*k*) statistic.

To assess whether any linear relationship existed between the total breast volume and the 3-slice volume, we calculated the correlation coefficient. We then calculated, by regression analysis, a formula to calculate the total breast volume from the 3-slice volume. We then selected 15 cases in which the n^{th} slice coincided almost exactly with the anatomical middle slice of the breast and calculated the total breast volume and the 3-slice volume and assessed whether there was a linear relationship between the two sets of values.

The measurement time for each breast by both methods was measured and the mean time was calculated for each method and the results compared.

All statistical analyses were done using IBM SPSS Statistics software (version 19) and MedCalc software (Version 12.1.4.0).

RESULTS

The two methods of measurement of VPD were not significantly different from each other. The mean VPD measured from 3 representative slices was not significantly different from that measured from the whole breast (24.32% vs. 24.55%, $p = 0.39$). The mean absolute difference of VPD values between t he two methods was 2.45%. (Table 1.)

The two methods showed excellent agreement (ICC = 0.9617; 95% CI = 0.947 6 - 0.9721). The coefficient of variation was 9.74%.

The two methods showed better agreement for denser breasts (>40% VP D; ICC = 0.8183) than for fatty breasts (<20% VPD, ICC = 0.7048).

The mean measurement time for 3 Slice method was significantly lower than t hat for Whole Breast VPD measurement (133 sec vs. 572 sec; $p < 0.0001$). The 3-slice method reduced the measurement time by a factor of **4**.

For inter-observer reproducibility, the Intra-class correlation coefficients for the 3-slice VPD measurements ranged between 0.94 and 0.98. The Coefficients of variation ranged between 5.1% and 9.6%. The Kappa test values ranged from 0.807 and 0.828.

Table 2. Comparison of 3-Slice VPD with Whole Breast VPD

STATISTICAL TEST	Whole Breast VPD (%)	3 Slice VPD (%)
Mean VPD	24.55%	24.32%
Mean Measurement Time	572 sec	133 sec
Mean Absolute Difference	2.45%	
Coefficient of Variation	9.74%	
Intra-observer Agreement	0.9131 (0.7530-0.9672)	0.9294 (0.8159-0.9724)

Table 3. Difference between the 2 methods based on VPD

	Whole Breast VPD (%) Vs. 3 Slice VPD (%)		
VARIABLE	0-20% (63 cases)	20-40% (72 cases)	>40% (16 cases)
Mean Absolute Difference	2.37	3.06	2.62
Coefficient of Variation	15.33%	9.06%	5.11%
Standard Deviation	3.02	3.49	3.64

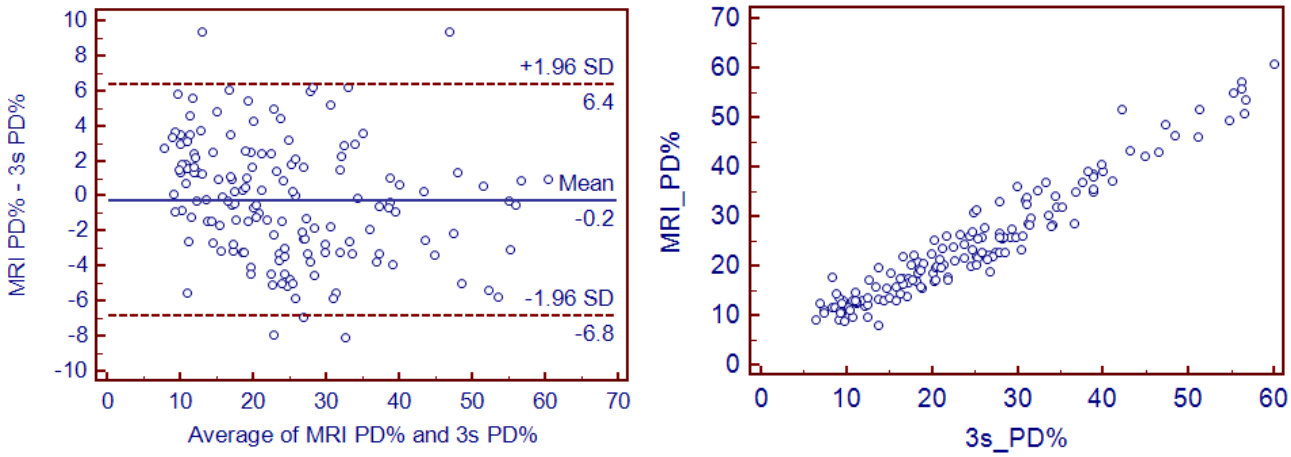

Figure 5. Bland-Altman plot to analyze the agreement between the two methods

The total volume of the breast and the 3-slice volume showed a strong correlation, and an almost linear relationship when the two sets of values were plotted on a graph. Figure 6 shows the linear relationship between the total breast volume and the 3-slice volume. The correlation coefficient (r) was 0.9670 ($p < 0.0001$; 95% CI = 0.9548 – 0.9760). We then selected 15 cases in which the n^{th} slice coincided almost exactly with the anatomical middle slice of the breast and calculated the total breast volume and the 3-slice volume. The total breast volume and the 3-slice volume for the 15 selected cases showed strong correlation (r) of 0.9530 ($p < 0.0001$; 95% CI = 0.8611 – 0.9846). We also tried to factor in the number of slices included in the measurement of each case to determine whether the results were better. After

factoring in the number of slices, the correlation was weaker (r = 0.5639; p .0286; 95% CI = 0.07262 – 0.8350) and the results were significantly different from each other.

The correlation between the total and 3-slice volumes from the 15 selected cases was not found to be significantly better than the correlation between the total breast volumes and 3-slice volumes for the entire data set. Figure 7 shows the correlation between the total breast volume and the 3-slice volume for the 15 selected cases. We obtained a formula for calculation of the total breast volume from the 3-slice volume, by logistic regression using half of the sample cases (75 cases) and obtained a formula of:

TOTAL BREAST VOLUME = (3-Slice Volume x 21.567) - 89700

We applied this formula to the rest of the sample and calculated the correlation of the calculated total breast volume (from the 3-slice volume using the above derived formula) and the measured total breast volume. The two sets of values showed good correlation (r = 0.9734, 95% CI = 0.9582-9831; $p < 0.0001$).

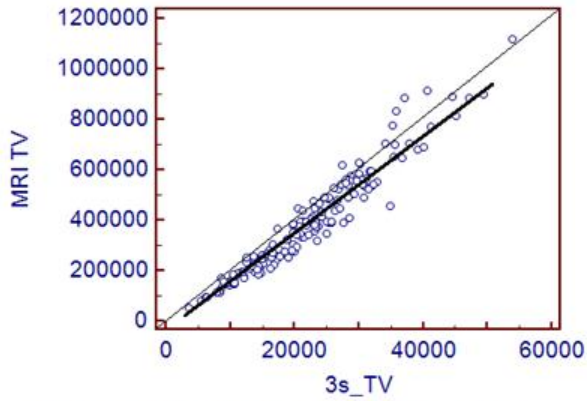

Figure 6. Comparison between the total breast volume and the 3-slice volume

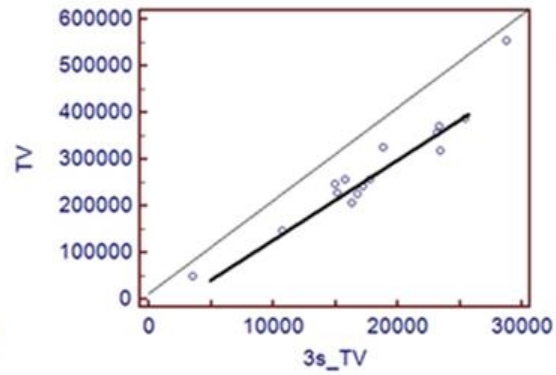

Figure 7. Comparison between the total breast volume and the 3-slice volume for 15 selected cases

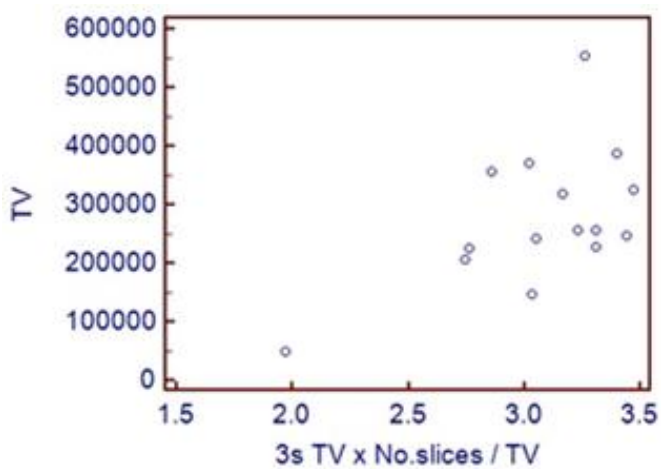

Figure 8. Comparison between the total breast volume and the 3-slice volume for the 15 selected cases after factoring in the number of slices

To analyze whether the correlation between the total breast volume and the 3-slice volume varied depending on the size of the breast, we classified the cases into four categories based on the total breast volume and calculated the correlation coefficient for the two sets of values. The correlation was strong for small breasts (size < 250 cm^3, $r = 0.9209$, $p < 0.0001$). For very large breasts (size >1000 cm^3) the values were significantly different from each

other ($r = 0.7087$, $p = 0.0218$).

Table 4. Comparison of Total Breast Volume with 3-slice Volume

	Total Breast Volume (cm^3) Vs.3 Slice Volume (cm^3)			
VARIABLE	<250cm^3 (44 cases)	250-500cm^3 (66 cases)	500-750cm^3 (31 cases)	>750cm^3 (10 cases)
Correlation Coefficient				
r	0.9209	0.7938	0.7539	0.7087
95% CI	(0.859-956)	(0.683-869)	(0.545-874)	(0.142-925)
p	<0.0001	<0.0001	<0.0001	0.0218

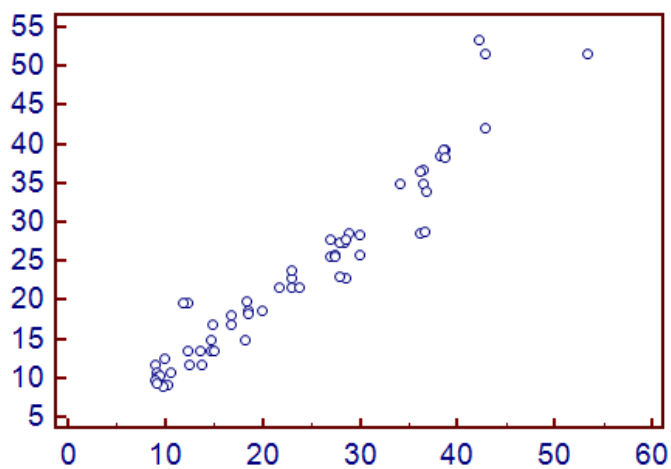

Figure 9. Scatter diagram showing the correlation between the MRI VPD and 3-slice VPD for the cases measured for reproducibility and the corresponding original measurements

To determine whether measurements made by selecting the middle slice showing the nipple showed stronger or weaker correlation with the 3-slice VPD measurements with the middle slice as '*n*', we selected 50 cases at random and performed the 3-slice VPD measurements in two ways – (1) with the middle slice as 'n', the middle slice in the MRI study; and (2) selecting the slice in which the nipple is seen most prominently as the middle slice. We then compared the results with the whole breast VPD. The 3-slice VPD measurements made with the middle slice 'n' showed a slightly better correlation than the 3-slice VPD measurements made with the middle slice with the nipple (Correlation coefficient $r = 0.9620$ vs. 0.9441)

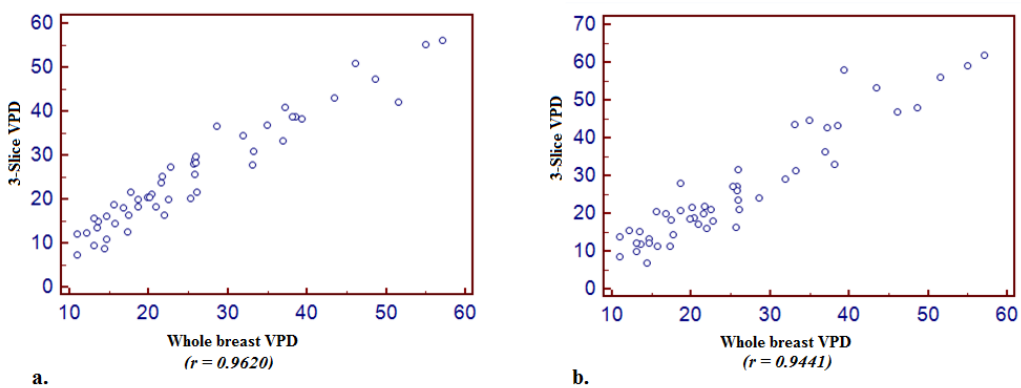

Figure 10. Comparison of 3-slice VPD measurements with middle slice '*n*' (a) and middle slice in which the nipple is seen most prominently (b).

DISCUSSION

This paper described a new semi-automated method of measurement of fibro-glandular tissue of the breast from MRI images which is both reliable and time saving. Pre-contrast, T1 weighted, pre-contrast, sagittal section MRI images of the contralateral breast are routinely obtained from patients in our hospital with confirmed breast lesions as part of pre-operative screening of the contralateral breast. These images were suitable for the study as the fat suppression was adequate. The time taken to measure the VPD from all the slices of a MRI study is time consuming and not practical for screening purposes. In this aspect, our method is quicker and makes measurement of VPD from MRI data more feasible.

Two types of error arose in or study. Firstly, in the case of extremely fatty breasts, on application of FCM algorithm, the pixel count is overestimated and the threshold had to be altered depending on the quality of each image. But the final measurements were well within acceptable limits. Also, since the risk of breast cancer is low in patients with fatty breasts, this issue would not be of much concern. Secondly, in some MRI studies, the fat suppression is not complete especially in the upper regions of the breast and this would again lead to overestimation of VPD measurements, although still the final results

were within acceptable limits.

By selecting just 3 slices, we also reduce the possibility of errors that would occur if we had the measure the VPD from all the slices in the MRI study. In this study, we did not exclude the skin during measurements, but the VPD of the breast excluding the skin can be calculated as performed by other researchers [31]. In our opinion, inclusion of skin is not a major factor during VPD measurement, especially in dense breasts. We have also observed a linear correlation between the total volume of the breast and the volume measured from the 3 representative slices and derived a formula by regression analysis to calculate the total volume of the breast from the 3-slice volume data.

At present, only mammograms are routinely performed as part of screening studies. Since breast density is a major risk factor, MRI would be more suitable for screening purposes. With the advent of less expensive machines and more studies, MRI density measurements should become routine. Until a fully automated method of measurement of breast is developed, our method would be a useful tool in measuring VPD from breast MRI studies. This concept can also be applied to automated studies [26-30] to limit the number of slices measured and therefore increase reliability.

CONCLUSION

Breast density assessment from MRI is a more accurate representation of the actual breast density than the density values obtained from mammograms. Our method of measuring the volume percentage density using 3 representative slices instead of the whole breast helps us in saving measuring time and thus makes it more practical and possible to apply to large databases of breast MRI. The 3-slice method also reduced the measurement time by a factor of 4. The reduction in measurement time would be even greater in western population where the average size of the breasts is larger compared to the population included in our study. We have also shown that it is possible to calculate the volume of the entire breast from the 3-slice volume with acceptable accuracy.

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국문 초록

서 론: MRI를 이용하여 유방 치밀도를 정량화 하는 방법은 맘모그래프를 이용한 유방 치밀도의 정량화 방법보다 유방 치밀도에 대한 정확한 측정 결과를 얻을 수 있다. 그러나 유방 전체에 대한 치밀도 정량화 방법은 분석 시간 소요가 많아 임상에서 실질적으로 이용되기는 어렵다. 본 연구의 목적은 대표 표본을 이용한 정량화 방법이 유방 전체를 분석하여 얻은 치밀도 볼륨 백분율 값에 상응하는 측정 값을 얻을 수 있는지 확인하는 것이다.

방 법: 치밀도 볼륨 백분율 분석을 위해 총 151명의 유방암 환자 MRI 영상을 이용하였다. MRI 프로토콜은 조영 증강 없이 지방 억제 기법을 이용한 T1 강조 시퀀스를 사용하였으며 유방의 시상 면에 대하여 얻은 영상을 사용하였다. 치밀도 볼륨 백분율은 MIPAV 소프트웨어를 이용하여 얻었다. 유방 경계면은 수동으로 지정하였으며 지방 조직으로부터 섬유-유선 조직 부위의 분리는 Fuzzy C-Means 알고리즘 기법을 이용하였다. 유방 전체 치밀도 볼륨 백분율 값은 MRI 영상의 30에서부터 72번까지의

표본 분석으로 얻었고 대표 표본을 이용하여 얻은 치밀도 볼륨 백분율 값은 전체 표본의 정중앙 표본과 그 표본을 중심으로 전, 후 15번째 해당하는 표본의 분석을 통하여 얻었으며 통계 분석에는 평균 값 분석, 급내 상관 계수 분석, 변동 계수 분석을 사용하였다. 두 가지 정량화 방법에 소요된 평균 분석 시간을 측정하였다.

결 과: 통계적 분석 결과, 3장의 대표 표본을 이용하여 얻은 유방 치밀도 볼륨 백분율 값은 유방 전체의 정량화를 통해 얻은 치밀도 볼륨 백분율 값과 다르지 않았다 (24.32% vs. 24.55%, P=.39, 절대 평균 편차=2.72). 변동 계수 값은 9.74%를 보였다. 급내 상관 계수 분석 값은 0.96 (신뢰구간 0.95-0.97)이었다. 분석에 걸린 시간을 비교한 결과는 대표 표본 정량화 방법이 전체 정량화 방법에 비하여 8분 가량 적게 걸렸다 (133 초 vs. 572 초; P <0.0001). 치밀형 유방과 지방형 유방 내에서의 두 방법 간의 절대 평균 편차 값은 다르지 않았으나 (2.37% vs. 2.62%; P=0.67), 변동 계수 값은 지방형 유방 분석 결과가 치밀형 유방 분석 결과보다 높았다 (15.33% vs. 5.11%).

결 론: 대표 표본 분석 방법을 이용한 유방 치밀도의 볼륨 정량화는 전체 표본 분석

방법을 이용한 정량화 결과에 비견하는 분석 결과를 얻을 수 있었다. 결론적으로 대표 표본 분석 방법은 분석 시간은 적게 걸리면서도 전체 표본 분석과 유사한 수준의 정확성을 갖고 있음을 확인할 수 있었다.