

Original article

Volumetric kinetic assessment in dynamic contrast enhanced-MRI (DCE-MRI) of breast cancer: A new method for evaluation of whole tumor enhancing pattern

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Background: At present, dynamic contrast enhancement-MRI (DCE-MRI) has an immense role in the diagnosis and evaluation of the extent of breast cancer. As for diagnosis, evaluation of patterns of kinetic enhancement in dynamic contrast studies is performed after gadolinium injection. Since each breast cancer has internal pathophysiological variety, the kinetic enhancement patterns are supposed to be varied within each mass as well.

Objective: This study aimed to investigate the characteristics and additional value of volumetric analysis of kinetic enhancement patterns on DCE-MRI in evaluating breast cancer in Thai patients.

Methods: We retrospectively studied 52 women, and 67 lesions which were histologically proven breast cancers, using software of breast MRI and generating 3D volumetric voxels covering the total tumor volume in DCE-MRI performed between January 2014 and December 2017. Measurement of enhancement patterns was categorized by software into the percentage of part of the tumor which enhanced in each pattern. Consequently, percentages of enhancement in different type were collected and allocated into type I (persistent), type II (plateau), and type III (washout) enhancements. Analysis of the kinetic pattern was done together with subgroup analysis of each type of tumor (IDC, DCIS, and other subtypes of breast cancer), as well as tumor grades.

Results: The mean percentages of enhancement pattern in kinetic assessment by 3D voxels of tumor volume showed the most common type I enhancement (72%), followed by type III enhancement (14.3%) and type II enhancement (13.7%). Subgroup analysis showed similar higher type I enhancement in both IDC (68.3%) and DCIS (81.3%). However, there were slightly higher suspicious malignant patterns of enhancement (31.7% type II and 18.7% type III enhancements) in IDC than DCIS, as well as in high tumor grade (grade 3) than low tumor grade (grade 1) (37% type II and 30.7% type III enhancements), but there were no significant differences.

Conclusion: Volumetric analysis showed heterogeneity of kinetic curve enhancement patterns inside each tumor. That means each tumor has a variety of enhancement patterns in itself and dissimilarity with others. The majority of patterns were found as type I enhancement which was not particular for malignant, whereas there was only 28% with suspicious kinetic enhancement patterns (type II and type III enhancements). The slightly higher suspicious malignant patterns of enhancement (type II and III enhancements) in IDC more than DCIS along with high tumor grade was observed, deprived of statistical significance.

Keywords: Breast MRI, breast cancer, volumetric kinetic assessment, color coded breast MRI.

Nowadays, the incidence and prevalence of breast cancer in many countries in the worldwide has been increasing, and is now the most common in all Asian woman cancer. The highest incidence in Asian women is at 40 - 50 years, whereas 60 - 70 years is most

common in Western Countries.^(1, 2) However, the mortality rate of breast cancer in Asian countries is higher, this may result from advanced disease progression at the first diagnosis, type/grade of tumor, and high severity in young breast cancers due to delayed diagnosis.⁽³⁾ Currently, dynamic contrast enhancement-MRI (DCE-MRI) has an immense role in diagnosis and evaluation of the extent of breast cancer detecting gadolinium enhancement in the abnormal angiogenesis of tumor vessels in dynamic contrast study, apprising restricted diffusion on diffusion weight imaging (DWI) and value of tumor metabolite (choline) in MR spectroscopy are the principals of DCE-MRI.

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Thus, DCE-MRI is now believed to be the most effective diagnostic modality correlated with the clinical information of tumor patients.⁽⁸⁾

Since each breast cancer has internal pathophysiological variety, the kinetic enhancement patterns also vary within each mass.^(4,5) Therefore, if we created sampling only a part of the mass to perform kinetic time curve, it could instigate error of the results in both inter- and intraobserver reliabilities.^(6,7) Accordingly, this study aimed to find the reliable method of kinetic assessment by using volumetric measurements of the whole lesion of breast cancer in DCE-MRI.

Material and methods

Population

This retrospective study of new or recurrent breast cancer patients examined breast DCE-MRI at affiliated educational medical centers in Thailand. Four hundred and fifty-nine examinations that underwent breast DCE-MRI examinations from January 2014 to December 2017 were reviewed. One hundred and one studies were included because of pathological-proven breast cancer by a pathologists after definitive surgery, identified by size, type and tumor grade. We excluded cases of prior received neoadjuvant chemotherapy, excisional or incisional biopsy, and surgery at the site of interesting and breast implantation. Other exclusion criteria were non-mass enhancement with faint contrast enhancement and the region of interest on post-processing DCE-MRI of less than 5 mm (solid portion) in minimal dimension. Fifty-two remaining patients, and 67 lesions of breast cancers were included.

MRI technique and analysis

MRI examination with 1.5 tesla (Magnetom Espree, Global Seimens Healthcare, Germany) was used. Patients were in a prone position and using 6-channels bilateral breast surface coils.

The pre-contrast sequences were performed by axial T1-weighted images with fat suppression, axial T2-weighted images, axial T2-weighted images with STIR, and coronal T1-weighted images.

The post-contrast enhanced sequences were performed by using the protocol as follows: T1-weighted images with fat suppression, TR/TE

of 4.75/1.45, flip angle of 10°, the field of view of 340 mm, matrix of 336 × 448 and 1.30 mm slice thickness. The dynamic contrast enhancement sequences were performed before and after injection of 0.1 mmol/kg gadopentetate dimeglumine (Gadovist) at 60, 120, 180, 240, 300, and 360 seconds. Our protocol was obtained by post-processing subtracting images and computer-aided detection (CAD) with color coding assessment. The magnetic resonance spectroscopy (MRS) and apparent diffusion coefficient (ADC) values were performed in some patients.

The region of interest (ROI) of volumetric kinetic assessment on DCE-MRI was performed on the work station by two radiologists who has 10- and 30-years of experience in breast imaging. The most visible in the cut of the tumor was carefully selected and drawn in a square or rectangular shaped 3D voxels to include whole tumor. The background parenchymal enhancement were avoided. The CAD software generated a color coded image and then analyzed the pattern of enhancement after creating voxels on the tumor. Subsequently, the percentages of the part of tumor which enhanced in each pattern were obtained. According to the Breast Imaging-Reporting and Data System (BI-RADS) 2013 (fifth edition) from the American College of Radiology (ACR), kinetic assessment has been described in the early phase (within 2 minutes) and delayed phases (after 2 minutes). Types of enhancement patterns in the delayed phase are categorized into, namely: a) type I (persistent)- continuous enhancement more than 10% increase in signal over time; b) type II (plateau)- signal intensity does not change over time after its initial rise or flat; and, c) type III (washout)- signal intensity decreases more than 10% after its highest point from its initial rise (Figure 1). Type II and Type III enhancements are known as suspicious patterns for malignancy with increased concern in Type III, while Type I is recognized as a benign pattern. Finally, data of each tumor were collected and the percentage of enhancement categorized in each pattern.

All patients were confirmed by definitive surgery and pathohistology with identified size, type, and tumor grade. Tumor grades were classified as grade 1, 2 and 3, corresponding with low, intermediate, and high, respectively.

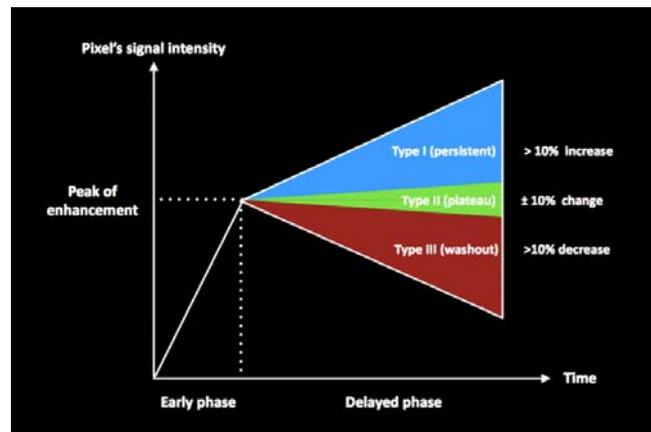


Figure 1. CAD with color coding was performed of the delayed phase on volumetric analysis. Type I (persistent) - increase signal intensity more than 10%; Type II (plateau) - signal intensity not change more than 10%; and, Type III (washout) - decrease signal intensity more than 10%.

Statistical analysis

The mean \pm standard deviation (SD) was used in the continuous data such as age, size of the tumor, and timing between operation and breast DCE-MRI.

Our study used three different patterns of enhancement in the delayed phase for analysis. The percentage of each pattern from the volumetric kinetic study was assessed using mean (\pm SD) and median.

As for comparison of the 3 groups of kinetic patterns, one-way ANOVA were performed or the Kruskal-Wallis test. $P < 0.05$ indicated a significant statistical difference. Statistical analysis was performed using SPSS, version 22.

Results

Fifty-two women, and 67 lesions of breast cancers were included. Their mean age was 47.8 years, and the range was 24 - 74 years old. The majority of malignant types was invasive ductal carcinoma (IDC)

with 45 lesions (67%) followed by 12 (18%) ductal carcinoma in situ (DCIS) lesions and 10 lesions (15%) of other subtypes of breast cancer. The other subtypes of breast cancer included 4 invasive lobular carcinomas, 2 invasive micropapillary carcinomas, 1 malignant phyllodes tumor, 1 tubular carcinoma, 1 secretory carcinoma, and 1 mucinous carcinoma. The sizes of the tumors reported by the histologic reports were, 2.7 cm (mean) and 1.9 cm (median). The mean time between breast DCE-MRI and operation was 2.1 months (range = 1 - 9 months) (Table 1).

Finally, the mean and the median percentages of the kinetic assessment using volumetric evaluation of total tumor volume showed a majority of 72.0% and 72.5% for type I enhancement (Figure 2), followed by 13.7% and 11.7% for type II enhancement, and 14.3% and 9.1% for type III enhancement (Figures 3 - 4) (Table 1).

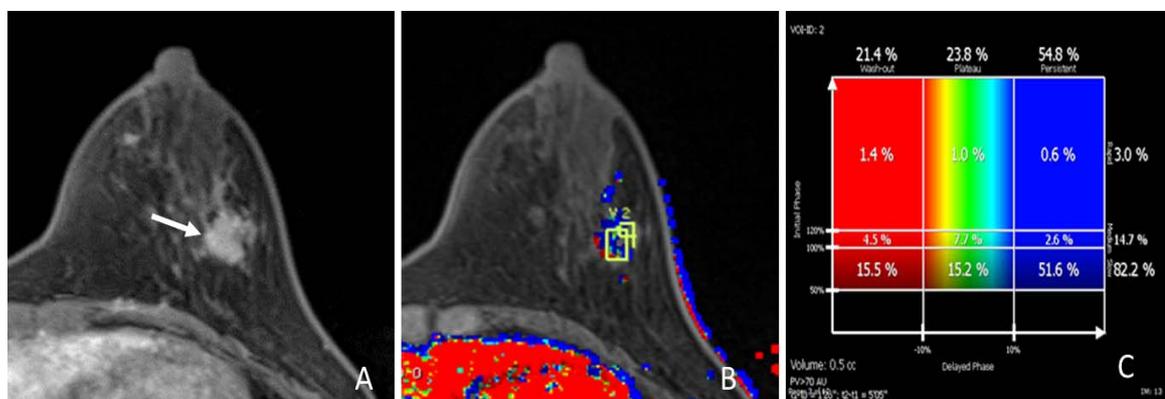


Figure 2. 51-year-old woman with computer-aided detection (CAD) with color coding on DCE-MRI assessment of grade 2, invasive ductal carcinoma (IDC): (A) Axial contrast-enhanced T1-weighted imaging with fat suppression at 180 seconds after contrast injection, shows a 1.5 \times 2.7 \times 1.7 cm irregular enhancing mass at the outer part of the left breast (arrow); (B) the color overlay map of CAD shows a rectangular shape of region of interest (ROI). The persistent enhancement is shown in the blue area, the plateau enhancement showed in the green area and the washout enhancement in the red area; and, (C) the calculated type of enhancement is 21.4% washout, 23.8% plateau, and 54.8% persistent enhancements.

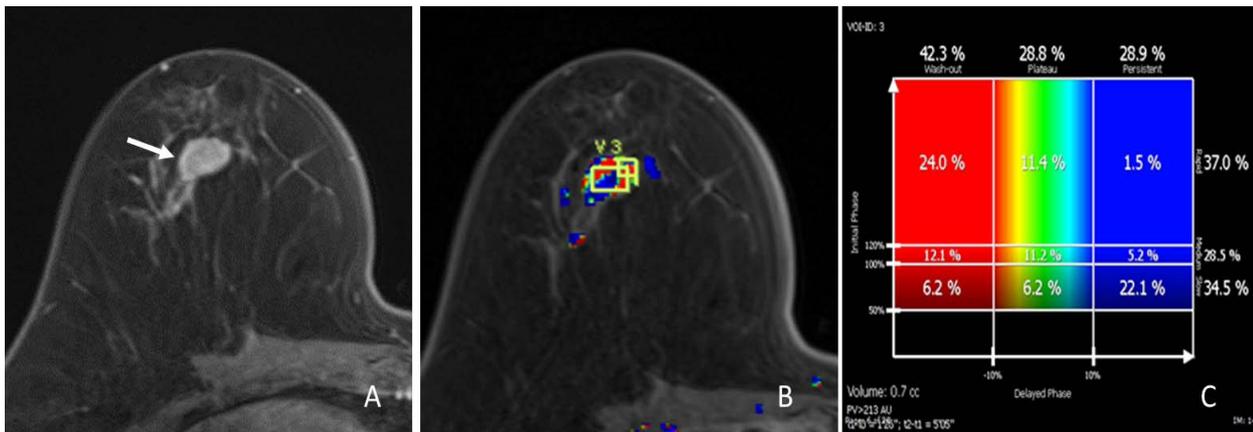


Figure 3. 62-year-old woman with computer-aided detection (CAD) with color coding on DCE-MRI assessment of grade 2, invasive ductal carcinoma (IDC): (A) Axial contrast-enhanced T1-weighted imaging with fat suppression at 120 seconds after contrast injection, shows a 1.8 × 1.2 cm enhanced mass at the upper mid quadrant of the right breast; (B) the color overlay map of CAD shows a rectangular shape of region of interest (ROI). The persistent enhancement is shown in the blue area, the plateau enhancement in the green area and the washout enhancement in the red area; and, (C) the calculated type of enhancement is 42.3% washout, 28.8% plateau and 28.9% persistent enhancements.

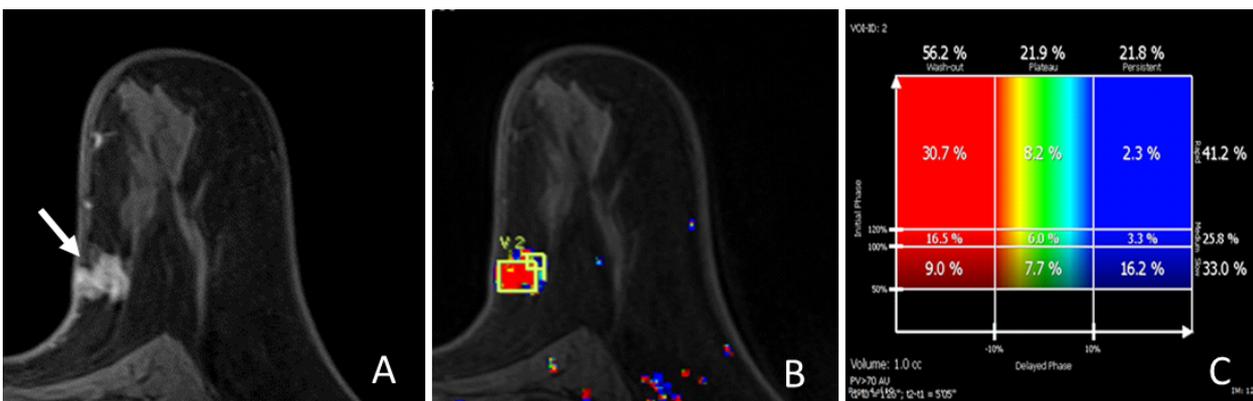


Figure 4. 64-year-old woman with computer-aided detection (CAD) with color coding on DCE-MRI assessment of grade 1, invasive ductal carcinoma (IDC): (A) Axial contrast-enhanced T1-weighted imaging with fat suppression at 120 seconds after contrast injection shows a 1.7 × 1.4 cm irregular enhancing mass at the upper inner quadrant of the left breast (arrow); (B) the color overlay map of CAD shows a rectangular shape of region of interest (ROI). The persistent enhancement is shown in the blue area, the plateau enhancement showed in the green area and the washout enhancement showed in the red area; and, (C) the calculated type of enhancement is 56.2% washout, 21.9% plateau and 21.8% persistent enhancements.

Table 1. Demographic data and percentages of volumetric kinetic assessment in different enhancement patterns.

Characteristics (n = 67)	Value
	Mean ± SD (Range/Median)
Age (years)	47.8 (24 - 74)
Size of tumors (cm)	2.7 ± 2.1 (1.9)
Time between operation and breast DCE-MRI (months)	2.1 ± 1.8 (1 - 9)
Percentages of volumetric kinetic assessment in DCE-MRI (%)	
Type I enhancement	72.0 ± 21.6 (72.5)
Type II enhancement	13.7 ± 9.9 (11.7)
Type III enhancement	14.3 ± 14.4 (9.1)

Histologic Types

The three subgroups include 67% IDC, 18% DCIS and 15% other subtypes of breast cancer. We found type I enhancement is the majority of all types of breast cancer (Table 2). IDC shows the highest (68.3%) type I enhancement, followed by (16.7%) type III enhancement and (15.0%) type II enhancement. The DCIS showed the same result as IDC, the highest (81.1%) type I enhancement (9.8%) type III and (8.9%) type II enhancements.

Comparison between the mean percentages of different enhancement patterns and each histologic type of cancer were as follows: a) type I enhancement; DCIS (n = 12) of 81.3%, other subtypes of breast cancer (n = 10) of 77.3%, and IDC (n = 45) of 68.3% ($P = 0.125$), b) type II enhancement; IDC of 15.0%, other subtypes of breast cancer of 13.6%, DCIS of 8.9% ($P = 0.166$), c) type III enhancement; IDC of 16.7%, DCIS of 9.8%, other subtypes of breast cancer of 9.1% ($P = 0.377$) (Table 2).

We found a higher percentage of suspicious enhancement patterns (Type II and Type III) in the IDC group (31.7%) than the DCIS group (18.7%). However, there was no significant difference.

Tumor grades

Among the three tumors grades, grade 2 was the largest group (65%), followed by grade 3 (21%) and grade 1 (14%). Comparisons between the mean percentages of each enhancement pattern and tumor grades were also calculated using the volume study of kinetic assessment. The majority was type I enhancement in which, 69.3% were found in grade 1,

75.2% in grade 2, and 63.0% in grade 3 ($P = 0.224$). Followed by type II and type III enhancements of which 12.5% and 18.2% were respectively found in grade 1, 11.6% and 13.1% grade 2, 18.3% and 18.7% grade 3 ($P = 0.096$ and $P = 0.713$) (Table 2).

There were higher percentages of type II enhancement and type III enhancement, which are suspicious enhancement patterns for malignancy in grade 3 tumor but they did not reach statistical significance.

Discussion

We assessed both information of tumor morphology and kinetic assessment in breast MRI for diagnosis of breast cancer based on the ACR BI-RADS 2013 (fifth edition). Kinetic assessment aimed to determine the uptake and washout of contrast media in tissue as time passed. (4) There were many factors that affected the rate of contrast media uptake such as capillary permeability, blood volume, contrast media distribution volume, and other aspects of local anatomy and physiology. (4) In general, the type III enhancement in the delayed phase indicated malignancy due to abnormal tumor vessels which have intense microvessels and high permeability. (4) For this reason, cancers seem to have vascular shunts that consequently result in early wash out. The type I enhancement was suggested benign lesions whereas the type II enhancement is classified as intermediate and can be both benign and malignant lesions. However, the overlapping of enhancement patterns in one tumor of either benign or malignant lesions were discovered.

Table 2. Different enhancement patterns of volumetric kinetic curve assessment compared with histologic type and tumor grades of the breast cancer.

	Delayed Enhancement Patterns (%)					
	Type I	P - value	Type II	P - value	Type III	P - value
Histologic types						
IDC (n = 45)	68.3 ± 23.2 (70.5)	0.125	15.0 ± 10.0 (11.8)	0.166	16.7 ± 15.9 (12.7)	0.377
DCIS (n = 12)	81.3 ± 17.0 (88.8)		8.9 ± 8.0 (6.9)		9.8 ± 10.9 (7.1)	
Other* (n = 10)	77.3 ± 15.1 (75.3)		13.6 ± 10.5 (12.0)		9.1 ± 7.5 (6.3)	
Tumor grades						
1 (n = 8)	69.3 ± 28.6 (73.7)	0.244	12.5 ± 11.6 (7.8)	0.096	18.2 ± 21.2 (7.3)	0.713
2 (n = 37)	75.2 ± 19.2 (74)		11.6 ± 8.5 (11)		13.1 ± 12.7 (9.1)	
3 (n = 12)	63.0 ± 26.0 (59.7)		18.3 ± 11.1 (21.0)		18.7 ± 17.6 (14.0)	

Note.- IDC= invasive ductal carcinoma; DCIS= ductal carcinoma in situ.
Other*= other subtypes of breast cancer

In our study, we confirmed that overall cancers had heterogeneity of kinetic patterns inside each tumor as using 3D voxels covered the whole tumor volume. Therefore, each tumor had a variety of enhancement patterns in itself and dissimilarity with others. The majority of enhancement patterns of kinetic assessment were found as type I enhancement that was not particular for malignant, while only 28% of malignant showed the suspicious kinetic assessment (type II and type III). Our findings were in accordance with the results of Leong LC, *et al.*⁽¹⁴⁾ They reported different heterogeneous component of the mean percentages of tumor volumes in the delayed phase. They found the majority of (51%) type I enhancement, followed by (28.8%) type II enhancement, and (19.9%) type III enhancement.

In addition, subgroup analysis of different histologic types and tumor grades also presented slightly higher suspicious enhancement patterns (type II and type III enhancements) in IDC than DCIS as well as in high tumor grade (grade 3) compared to low tumor grade (grade 1), depriving statistical significance.

This result is also in concordance with Leong LC, *et al.*⁽¹⁴⁾ Therefore, volumetric kinetic measurements for the whole tumor volume has not provided an advantage in distinguishing tumor subtypes and tumor grades.

Few prior studies^(11 - 13) found that the most common presentation of DCIS was type I enhancement, especially in non-mass DCIS. This is explained by the fact that DCIS mostly grow in the normal breast tissue without expression of vascular endothelial growth factor (VEGF), related to poor angiogenesis.⁽¹⁰⁾ Thus, poor washout of contrast media was seen.

In the other subtypes of breast cancer which comprised of 40% ILC, higher percentages of type I enhancement patterns were seen when compared with the IDC group. As similar theory is also applied to ILC, due to no expression of VEGF and poor angiogenesis.^(9, 10)

For our suggestion, focusing on the kinetic assessment parameter in order to diagnosis breast cancer, we could not use only kinetic enhancement patterns for the diagnosis of breast cancer, even performing the whole tumor volume. Multiple selective sampling of the kinetic measurement at various parts of the tumor and correlation with other parameters such as tumor morphology, apparent diffusion

coefficient (ADC) value, and MR spectroscopy (MRS) are recommended.

Lastly, there is a limitation of our study due to small sample size. Larger studies should be performed in the future.

Conclusion

For interpretation of breast cancer, the kinetic assessment of DCE-MRI with 3D voxels of whole tumor volume has not provided an advantage in distinguishing tumor histologic subtypes and tumor grades. The confirmation of heterogeneity of kinetic enhancement patterns inside each tumor was obtained, which implied a variety of tumors and multiple factors related to enhancement patterns. Thus, we could not merely use only kinetic assessment dissemination as the only criteria for the diagnosis of breast cancer. The correlation of other information is necessary including tumor morphology, ADC value, and MRS.

Conflict of interest

The authors, hereby, declare no conflict of interest.

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