

Original article

The Effect of Semi-Quantitative Analysis of Dynamic Contrast Enhanced MRI on Differential Diagnosis of Breast Masses

(Uygulanan semikantitatif analizin dinamik kontrastlı MR incelemesinde memenin kitlesel lezyonlarının ayırıcı tanısına katkısı)

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Amaç: Bu çalışmanın amacı semikantitatif değerlendirmenin, manyetik rezonans görüntülemesinde meme lezyonlarının malign-benign ayırımında özgüllüğü artırma ve objektif veriler sağlayabilme konusundaki etkinliğini değerlendirmektir.

Materyal ve Metot: Değerlendirmeye 95 lezyon alındı. Her bir lezyon için TIC ("Time intensity curve"- zaman-kontrast eğrisi) eğrileri oluşturuldu. Postprosesing işlemlerinden yararlanılarak TIC eğrilerinden tüm lezyonların semikantitatif analiz değerleri elde edildi. Ayrıca kinetik eğrilerin kalitatif değerlendirilmesinde TIC eğrileri geç evredeki seyrine göre, progresif, plato ve yıkanma (veya "wash-out") olarak üçe ayrıldı. Elde edilen veriler istatistiksel değerlendirmeye katıldı.

Bulgular: "Time-to-peak" değerleri malign lezyonlar için daha kısa sürmekte ve istatistiksel olarak anlamlı sonuç vermektedir ($p=0,01$). Diğer kantitatif parametrelerde malign ve benign lezyon ayırımında kullanılabilecek anlamlı istatistiksel veri sağlanmamıştır. Elde ettiğimiz eğri tiplerinin lezyonların ayırımında tanısallık değeri olduğunu görmekteyiz.

Sonuçlar: Çalışmamız sonucunda, TIC eğri paterninin değerlendirilmesi ve semikantitatif parametrelerden T_{peak} değerinin lezyonların benign-malign ayırımında istatistiksel olarak anlamlı olduğunu bulduk.

Anahtar Kelimeler: DCE-MRI; meme kitlesi; semikantitatif parametreler; zaman sinyal eğrisi

ABSTRACT

Background: The aim of this study is to assess the value of semi-quantitative analysis of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) in distinguishing malignant lesions from benign lesions, and providing objective data.

Materials and Methods: 95 mass lesions in 49 female patients were included. Time intensity curves (TIC) were created for each lesion. Semiquantitative analysis was provided from the TIC curves using the postprocessing software. In the evaluation of qualitative assessment of kinetic curves, TICs were divided into three categories as progressive, plateau and wash-out, according to their behavior at mid-to-late stage.

Results: The time-to-peak (Tpeak) values were significantly shorter for malignant lesions ($p=0.01$). No other semiquantitative parameter showed statistically significant differences between two groups. Curve type was significant in discriminating malignancy.

Conclusions: The evaluation of TIC patterns and Tpeak are valuable for differentiation of benign and malignant lesions

Key Words: DCE-MRI; breast mass; semiquantitative parameters; time intensity curve

INTRODUCTION

Breast magnetic resonance imaging (MRI) has found increasing use in the detection and characterization of breast lesions. In addition to the morphological analysis, analysis of contrast dynamics is described in the BIRADS lexicon as an adjunct to diagnosis. However, contrast dynamics need to be improved in terms of specificity¹.

Quantitative analysis of contrast-enhanced dynamic MRI is a difficult method to use in daily practice. Complexity of the mathematical process also makes its use impossible for the average radiologist. However, semiquantitative analysis can be provided by most software packages already installed in MRI workstations. Therefore, this study aims to evaluate the use of semiquantitative analysis in providing a discrimination between benign and malignant breast masses.

MATERIALS and METHODS

The study includes 95 mass lesions of 49 female patients, who were referred to the MRI unit of Haydarpasa Numune Education and Research Hospital for evaluation of a suspicious finding in

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either clinical examination, ultrasound or mamography. Mean age was 46 years (range 27-78 years). Two patients had 5, three patients had 4, seven patients had 3 and fifteen patients had 2 different lesions. Foci, as defined by the BIRADS MRI lexicon, were not included. Dynamic contrast-enhanced breast MRI (DCE-MRI) exams were performed within two weeks of the menstrual cycle but under clinical emergency conditions, this timing was not considered.

Dedicated bilateral breast coils of a 1,5T MRI scanner (Philips Achieva) were used with the following parameters of acquisition: Axial T1 TSE (TE 10 ms, TR 457 ms, slice thickness 4 mm, gap 0.5 mm, matrix 272x512, FOV 340 mm), axial T2 SPAIR (TR 4135 ms, TE 120 ms, slice thickness 4 mm, gap 0.5 mm, matrix 216x512, FOV 324 mm), axial dynamic contrast-enhanced 3D THRIVE (TE 3.4 ms, TR 6.9 ms, flip angle 12°, FOV 340 mm, slice thickness 2 mm, gap 1 mm, matrix 266x352). THRIVE sequences were obtained before and immediately after contrast injection with a power injector, at a rate of 2 ml/sec and 0.1-0.2 mmol/kg, and the sequences were repeated for 6 times. Subtraction images were then calculated automatically.

At the workstation, a regions of interest (ROI) was placed within the most enhancing area of the lesion as identified on subtraction images, a new time intensity curve (TIC) was obtained for each lesion and multiple measurements were taken before identifying the most suspicious curve for each lesion.

Semiquantitative analysis was provided from the TIC curves using the postprocessing software (Figure 1). In addition, TIC curves behavior were evaluated for mid-to-late term postcontrast dynamics and curves were identified as progressive, plateau or wash-out as in the study of Kuhl et al. and Kinkel et al.^{2,3}.

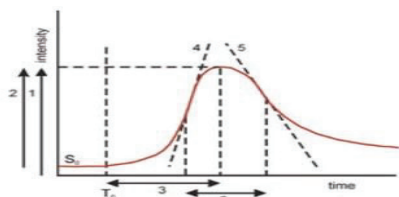


Figure 1. Semiquantitative parameters as described on a typical TIC. (1) Maximum intensity, (2) maximum enhancement, (3) time to peak, (4) wash-in, (5) wash-out, (6) brevity of enhancement and AUC (area under the curve)

Lesions were histopathologically identified when there was a suspicion for malignancy. However, some benign lesions were biopsied while some were considered benign if they did not demonstrate a change in size within two years².

Therefore subtyping was not possible for all benign lesions.

NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used for statistical analysis of the obtained data. The parameters showing normal distribution were analyzed with Student's t test. For the parameters without normal distribution Mann-Whitney U test was used. Yates Continuity Correction and Fisher's Exact test were used in comparison of quantitative data. Results were evaluated in 95% confidence interval and $p < 0.05$ was considered statistically significant.

RESULTS

95 lesions in 49 women were evaluated. 47 lesions were benign and 48 lesions were malignant. Lesions size ranged from 5x5 mm to 45x60 mm in diameter, having a similar range for benign and malignant groups; 12x8,5 mm and 20x16 mm respectively.

37 out of 48 malignant lesions had a definite subtyping while 11 were classified as malignant change in fine-needle aspirates. Only 21 benign lesions received histopathological classification, while 19 were again defined as benign aspirates and 7 were accepted to be benign after two year follow-up did not demonstrate any change in size or appearance (Table 1).

Table 1. The Distribution of Lesions According to Their Histological Subtype

Malignant	48	Benign	47
Invasive ductal carcinoma	23	Fibroadenoma	11
Invasive ductal and lobular carcinoma	3	Fibrocystic change	9
Medullary carcinoma	4	Intraductal papilloma	1
Invasive micropapillary carcinoma	1	Benign aspirate	19
Cribriform carcinoma + DCIS	1	Follow up	7
Paget's disease	3		
Metaplastic carcinoma	2		
Malignant aspirate	11		

Among the semiquantitative analysis parameters, malignant lesions demonstrated a significantly longer period to reach peak enhancement (time-to-peak) ($p=0.001$). There was no significant overlap between malignant and benign lesions (Table 2). The mean wash-in value was 11.89 ± 4.85 for malignant lesions and 10.22 ± 3.97 for benign lesions. Other quantitative parameters showed no significant differences among two groups.

Table 2. Evaluation of Semi-Quantitative Data

	Pathology		p
	Benign (n=47) (Mean±SD)	Malignant (n=48) (Mean±SD)	
Maximum enhancement	1985.79 ± 644.65	1867.36 ± 645.79	^a 0.373
Maximum relative enhancement (%)	182.33 ± 88.76	159.06 ± 37.37	d0.102
Time to peak (s)	388.38 ± 82.48	309.91 ± 100.49	d0.001**
Wash-in rate (1/s)	10.22 ± 3.97	11.89 ± 4.85	d0.070
Wash-out rate (1/s)	1.14 ± 1.18(0.86)	1.12 ± 1.25(0.72)	e0.512
Brevity of enhancement (s)	321.73 ± 78.33	318.26 ± 67.69	d0.868
Area under curve	61383* ± 248179.79	662046.1 ± 246004.09	d0.344

dStudent's t test, eMann Whitney U test, * p<0.05, **p<0.01

Table 3. Evaluation of TIC Profile in the mid-to-late term

		Pathology		
		Benign n (%)	Malignant (%)	p
Kinetic Curve Assesment				
	1	35 (74.5%)	11 (22.9%)	a0.001**
Delayed	2	10 (21.3%)	28 (58.3%)	a0.001**
	3	2 (4.3%)	9 (18.8%)	a0.059
	2-3	12 (25.5%)	37 (77.1%)	a0.001**
aYates Continuity Correction. **p<0.01				

aYates Continuity Correction, **p<0.01

The qualitative evaluation of mid-to-late stage behavior profiles of TICs in benign and malignant lesions are summarized in Table 3. Type 1 pattern is seen in benign lesions (74.5%), while type 2 and 3 are observed in malignant lesions (77.1%).

DISCUSSION

Standard evaluation criteria have not been optimized for evaluating dynamic contrast-enhanced breast MRI (DCE-MRI)^{4,5}. Most evaluation criteria, especially morphologic criteria, are subjectively interpreted. Developed to reduce the subjectivity both in terms of morphology, contrast dynamics and kinetic curves and aiming to provide an insight to pathology, even the BI-RADS classification system is subjectively used among readers⁶. The scoring system described by Fischer⁷ is based on points assigned to predefined morphological features and contrast enhancement specifics to obtain a relatively objective and reproducible evaluation. The Fischer system divides early contrast enhancement into three groups; below 50%, between 50-100% and over 100% signal increase compared to precontrast values, while the late enhancement stage considers $\pm 10\%$ signal change compared to maximum signal intensity achieved in the early stage, creating progressive, plateau and wash-out groups. This scoring system is reported to have 92% sensitivity and 65% specificity in discriminating benign and malignant breast masses with DCE-MRI⁷.

Kuhl et al.² described relative contrast enhancement in the early phase and 60-80% limits were used to discriminate benign, indeterminate and malignant lesions. Accordingly, the early post-contrast signal intensity increase

was found significantly high in malignant lesions compared to benign lesions. In the same study, late contrast curves were evaluated to reveal that 8.9% of malignant lesions demonstrated type 1, 33.6% type 2 and 57.4% type 3 curves, while benign lesions showed 83% type 1, 11.5% type 2 and 5.5% type 3 curves. Using type 2 and 3 curves to discriminate malignant and type 1 curve benign lesions, the sensitivity and specificity were found to be 91% and 83% respectively.

El Khouli et al.⁸ compared quantitative and qualitative methods in the evaluation of kinetic curves in DCE-MRI. Quantitative analysis was found to have statistically significant accuracy compared to qualitative analysis (p<0.01). Type 2 and 3 curves obtained with quantitative analysis were more accurate in discriminating malignant lesions in contrast to qualitatively obtained curves. However, sensitivity and specificity did not differ significantly among both methods (p=0.06)⁸.

Our study also involved qualitative evaluation of time-intensity curves and revealed that 18,8% and 58,3% of malignant lesions demonstrated type 3 and type 2 curves respectively, and %74,5 of benign lesions showed type 1 curves. Curve type was, therefore, significant in discriminating malignancy. Maximum relative enhancement values were not significantly different among groups in contrast to the studies of Kuhl et al.² and Fischer et al.⁷.

Many studies in the literature have taken into consideration the quantitative parameters of maximum enhancement rate (slope of the curve), maximum enhancement and time-to-peak values^{5,9-14}. Some authors indicate that malignant lesions show stronger and faster enhancement compared to benign lesions, they also believe that

early enhancement rate may be used for distinguishing pathology^{5,12}. However, others argue that malignant lesions may be prone to enhance faster than benign lesions, but significant overlaps between both groups hinder the use of enhancement rates for discrimination^{9-11,14}.

Sivarajan et al.⁴ evaluated the quantitative parameters like maximum slope of the curve, time-to-peak and wash-out rate. Malignant lesions in this study demonstrated a higher slope, shorter time-to-peak values and more prominent washout compared to benign lesions. However, significant overlap is present, causing a weak predictive effect. The positive predictive value for the washout pattern described for malignant lesions was 62.5%; however, fibroadenomas containing atypical ductal hyperplasia, mastitis and benign proliferative lesions also showed the same pattern.

Similar results were obtained by Siegmann et al.¹⁵, Stomper et al.¹², and Orel et al.¹⁴. Contrary to these studies, studies by Kaiser and Zeitler⁹ and Gribbestad et al.¹⁶ showed that all carcinomas could be distinguished by the early contrast enhancement. The lack of significant differences in quantitative parameters among benign and malignant lesions is explained by Siegmann et al.¹⁵ with the fact that their series consisted of mostly proliferative type of benign lesions, that is, enhancement parameters were related to the vascularisation pattern of the mass, but this does not necessarily occur in malignancy. Although Kaiser and Zeiter's⁹ series also consisted of a number of young, proliferative fibroadenomas and proliferative dysplasias, which demonstrated significant and early enhancement, Gribbestad et al.'s¹⁶ series contained only one juvenile fibro-

adenomas.

In a larger study, Kaiser and Mittelmeier¹⁷ indicated that fibrocystic change demonstrated a significantly lower signal intensity compared to carcinomas, however, an increase in proliferation could cause an enhancement rate comparable to carcinomas in some cases. Moreover, almost 50% of the invasive carcinomas in Siegmann et al.'s series¹⁵ were of the lobular subtype, which is known to have less tendency to enhance.

Our study group consisted of 47 benign lesions, of which only 21 received histopathological subtyping. Proliferation indexes were not measured in these 21 cases. However, only 3 out of 33 histologically malignant lesions were invasive lobular carcinomas. These numbers are not high enough to cause controversial results. Time-to-peak values of benign lesions were shorter for malignant lesions in our study group. In terms of brevity of enhancement, wash-out rate, maximum enhancement, wash-in rate and area-under-the-curve (AUC), benign and malignant lesions did not demonstrate significant differences. However, we believe that the wash-in values can be found significantly different among groups in a larger study group.

The major limitation in our study was the lack of histopathology of all lesions, preventing interpretation of results about vascularisation patterns. Also, the ROIs were placed by a single observer (DOA). In heterogeneously enhancing lesions, ROIs should be placed at the faster enhancing area of the lesion, but this approach hinders evaluation of the lesion as a whole.

Conflict of interest statement: None declared.

REFERENCES

1. Lee CH. Problem solving MR imaging of the breast. *Radiol Clin North Am* 2004;42:919-34.
2. Kuhl CK, Mielcareck P, Klaschik S, et al. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? *Radiology* 1999;211:101-10.
3. Kinkel K, Helbich TH, Esserman LJ, et al. Dynamic high-spatial-resolution MR imaging of suspicious breast lesions: diagnostic criteria and interobserver variability. *AJR* 2000;175:35-43.
4. Sivarajan U, Jayapragasam KJ, Abdul Aziz YF, et al. Dynamic contrast enhancement magnetic resonance imaging evaluation of breast lesions: a morphological and quantitative analysis. *JHK Coll Radiol* 2009;12:43-52.
5. Orel SG. Differentiating benign from malignant enhancing lesions identified at MR imaging of the breast: Are time-signal intensity curves an accurate predictor? *Radiology* 1999;211:5-7.
6. American Collage of Radiology Breast Imaging Reporting and Data System (BIRADS) 4th edition. Reston (VA): American Collage of Radiology 2003.
7. Fischer U, Kopka L, Grabbe E. Breast carcinoma: effect of preoperative contrast enhanced MR imaging on the therapeutic approach. *Radiology* 1999;213:881-8.
8. El Khoul RH, Macura KJ, Jacobs MA, et al. Dynamic contrast-enhanced MRI of the breast: Quantitative method for kinetic curve type assessment. *AJR* 2009;193:295-300.
9. Kaiser WA, Zeitler E. MR imaging of the breast: fast imaging sequences with and without Gd-DTPA-preliminary observations. *Radiology* 1989;170:681-686.
10. Heywang SH, Wolf A, Pruss E, Hilbertz T, Eiermann W, Permanetter W. MR imaging of breast with Gd-DTPA: use and limitations. *Radiology* 1993;171:95-103.
11. Gilles R, Guinebretiere JM, Lucidarme O, et al. Nonpalpable breast tumors: diagnosis with contrast-enhanced subtraction dynamic MR imaging. *Radiology* 1994;191:625-31.
12. Stomper PC, Herman S, Klippenstein DL, et al. Suspect breast lesions: findings at dynamic gadolinium enhanced MR imaging correlated with mammographic and pathologic features. *Radiology* 1995;197:387-95.
13. Boetes C, Barentsz JO, Mus RD, et al. MR characterization of suspicious breast lesions with a gadolinium-enhanced turbo-FLASH subtraction technique. *Radiology* 1994;193:777-81.
14. Orel SG, Schnall MD, LiVolsi VA, Troupin RH. Suspicious breast lesions: MR imaging with radiologic-pathologic correlation. *Radiology* 1994;190:485-93.
15. Siegmann KC, Müller-Schimpfle M, Schick F, et al. MR imaging-detected breast lesions: histopathological correlation of lesion characteristics and signal intensity data. *AJR* 2002;178:1403-9.
16. Gribbestad IS, Nilsen G, Fjosne H, et al. Contrast enhanced magnetic resonance imaging of the breast. *Acta Oncol* 1992;31:833-42.
17. Kaiser WA, Mittelmeier O. MR mammography in patients at risk. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* 1992;156:576-81.