# A method for limiting pitfalls in the production of enhancement kinetic curves in 3T dynamic magnetic resonance mammography

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**ABSTRACT**

**Purpose:** The aim of the present study is to investigate means for the reduction or even elimination of enhancement kinetic curve errors due to breast motion in order to avoid pitfalls and to increase the sensitivity and specificity of the method.

**Methods:** 115 women underwent breast Magnetic Resonance Imaging (MRI). All patients were properly immobilized in a dedicated bilateral phased array coil. A magnetic resonance unit 3-Tesla (Signa, GE Healthcare) was used. The following sequences were applied: (I) axial T2-TSE, (II) axial STIR and (III) Vibrant axial T1-weighted fat saturation (six phases). Kinetic curves were derived semi-automatically using the software of the system and manually by positioning the regions of interest (ROI) from stable reference points in all the phases.

**Results:** 376 abnormalities in 115 patients were investigated. In 81 (21.5%) cases, a change of the enhancement kinetic curve type was found when the two different methods were used. In cases of large fatty breasts, a change of the enhancement kinetic curve type in 13 lesions was found. In cases of small and dense breasts, only in 4 lesions the kinetic curve type changed, whereas in cases of small and fatty breasts, the kinetic curve type changed in 64 lesions (50 were observed in left breasts and 14 in right breasts).

**Conclusions:** The derivation of enhancement kinetic curves should be performed by controlling and verifying that the ROIs lay at the same location of the lesion in all the phases of the dynamic study.

**KEY WORDS** Dynamic magnetic resonance mammography; enhancement kinetic curves; 3 Tesla

*J Thorac Dis 2012;4(4):358-367. DOI: 10.3978/j.issn.2072-1439.2012.07.15*

## Introduction

Among the most promising methods for non-invasive grading to date is the dynamic contrast-enhanced MR imaging (DCE-MRI). Dynamic contrast-enhanced magnetic resonance mammography (DCE-MRM) is increasingly used as an adjunct to mammography and ultrasonography (US) to improve the detection and characterization of primary and recurrent breast cancers and for evaluation of the response to therapy (1,2). The sensitivity of MR imaging for the detection of breast cancer, especially of invasive types, is very high, and it ranges between 95-99% (3-5).

Dynamic acquisition of images during contrast enhancement allows calculation of specific descriptive parameters related to local microvasculature characteristics. High-grade tumors are characterized by a high proportion of immature and hyperpermeable vessels (6). The transfer coefficient will be affected by both flow and permeability surface area product, however, because both of these values are expected to increase with increasing tumor grade their effects on measured Ktrans can be confidently predicted to be cumulative (6). Consequently, measurements of Ktrans might be expected to be related to tumor

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Submitted Jun 06, 2012. Accepted for publication Jul 27, 2012.
Available at www.jthoracdis.com

ISSN: 2072-1439

grade. This has led several authors to examine the relationship between the transfer coefficient and tumor grade (6-9). The results from these studies are, however, conflicting.

There is broad agreement that, at the evaluation of MRM both morphologic features and enhancement kinetics criteria should be included (10,11). So, in clinical routine practice, MRM diagnosis is based on the BI-RADS classification which includes both morphologic and dynamic evaluation criteria. Furthermore, this protocol correlates the lesions' morphologic and dynamic findings to the results of histopathology and/or follow-up.

The kinetic curves describe both the initial peak (slow, medium, rapid) and the delayed phase (persistent, plateau, or washout) of a lesion's contrast uptake (1). In order to acquire the kinetic curves, a small region of interest (ROI) must be located at the lesion and to record the dynamic behavior of the same tissue compartment in all the phases of the examination. The ROI should be placed selectively in the area of the most rapid, homogenous and intense enhancement of the lesion. A major problem emerges when there is even a slight motion of the patient (12,13). In that case, the location of the ROI changes between the different phases of the dynamic study and a different tissue compartment is evaluated in every phase.

High-field-strength (3.0T) Magnetic Resonance Imaging (MRI) systems are becoming increasingly available in the clinical setting (14). With the inherently high signal-to-noise ratio of these systems, appropriate acquisitions can be used to achieve high spatial and temporal resolution that ensures accurate detection of a lesion and its pattern of enhancement (3,15,16). These advantages of 3.0T MRI have raised expectations about overcoming previous limitations in evaluating breast cancer (14). However, we observed a kinetic curve error at 3.0T, which has not been reported in the literature until now (17). Since there are not relevant reports in the literature, we suspect that in lower magnetic fields this phenomenon may not be so pronounced because of the larger pixel size or lower spatial resolution that is generally used at 1.5T MRI in comparison to 3.0T.

The aim of this study is to assess the magnitude of the errors at the production of the kinetic curves due to technical artifacts following motion or breath movements and suggest new methods for the reduction or even elimination of these errors.

## Materials and methods

In this retrospective study 115 women were included (227 breasts) who underwent breast MRI at the department of Radiology, (University Hospital of Larissa, Greece) during an 18-month period (May 2008-October 2009). The mean age was 53 years (range, 31-82 years).

The MRI examinations were carried out on a 3T system (Signa, GE Healthcare) and the array spatial sensitivity encoding technique (ASSET) or parallel imaging technique was used. All MRI examinations were performed with a bilateral dedicated phased-array breast coil and the woman was in the prone position. The smallest dimensions of the coil were 12 cm × 8 cm. In order for small breasts to be properly immobilized, cotton and cotton-paper was used. MRI examinations for all premenopausal patients were performed in the second week of the menstrual cycle (7th-13th day) to minimize glandular tissue enhancement. The MRM protocol was the following:

(I) axial T2-TSE sequence (TR=3,600 msec, TE=100 msec, NSA=4, FOV=400 mm, asset factor=2, bth.slice=4, slice thickness=4 mm);

(II) axial STIR sequence (TR=3,800 msec, TI=180 msec, TE=90 msec, NSA=2, FOV=400 mm, asset factor=2, slice thickness=4 mm);

(III) axial Vibrant sequence T1-weighted fat saturation (GE Healthcare) (TR=5,8 msec, TE=2.1 msec, NSA=1, Matrix=350×350, FOV=400 mm, asset factor=3, slice thickness=1.2 mm, Phase acquisition time=84 sec). This sequence was performed both prior to and then five times after the dynamic intravenous;

(IV) injection of 0.1 mmol/kg of gadopenate dimeglumine (Omniscan, Magnevist, Multihance) followed by a 10-mL saline solution flush, over a period of 5-8 sec.

After the dynamic series, image subtraction was performed to suppress the signal from fat in order for the enhancing lesions to be better identified on the subtracted images. The enhancing lesions on the subtracted images were also identified on the nonsubtracted images in order to exclude subtraction artifacts or other normal enhancing structures such as dilated vessels.

Furthermore, we employed color-coded image mapping, which highlights anatomic locations that are enhancing beyond a threshold. Image maps primarily serve two purposes in clinical use. First, they highlight areas that might have normally been missed. A second use for image mapping is to find proper placement of the ROI when computing uptake and washout curves. The information available in either the subtraction or the post contrast image data sets can be insufficient to determine where to place the ROI (18).

Kinetic analysis was performed for ROIs based upon determination of lesion signal intensity before and after the injection of contrast medium. Special care was taken during the placement of ROI so that it was placed selectively in the area of the most rapid and intense enhancement. The size of the ROI was adjusted to the size of the enhancing lesion so as to include as much of the enhancing part of the tumor as possible, yet being small enough to exclude any artifact or inhomogeneity of the enhancing lesion. In clinical practice the size of the ROI should not exceed 4-5 pixels. The standard procedure for deriving kinetic curves is by using special software, which produces the points of the signal intensity-to-time plot, semi-automatically.

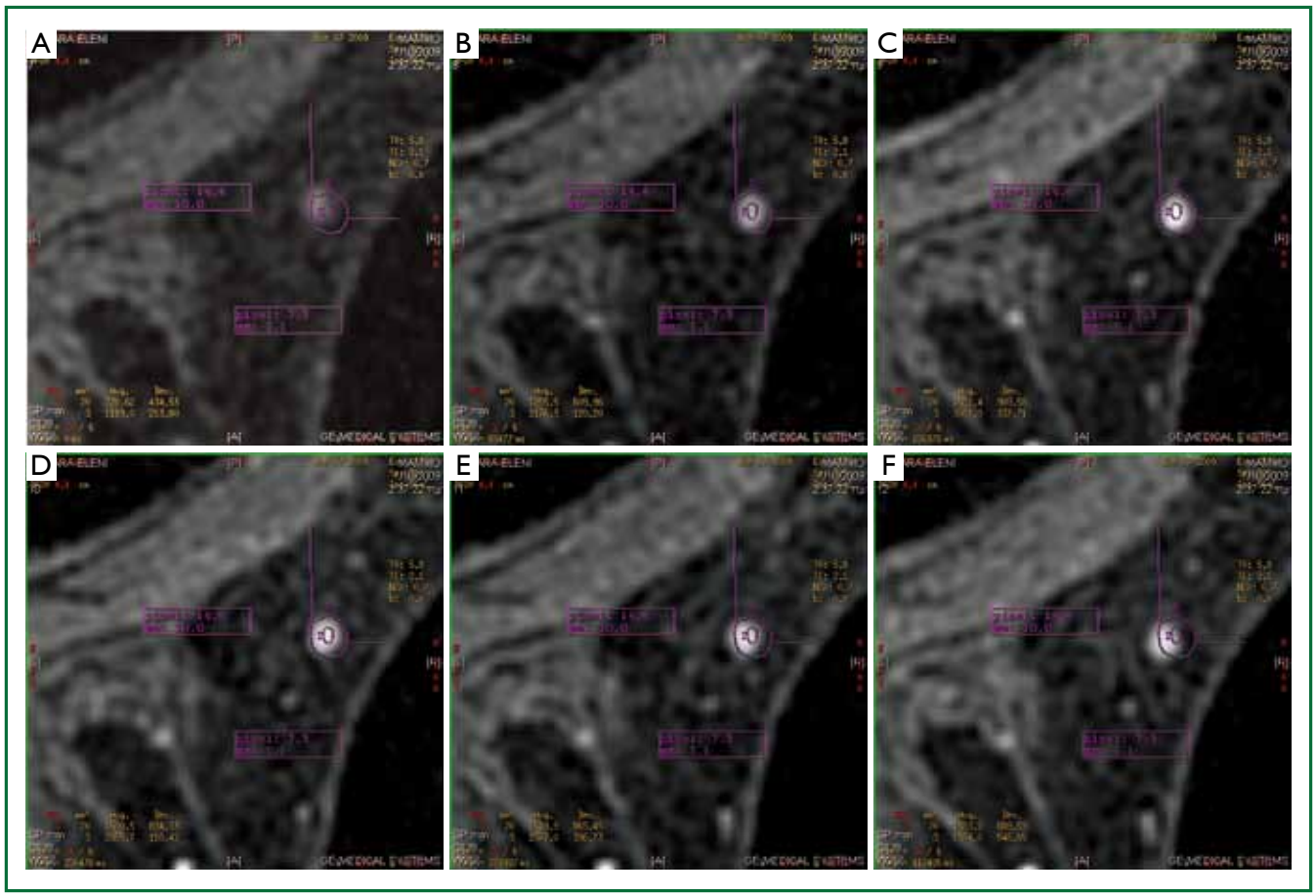


**Figure 1. Six images (A-F) representing the different phases of the dynamic image acquisition at the same position.** In the third phase of the dynamic sequence (C), two ROIs (a large peripheral and a small central) were delineated. It is observed that by deriving the kinetic curves using the software of the system, apart from the lesion, a part of the surrounding tissue is included in the two ROIs in the phases A, E and F compared to phase C. Also, the distances of the large ROI from stable reference point (muscle and skin) that were measured in phase C, were not the same in the phases A, E, and F.

The placement of the ROI was performed at the second or third dynamic phase. When large lesions were investigated, the ROI had to be placed at the periphery of the lesion because at the center of those lesions necrotic areas usually exist. However, with the derivation of kinetic curves using the software of the system, when eventual movements of the patient are present it is possible that different tissues may be registered in the ROI in the different phases of the acquisition.

We observed that in a number of cases of MRM lesions, there was a movement of the ROI in different phases of the dynamic study of a lesion, possibly due to respiratory motion artifacts (Figure 1). For example, at the third phase of the dynamic study the ROI was located in the center of the lesion, while in other phases ($1^{rst}$, $5^{th}$, $6^{th}$) the ROI was found at the periphery of the lesion or even outside the lesion and vice versa.

That observation motivated us to conduct a retrospective study of 115 MRMs in order to find the reason for this artifact and to find out ways of avoiding it. For each lesion, the ROI was placed manually in the six images, which correspond to the six phases of the dynamic acquisition, and the signal intensity was measured. Moreover, it was ensured that the ROI was positioned in the same area of the lesion by measuring the distances from the periphery of the ROI to stable points on skin, muscle, ribs and sternum that appear at the image (Figure 2) due to the fact that these points do not significantly change during enhancement in dymanic sequences. It must be stated that these stable points had a specific characteristic, which could be easily identified in all the phases. Furthermore, at least two such stable points were used in positioning the ROI in each phase based on both the distance and angle between the periphery of the ROI and each stable point. In homogeneous lesions, the ROI was positioned in the center of the lesion and subsequently the measurements from the stable points were used to verify the correct of position of the ROI. Skin and muscle have a homogeneous enhancement, whereas the periphery of sternum and ribs have no enhancement whatsoever since they are composed of ossified tissue. Finally, the kinetic curves were manually derived based on the signal intensity-to-time. The

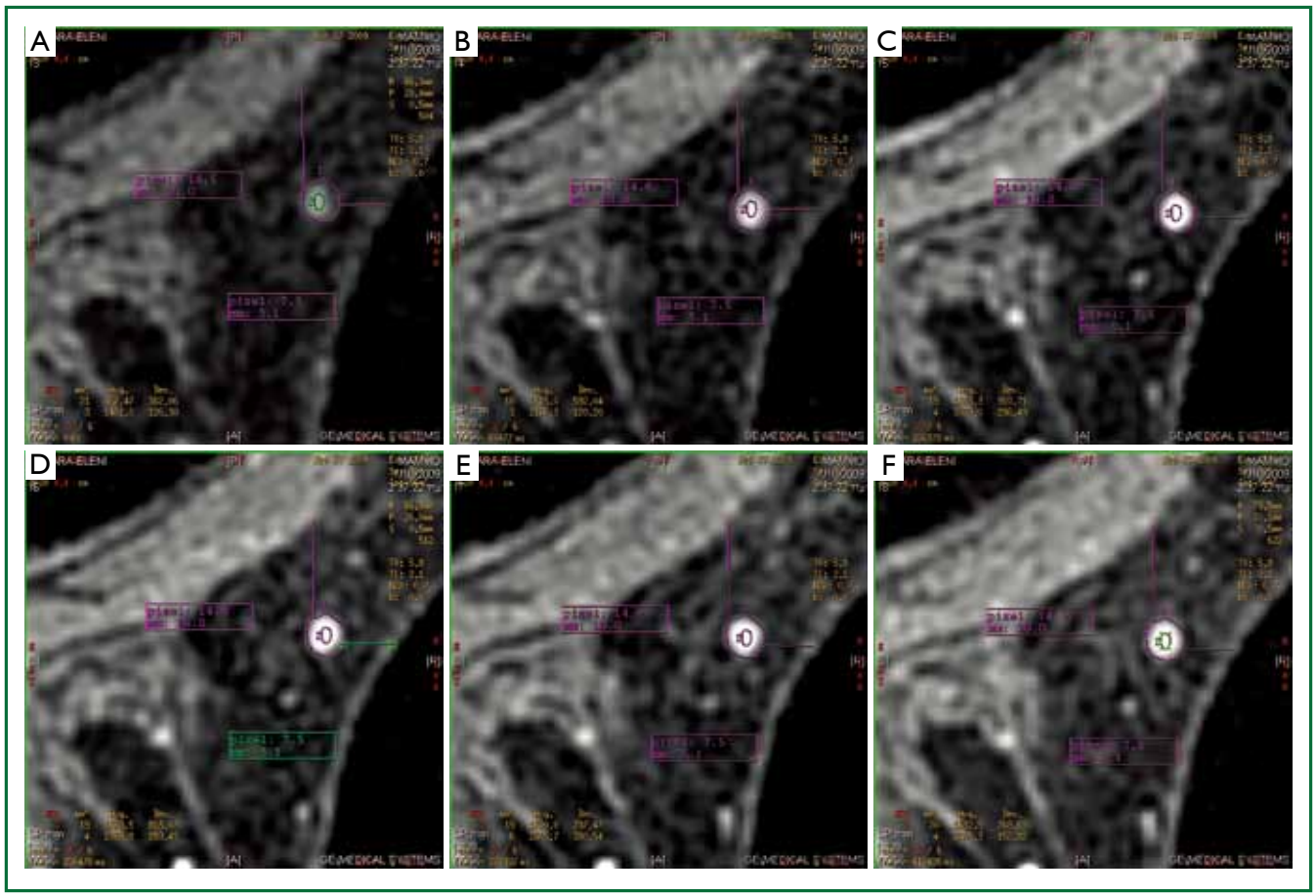


**Figure 2. Six images (A-F) representing the different phases of the dynamic image acquisition at the same position.** In the third phase of the dynamic sequence (C), two ROIs (a large peripheral and a small central) were delineated. The two ROIs were placed in the rest five phases using the manual procedure based on the distances from stable reference points (muscle and skin) that were measure in phase C. Note that there is no shift of the ROI in the different phases of the dynamic study.

manually derived curves were compared to the derived curves by the software of the system regarding their type (Figure 3). The whole procedure was performed by the same radiologist with experience in breast MRI.

We evaluated if the consequent differences were in consistence with (I) the laterality of the lesion namely if the lesion is located to the right or left breast related to heart motion, (II) the size of the breast, where a cut-off value was selected, based on the size of the coil. The coil had a dimension of 12 cm × 8 cm and if one of the two dimensions of the breast (anteroposterior and lateral) was smaller than the corresponding dimension of the coil, the breast was categorized as small breast. The difficulty in stabilizing smaller breasts, our query focused on whether that could affect motion artifacts, (III) the correlation between dense breasts and motion artifacts since those types of breast are easier stabilized and intrinsically have less freedom to move with a consequence of being less prone to breathing movements, and (IV) combination of all the previous factors.

## Results

For the verification of the kinetic error it should be checked if the measurement was taken place at the same location of the lesion in all the images of the dynamic phases. Each lesion had been delineated at the second or third phase of the dynamic sequences and when the location of the lesion at the subsequent phases had been shifted in relation to the initial delineation we confirmed that there is a kinetic error (Figure 1). In these cases, we placed a ROI in the third phase of the dynamic sequences and by measuring the distances of that ROI from stable fiducial points (thoracic muscle and skin) we placed the corresponding ROIs in the subsequent phases based on those stable points and distances (Figure 2). Furthermore, when there was a kinetic error, it was also observed in the image mapping and subtraction image (Figure 4).

In 115 patients that were examined, 376 abnormalities were investigated. For each one of them, an enhancement kinetic curve was derived (from the images of the multi-phasic sequence - Vibrant) both using the calculation software of the system and

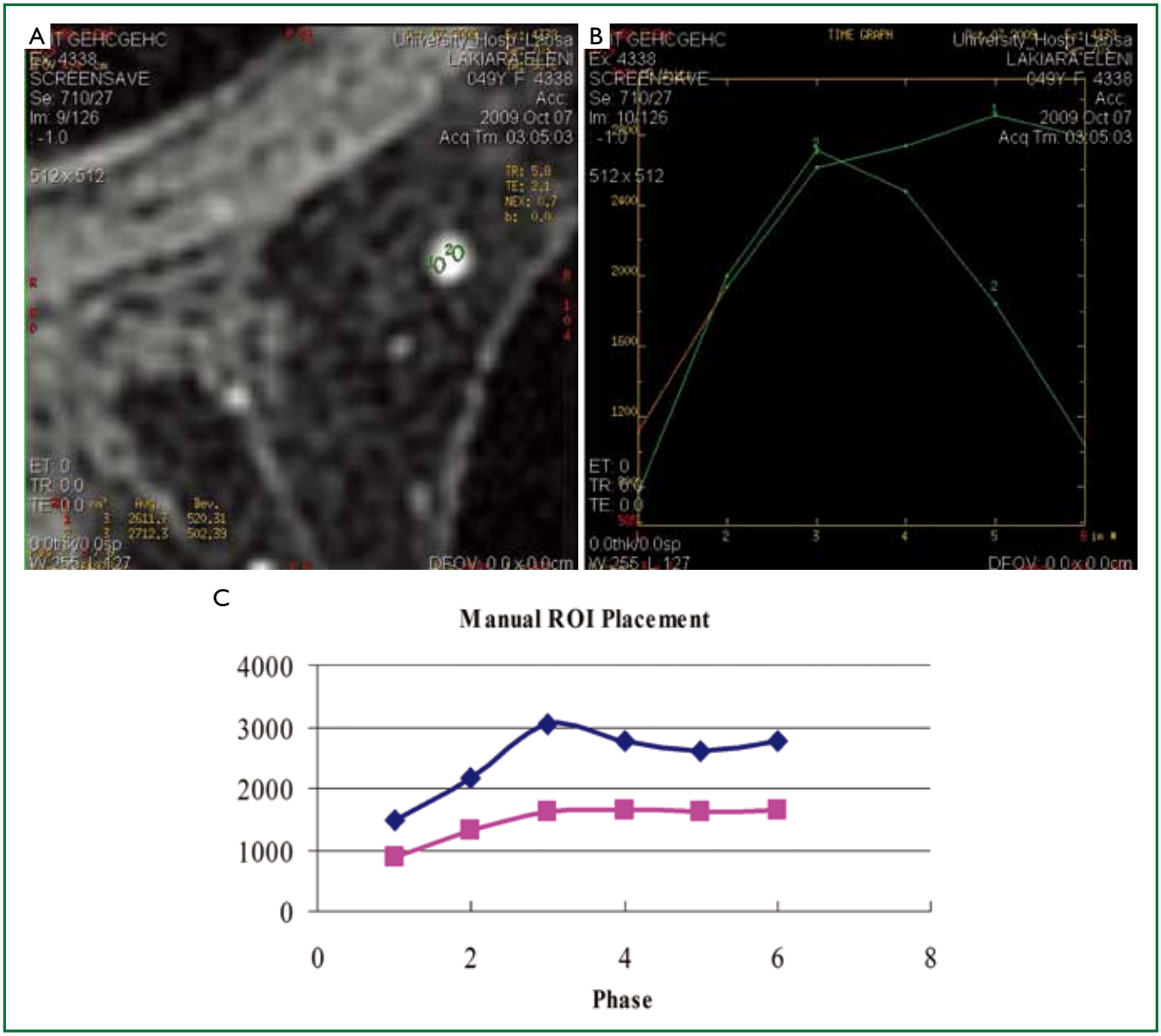


**Figure 3. (A) Placement of two different ROIs in the same lesion shown in Figure 1, in the third phase of the dynamic sequence, at the periphery of the lesion. (B) The kinetic curves, which have been produced using the software of the system and correspond to the ROIs of image (A). (C) Derivation of the kinetic curves using the manual procedure. We observe that there is an extensive change in the type of the kinetic curves between the two procedures (system software, manual) of kinetic curve derivation. Furthermore, the kinetic curves that are produced using the software of the system show a large variation depending on the position of the ROI used, even though the lesion is fairly homogeneous, whereas the kinetic curves that are produced manually show consistency (type II).**

manually. In 81 (21.5%) cases, a change of the enhancement kinetic curve type was found between the two methods (Figures 3,5).

Regarding the impact of breast size, in large and dense breasts there was not any change in the type of the kinetic curves calculated between the two methods (Table 1). In the large but non-dense breasts, 13 lesions' curves were found to be of different type when the manual method was applied. In this case, the laterality of the breast did not show a statistically significant difference (P>0.05) since 5 of the lesions were observed in left breasts and 8 in right breasts. Similar findings were observed in the cases of small breasts, but even more pronounced. More specifically, in the case of small and dense breasts only 4 lesions' curves changed type without any breast laterality difference (2 were observed in left breasts and 2 in right breasts). In the case of small and non-dense breasts, 64 lesions' curves changed type, out of which, 50 were observed in left breasts and 14 in right breasts (Table 1). This means that in this case breast laterality show a statistically significant difference

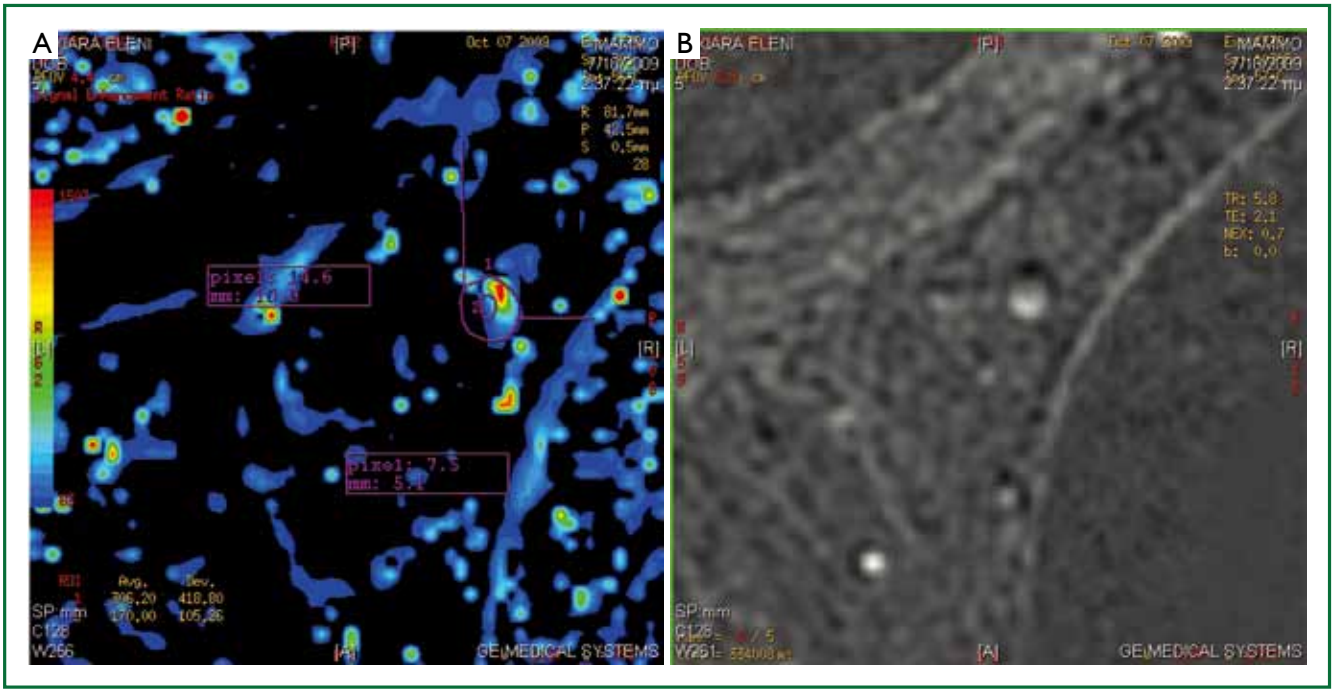


**Figure 4. (A) The mapping image corresponding to the clinical case shown in Figure 1 where the ROIs were placed in the third phase of the dynamic sequence using the software of the system. It is shown that the enhancement region is located in same region that a shift of the ROI was observed in Figure 1. (B) The subtraction image corresponding to the clinical case shown in Figure 1 where the low signal region (black) corresponds to the same enhancement region shown in (A). This is the same region that a shift of the ROI was observed in Figure 1 and due to motion it is not the same tissue that is subtracted in the images of the different phases.**

(P<0.05) regarding the frequency of kinetic errors.

We observed that the size of the breast influences the extent of deviation between the type of the enhancement curve determined using the software of the system compared to the type of the curve which is determined manually. The extent of this deviation was more pronounced in small breasts with the exception of the dense breasts where the extent of deviation was minimal. In this category, breast laterality plays a significant role with the large majority of the lesions that changed type located to the left breasts.

## Discussion

According to previous reports, the early enhancement is the maximal enhancement obtained within the first 3 minutes after contrast injection (19). When taking curves, in order to avoid partial volume effect or inclusion of necrotic tumoral areas, the use of small ROIs positioned on subjectively recognized areas of maximal constrast enhancement is proposed. That study (19) demonstrates that the type, the dimensions and the positioning of the ROI considerably influences the calculation of the early contrast enhancement which is an important parameter of the dynamic behavior of a breast lesion. The general effect is that as the size of ROI decreases on the maximal enhancement, it increases sensitivity and it reduces specificity and the number of uncertain curves. Vice versa, as the size of ROI increases, it reduces sensitivity and increases specificity and the number of uncertain curves (19). This is due to different possibilities that can take place by reducing or enlarging the ROI: (I) reducing the ROI to a small target on the most vascularized area in a malignant tumor (increasing sensitivity), (II) reducing the ROI to a small target on the most vascularized area in a benign lesion (decreasing specificity), (III) including internal (necrotic or low-vascularized) and/or external (non-neoplastic) areas in presence of a malignant tumor (decreasing sensitivity) and (IV) including internal (low-vascularized) and/or external (normal gland or fat) areas in presence of a benign tumor (increasing specificity) (19).

However, the factors mentioned above may significantly influence the kinetic curve analysis, which is based on the three patterns of signal-to-time curve. Curve type I is defined as a pattern of continuous increase in signal intensity. This enhancement pattern is usually associated with benign findings (83% benign, 9% malignant) (20). Its sensitivity and specificity for indication of a benign lesion are 52.2% and 71.0%, respectively (21). Curve type II is defined as the plateau pattern of enhancement, in which an initial increase in signal intensity is followed by a flattening of the enhancement curve. This pattern has a sensitivity of 42.6% and specificity of 75% for

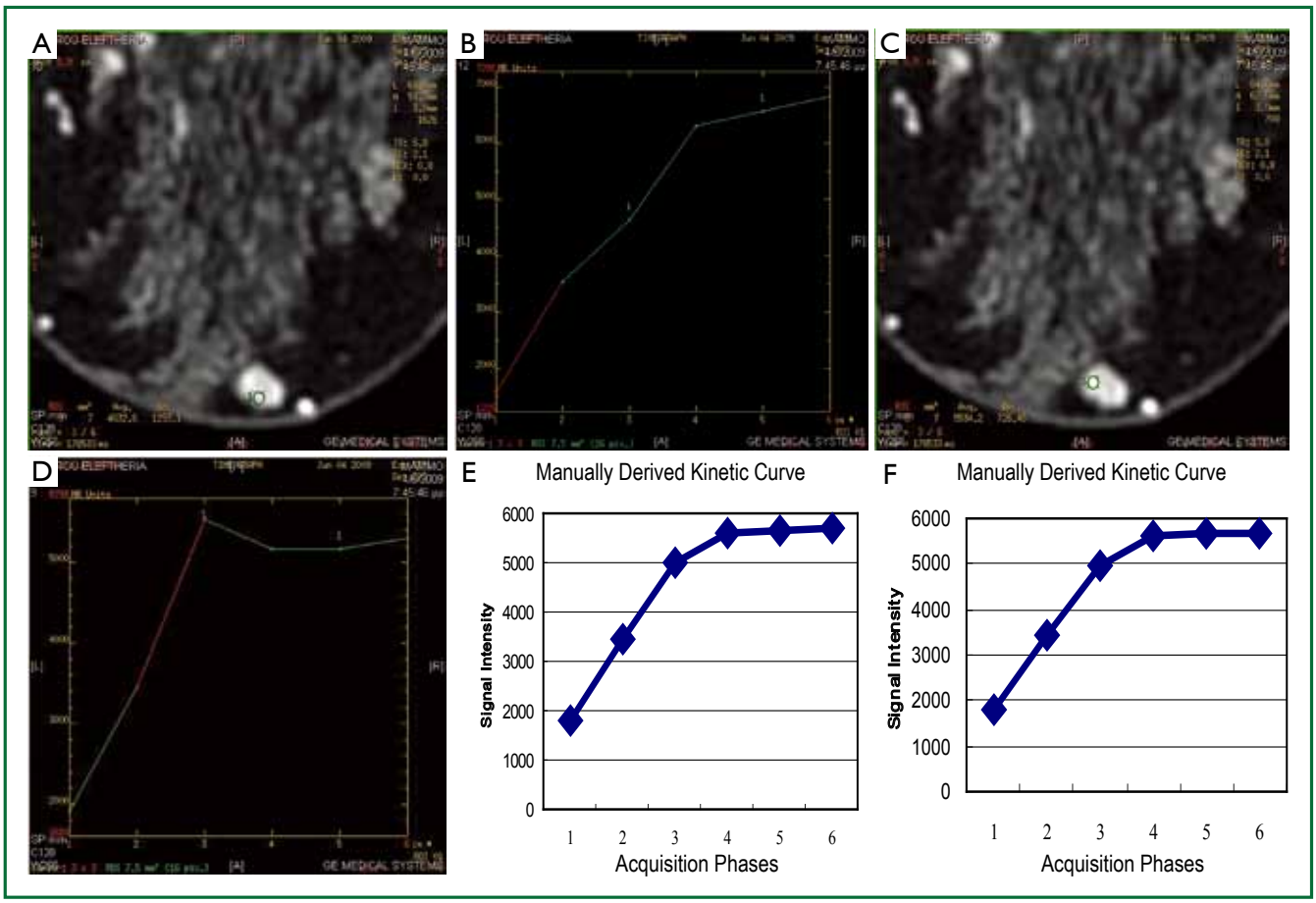


**Figure 5. In this case the ROI was positioned in two different regions [image (A), image (C)] in the third phase of the dynamic sequence. (B) Kinetic curve of type I, which correspond to the ROI of image (A). (D) Kinetic curve of type II, which correspond to the ROI of image (C). Image e and f show derivation of the kinetic curves corresponding to images (A) and (C) using the manual kinetic curve derivation procedure, which were found to be of type II.**

**Table 1. Summary of the kinetic curve type change for the different breast categories examined regarding size, density and laterality.**

| Type change | Yes | No |
|---|---|---|
| Large breast - Dense | | |
| Left breast | 0 | 16 |
| Right breast | 0 | 18 |
| Large breast - Not dense | | |
| Left breast | 5 | 81 |
| Right breast | 8 | 86 |
| Small breast - Dense | | |
| Left breast | 2 | 17 |
| Right breast | 2 | 22 |
| Small breast - Not dense | | |
| Left breast | 50 | 23 |
| Right breast | 14 | 32 |

the detection of malignancy. Schnall and colleagues reported that radiologists in a multi-institutional trial described the enhancement kinetics as persistent (plateau) in 45% of lesions that proved to be cancers (21). Type III curve represents the washout pattern of enhancement and it involves an initial increase and subsequent decrease in signal intensity (specificity 90.4%, sensitivity 20.5%) (21). Schnall and colleagues reported that 76.0% of lesions with washout curves were proved to be malignant (22). Both type II and type III curves should be considered suggestive of malignancy (1).

The inclusion of external non-neoplastic breast gland or fatty tissue in the calculation of the kinetic curves using large ROIs may be the result of inaccurate measurement not only in the same slice (when the ROI includes pixels that are external from the lesion) but also in between different slices (when a small lesion is depicted with a partial volume effect, probably when the size of the lesion is comparable with the slice thickness). The former type of error is easier to be recognized and may be

minimized when the ROI is placed very carefully.

In our study, we observed that in a number of cases of MRM lesions, there was a movement of the ROI in different phases of the dynamic study of a lesion. More specifically, although the ROI was located in a specific region of the lesion at the third phase of the dynamic study, in other phases the ROI was found to be located in another region of the lesion or even outside the lesion. It has to be mentioned that this was the first time that the magnitude of this problem was quantified and its clinical impact was evaluated. Additionally, in this study, the effects of motion were associated with factors such as the size of breast and the density of breast.

Magnetic Resonance Mammography requires a high spatial resolution to resolve morphologic and architectural details of even small tumors. At the same time, fast imaging is required to account for the transient enhancement of breast lesions. This is the "temporal versus spatial dilemma" that current breast MR imaging protocols face. Most of the researchers agree that the temporal resolution should be between 1-2 min with high spatial resolution compared to a more fast protocol of 40 sec temporal resolution and a little lower spatial resolution. In 3T MRI, the signal to noise ratio (SNR) is double compared to 1.5T achieving increased spatial resolution resulting in pixels of small size. We suspect that we could observe this kinetic error in 3T MRI because it becomes more pronounced when small lesions are examined due to the small pixel size and the increased signal-to-noise ratio.

According to Kuhl (23), 3D sequences have increased blurring compared to 2D sequences, especially in the subtraction images. In our protocol, a 3D sequence is used with high spatial resolution and an increased blurring is observed in the subtraction images. Furthermore, subtraction images of lesions with kinetic errors have artifacts in the region where the motion takes place (Figure 4B). It is expected that the subtraction image will have more blurring and a higher probability of showing an artifact because, due to motion, it is not the same tissue that is subtracted in the images of the different phases.

Furthermore, in the same region that we observed the artifact at the subtraction images, we also observed both increased enhancement and increased washout in the mapping images (Figure 4A). It is straightforward that, in order to have correct results in the subtracted and mapping images, we should not have motion of the patient involved.

Overall, there are three ways for identifying a potential kinetic error: (I) ROI placing, (II) image subtraction and (III) image mapping. Its observation in all three of them could ensure that there is an error, which will also introduce kinetic curve errors.

In recent years, there is a number of image registration methods that have been suggested for reducing kinetic errors (13,24,25). However, the non-rigid, inhomogeneous, anisotropic and temporally changing nature of breast tissue makes breast image registration a challenging task. Breast image registration methods are a compromise among accuracy, precision, reliability, robustness, and issues-like automation, interactivity, speed, and patient-friendliness (13). Despite these constraints, we propose the integration of such image registration tools in the existing breast image processing systems, especially in 3T where the impact of these kinetic errors is more pronounced.

Consequently, it is recommended that for the correct production of the kinetic curves, it should be examined if the ROI's placement remains at the same region of the lesion in all the series of the dynamic phase. In order to achieve this goal, the position of the ROI should be estimated from stable reference point (e.g., skin, sternum, muscle). Regarding the accuracy of the results produced by the manual method, the procedure was repeated by different users for a number of lesions and the results were found to be identical.

When the ROI is placed in the mapping images, it should also be examined if the position of the ROI coincides with the true area to be measured. Due to motion, the mapping images are more sensitive to false positive results because they will show increased signal intensity in the phase of enhancement or increased decay in the later phases (Figure 4). Working on the mapping images it is easier to place a ROI in the region with the highest enhancement due to the fact that this region is colored (red color). However, as we have already stated, the errors that we measured were the same irrespectively whether we placed the ROI using the mapping image or the DCE image. On the contrary, we tested all the different techniques (placing the ROI in the mapping image as well as in the DCE image) in order to avoid bias. Especially, in the mapping image, the red colored region was the one that was more prone to motion.

In our study we found that a change of the enhancement kinetic curve type was found in a considerable proportion of the cases (21.5%). This observation was most pronounced in the small and non-dense breasts and in this category most of the errors were observed in the left breasts. The fact that most of the curve errors were observed in small and non-dense breasts led us to suspect that the source of those errors may stem from non firm immobilization of the breasts due to the large size of the coil that was used. Large breasts usually have a more firm immobilization for the type of the coils used. In these cases, the lesions did not show kinetic errors. We propose the performance of prospective studies using coils of different sizes to prove if there can be any correlation between the reduction of curve errors and the size of the coil. Based on our experience, such a coil could have more than two depressors in order to achieve a more firm and homogeneous immobilization.

Based on our observation that left breasts were more prone to errors in the kinetic curves, we assume that these errors stem from the cardiac motions. In the future, it should be possible to perform dynamic studies using breathing or cardiac gating in case that the technical errors observed are characterized by

periodic patterns. However, in 3.0T MRI the increased signal/noise ratio combined with a reduced spatial resolution could keep the dynamic sequence time in clinically acceptable limits.

The manufacturers have developed tools for image registration but those tools are generic for all types of imaging examinations and they are usually used to eliminate the presence of motion or perform a correspondence between different sequences in order to apply a subtraction technique and there is movement of the patient. Furthermore, many imaging systems do not offer image registration tools (in their standard version or at all), which makes the use of a manual technique inevitable.

However, although a number of image registration techniques have been developed to account for the effects of motion, their efficiency and accuracy are limited by the complexity of the task to correct the presence of motion. So, although the use of image registration techniques offers speed and convenience at the same time they are subject to limitations. For example, the choice of algorithm magnitude of motion and timing of the motion are each shown to influence estimated pharmacokinetic parameters even when motion magnitude is small.

To overcome the problem imposed by motion in DCE-MRM, it is necessary to correct patient motion by deformable registration, before the acquisition of the DCE-MRI. However, the dramatic contrast change over time (especially between the precontrast and postcontrast images) makes the conduction of deformable registration of DCE-MR images difficult (26). Most existing methods typically register each postcontrast image onto the precontrast image independently, without considering the dynamic contrast change after agent uptake. This could lead to the inconsistency among the aligned postcontrast images in the precontrast image space, which will eventually result in worse performance in cancer detection (26). Similarly, Melbourne *et al.* (27) performed an analysis of the effect of registration completeness and timing of subject motion, which revealed that a higher degree of motion increases model-fit residuals. Motion at a time when contrast arrives is particularly undesirable and the choice of registration algorithm matters, even when motion artifacts are small (27).

Factors such as the Ktrans should be incorporated in the evaluation of the tumor histologic grade. Patankar *et al.* (6) reported that the Ktrans factor showed good discriminative power in distinguishing between low- and high-grade tumors with diagnostic sensitivity and specificity >90%. Similarly, Ah-See *et al.* (28) reported that Changes in breast tumor microvessel functionality as depicted by DCE-MRI early on after starting anthracycline-based neoadjuvant chemotherapy can predict final clinical and pathologic response with the Ktrans being the best predictor of pathologic nonresponse. Liu *et al.* (29) reported that indicators of a vascular response, such as the volume transfer constant (Ktrans) were calculated to assess the effect of treatment on tumor vascular function and they concluded that vascular response measured using DCE-MRI seems to be a useful indicator of drug pharmacology, and additional research is needed to determine if it is a suitable marker for predicting clinical activity. Finally, Springer *et al.* (30) reported argue that the ΔKtrans subtraction minimizes/eliminates many other systematic DCE-MRI quantification errors. However, none of all these studies investigated the impact of motion and proposed way for its elimination.

The present study, involves a manual approach, which is more accurate in order to demonstrate the extent of the uncertainty due to motion and be used as a benchmark for evaluating different automatic image registration algorithms and software. The presented technique can be easily applied without having as a prerequisite any special technology beyond the standard one and it may be time consuming only when there are many pathologies involved in a breast case. However, in cases involving many pathologies, the use of image registration tools may also be complex and time consuming because the magnitude of motion changes with the position of the breast and time. So, the different image registration algorithms have to be evaluated in such situations regarding their ability to reduce or even eliminate motion effects in the derivation of kinetic curves. The development of computational algorithms for automatic ROI placement based on the distances of the ROI from stable reference points (e.g., skin, sternum, muscle) is proposed. These algorithms should reduce or even eliminate the effects of the breast image registration constraints.

## Conclusions

Having examined a large number of kinetic errors, a direct effect on the type of the kinetic curves could be observed, which may lead to a reduction in the accuracy of the examination. In order to avoid potential errors in the kinetic curves, in all the measurements of kinetic curves, it should be verified that the ROIs are placed at the same location of the lesions in all the images of the dynamic phases. In the cases that a kinetic curve error is identified, the kinetic curve must be produced manually by measuring the distances of that ROI from stable fiducial points (thoracic muscle, skin, ribs and sternum). Further clinical studies should be carried out using larger patient populations and different MRI systems in order to cross-verify our observations and support the generality of our conclusions.

## Acknowledgements

*Disclosure:* The authors declare no conflict of interest.

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**Cite this article as:** Lavdas E, Mavroidis P, Roka V, Arikidis N, Arvanitis DL, Fezoulidis IV, Vassiou K. A method for limiting pitfalls in the production of enhancement kinetic curves in 3T dynamic magnetic resonance mammography. J Thorac Dis 2012;4(4):358-367. DOI: 10.3978/j.issn.2072-1439.2012.07.15