Analyzing DCE-MRI data

Min-Ying Lydia Su, PhD

Tu & Yuen Center for Functional Onco-Imaging, University of California, Irvine, CA, USA
E-mail: msu@uci.edu

I. Overview

Dynamic Contrast Enhanced MRI (DCE-MRI) is a rapidly evolving imaging technique. It is the current standard for breast MR imaging; also many research studies have been conducted to evaluate its application for various clinical problems. The development of gadolinium-based contrast agents in early 1980 opened a new era for imaging of tumors and vascular systems. Tumors require a higher supply of nutrients to support the rapid growth; as such it is necessary to induce formation of new blood vessels, termed "angiogenesis". One of the earliest applications of Gd-based contrast agents is for enhancement of viable tumors on post-contrast T1-weighted images. The typical scan protocol includes pre-contrast images and post-contrast images, and the enhanced tumors can be detected by visual inspection of post-contrast images referencing to pre-contrast images. Further research has found that if multiple sets of post-contrast images at different times after injection were acquired, the enhancement time course (or, enhancement kinetics) could be measured, and that provided additional information to aid in distinguishing malignant lesions from benign lesions and normal breast tissues. This technique was termed "dynamic contrast enhanced MRI" or "DCE-MRI". In conjunction with the development of pulse sequences by scanner manufactures, DCE-MRI can now be easily prescribed with preferred spatial and temporal resolution, and the total imaging period, by pushing buttons.

This tutorial is focused on the analysis of DCE-MRI data. I will begin by discussing the technical aspects of DCE-MRI. A simple approach of heuristic parameters from the time intensity curves will be contrasted with quantitative approach based on curve fitting using pharmacokinetic models and yielding parameters Ktrans and kep. Since DCE-MRI is most established for breast imaging, I will describe how the analysis is commonly applied to imaging of breast lesions. The ROI-based and pixel-by-pixel based analyses are the two main methods. For diagnosis, the hot spot ROI approach to characterize tissues with the most aggressive pathology should be taken; but for therapy response monitoring, the whole tumor should be analyzed. Following the application in the breast, I will briefly describe DCE-MRI applications to other organs. Lastly the available tools for analysis of DCE-MRI provided by major scanner manufactures and the two most-widely used commercial software (CADstream and DynaCAD) will be described.

The objective of this tutorial is to provide an overview for analysis of DCE-MRI data, first using the application in breast imaging to give in-depth examples, then extending to other organs; and lastly to illustrate the available tools provided by major manufactures.

II. Analysis of DCE Kinetics using Heuristic Parameters and Quantitative Ktrans and kep

Measurement of enhancement kinetics

The T1-weighted 3-dimensional gradient echo sequence is the most commonly used sequence for acquiring DCE-MRI. It covers the entire lesion without gaps, generates good quality images, and can be acquired within a short imaging time. The DCE kinetics can be analyzed using a straightforward approach to measure the increased signal intensity, or a more sophisticated approach to convert the measure signal enhancement to the concentration of the contrast agents to allow for pharmacokinetic modeling analysis to obtain parameters that are associated with physiological parameters. The most commonly used approach measures the percent enhancement at time t as: $[S(t)-S0] / S0 \times 100\%$. The signal enhancement is calculated by subtracting the pre-contrast signal intensity S0 from the post-contrast signal intensity S(t), and then normalized to the pre-contrast signal intensity S0 to calculate the percent enhancement. Normalization to S0 is necessary to handle the problem of varying coil sensitivity, thus allows for comparison of tissue enhancements across the entire imaging field of view. Because the pre-contrast signal intensity is also dependent on the pre-contrast T1 relaxation time (T10) of the tissue, the normalized % enhancement is also dependent on the T10. This approach is easy and does not require multiple calibration scans, and is commonly used in clinical examinations.

On the other hand, if the purpose is to obtain indirect physiological parameters from the transport kinetics of MR contrast agents as tracer, the concentration of the contrast agents needs to be measured to allow such precise analysis. All Gadolinium-based contrast agents are extracellular agents, and can be distributed in the vascular and interstitial spaces. Under assumption of the fast exchange regime, the concentration is proportional to the increased T1 relaxivity ($R1=1/T1$), thus the T1 relaxation time before injection (T10) and at post-injection time points have to be measured. The gradient echo sequences using different flip angles are commonly used. The T10 can be estimated using 3 flip angles (5°, 10°, and 15°). Given the needed temporal resolution during the DCE acquisition, most studies only use one flip angle after injection (e.g. 15°), and the T1(t) is estimated by referencing to the proton-density images acquired before injection using 5° flip angle. The next step is to convert the increased R1 to the concentration of the contrast agents based on the

linear relationship (R1[C]-R10 = constant x [C]). The proportional constant will be different in different tissues and cannot be accurately measured, but the common approach is to use the constant measured in water or saline to give an estimate. After the concentration kinetics is obtained, it can be analyzed using the pharmacokinetic model to obtain parameters that are associated with vascular properties (vascular perfusion and permeability). However, the clinically approved Gd-based contrast agents are low molecular weight agents, and they do not yield precise measurements that are respectively associated with perfusion and permeability; rather the combined effects are seen.

Analysis of enhancement kinetics

The enhancement kinetics can be evaluated using 3 distinct features, the was-in phase, the maximum enhancement, and the wash-out phase. Several heuristic parameters can be analyzed from the curve, such as wash-in slope (maximum slope, or the slope within a time period), the % maximum enhancement, time to maximum, and the wash-out slope (within a time period). Since these parameters may be affected by the noise level at different data points, a more robust and commonly used parameter is the IAUC (initial area under the curve), which integrates the area under the kinetic curve, usually during the early time period such as the first 90 seconds. This parameter reflects how fast and how much the contrast material is delivered to the lesion.

A more sophisticated analysis method is to perform pharmacokinetic analysis based on two compartmental models, commonly referred as the unified Tofts model [1-2]. The two compartments are the vascular space and the interstitial space, with the exchange rate constant Ktrans to leak from the vascular to the interstitial space, and the rate constant kep from the interstitial space back to the vascular space. The change of concentration in the interstitial space (Ce) is expressed as dCe/dt = Ktrans (Cb) – kep (Ce). Another parameter considered in the model is the distribution volume in the extravascular-extracellular space ve (within the interstitial space). The total concentration in the tissue can be written as the contribution from both vascular and interstitial compartments as Ct= vb Cb + ve Ce. Many parameters can be included in the fitting model, but the problem of over-fitting needs to be concerned. Although the vascular compartment has to be present, yet whether the fitted parameter, such as vb, is truly reflecting the vascular space is a great concern. Since all clinical Gd-based contrast agents are small agents that can quickly diffuse from the vascular space to the interstitial space, the fitted vb is very likely to contain the early leakage space in the interstitial space, thus not accurate. Due to this concern, the most commonly used model (Tofts model) assumes a relatively small vascular space compared to the interstitial space and ignores the distribution in the vascular space. Thus, the tissue concentration is expressed as Ct = ve Ce, where Ce is dependent on the blood concentration Cb. However, when the analysis is performed for highly vascularized lesion, the vb may not be ignored.

The blood kinetics is required to fit the measured concentration in the tissue. When the absolute concentration of the contrast agents (such as mmole/liter) in both the tissue and the blood are measured and used in the fitting, the unit for Ktrans and kep is 1/time (commonly used as [1/min]). If diffusion is the only process involved for transport of contrast agents between vascular and interstitial compartment, the exchange rate between Cb and Ce should be equal. The transport equation can be rewritten as dCe/dt = Ktrans (Cb) – kep (Ce) = Ktrans (Cb) – Ktrans (Ce/ve). As such, kep = Ktrans/ve, and ve can be obtained as Ktrans/kep (0<ve<1). If the absolute concentration is not obtained for either the tissue or the blood, the fitted parameters Ktrans will carry an arbitrary unit (depending on which parameter is used in fitting, such as the percent enhancement), but the unit for kep is always [1/min]. Nevertheless, when the changes of the fitted parameters are analyzed in therapy monitoring studies, a percent change can be calculated regardless of the unit that Ktrans carries, as long as the acquisition and the analysis are performed consistently.

The individually-measured versus the general-population arterial input function (AIF)

Since the blood concentration is required for fitting, one area of debate is whether the arterial input function should be measured from each individual patient. The advantage is to provide the most accurate blood kinetics taking into account the different hemodynamics of individual patients; but the disadvantage is the difficulty in measuring the AIF accurately and if the measurement is wrong, it may lead to a large error in the fitted parameters. The preferred artery for measuring the AIF from is the one directly feeding the lesion. As such, a high spatial resolution is needed to delineate the vessel and to avoid partial volume effect (the voxel has to be completely contained within the vessel); also a very high temporal resolution is needed to catch the maximum enhancement. Further, the image quality has to be good to obtain smooth enhancement kinetics without too much noise or fluctuation. The motion artifact, including respiratory motion and pulsation of vessels, may lead to degradation of the vessel image. All these problems lead to difficulty in measuring AIF accurately from the small feeding artery. The alternative approach is to measure the AIF from the large artery such as the aorta; but the high velocity of blood flow needs to be properly handled, also the AIF measured from the aorta may not truly reflect the AIF of the direct feeding artery to the lesion.

Due to these difficulties, the blood kinetics measured from the healthy general population provides a reasonable and acceptable approach. As long as the patient does not have cardiovascular problems or kidney diseases, the general population blood kinetics can be used in the pharmacokinetic model fitting to obtain Ktrans and kep; and since the results are obtained using the unified model, the fitted parameters may be compared between different studies. However,

while this is acceptable for studies dealing with lesion diagnosis or characterization, it is not appropriate for therapy monitoring studies, particularly for those designed to measure the vascular changes in clinical trails of anti-angiogenic or anti-vascular therapeutic agents. It is recommended that the individual AIF be measured and used as reference [3]. However, given the requirement of both high spatial and temporal resolution, the reliability of the measured AIF for the targeted organ needs to be investigated before designing the imaging protocol for such studies [4]. The reproducibility of the AIF measurement needs to be performed first to allow subsequent data analysis and interpretation, at least to estimate the possible error introduced by the variation in the measured AIF [5].

<u>Lesion ROI-based analysis and pixel-by-pixel analysis</u>
The choice of the Region of interest (ROI) based or pixel-by-pixel based analysis is usually dependent on the application. As described earlier, for diagnostic purpose the hot spot ROI approach should be used and for therapy monitoring study the pixel-by-pixel analysis should be applied. The advantages for ROI-based analysis include that it is less susceptible to noise and signal fluctuation through averaging over many pixels, and the fitting to obtain Ktrans and kep is unlikely to fail so that the obtained results can be directly used in the analysis. The advantage for the pixel-by-pixel analysis is the rich data obtained from the entire lesion that allows for histogram analysis within the lesion. The disadvantage includes that the kinetics measured from some pixels may be very noisy, and the fitting quality needs to be checked. Usually the pixels with unsatisfactory fitting quality need to be discarded in the analysis.

<u>Image registration for pre- and post-contrast DCE frames</u>
One major problem leading to poor quality of the DCE kinetics is the motion during the DCE acquisition, including both patient movement and physiological motion such as breathing and heart beat pulsation. A rigid-coregistration process is usually applied to spatially align all DCE frames with respected to one selected reference frame. One concern is that the co-registration should be applied to the organ of interest, not the entire image. For example, for breast imaging, the co-registration should not be done to align the thoracic body region while compromising the co-registration of the breast region. Regional co-registration is the commonly used approach.

III. DCE-MRI for Diagnosis of Breast Cancer
Tumors, particularly the more aggressive malignant tumors, need angiogenesis to support the rapid tumor growth. The angiogenic vessels are leakier (that is, with a wider endothelial junction), and that allows contrast agents to quickly leak from vascular space into the interstitial space, and then back diffuse to the vascular space to be cleared. Many studies have investigated the diagnostic capability of DCE-MRI to differentiate between benign and malignant breast lesions [6-7]. In general, malignant lesions are more aggressive, and require a higher angiogenic activity. More new vessels are formed, and these vessels are leakier. When the contrast agents are injected, the higher vascular space and higher vascular permeability allow more contrast agents to be quickly delivered into the interstitial space of the lesion, also the agents can quickly diffuse back to the vascular space to be cleared. As such, the enhancement kinetics shows a rapid wash-in, reaches to the maximum enhancement quickly, and then starts to show wash-out. In contrast, benign lesions may not have a large number of angiogenic vessels, but still have a high interstitial space to uptake contrast agents, and the enhancement kinetics shows a slow but persistent enhancing pattern. Although these two patterns have been proven as reliable diagnostic features, many lesions show the enhancement kinetics in between, reaching a plateau during the imaging period without clear wash-out or persistent enhancements. Particularly given the heterogeneous nature of lesions, the enhancement kinetics varies with tissue location, or the placement of the ROI within the lesions.

The research results obtained over a decade provide strong evidence suggesting that a higher spatial resolution to reveal the morphology of the lesion in greater details has a better diagnostic value [8]. The current protocol for diagnosis of breast lesions emphasizes the spatial resolution over the temporal resolution. As for the number of post-contrast imaging data sets to cover a time period, it needs to be long enough for evaluating the kinetic pattern, usually several more minutes after reaching the maximum. Given the concern of the total imaging time in clinical workflow, it is usually between 5 to 10 minutes. The general rule is that one set of high quality post-contrast images should be acquired within 2 minutes after injection of contrast agents for lesion detection and morphological characterization, and that the kinetics over a period of 5-10 minutes should be measured for determination of the pattern. Both lesion morphology and kinetic pattern need to be considered when giving a final diagnostic impression.

IV. DCE-MRI for Therapy Monitoring of Breast Cancer Undergoing Neoadjuvant Chemotherapy
In addition to diagnosis, another major application of DCE-MRI is for monitoring response of breast cancer undergoing neoadjuvant chemotherapy (or, pre-operative chemotherapy) [9-10]. The size or the disease extent of lesions before starting of therapy should be established as the baseline reference. For diagnosis of lesion size after therapy, the patterns of the enhancement kinetics should no longer be used as diagnostic criteria. Rather, any enhanced tissues within the tumor bed are considered as the residual disease. It is well known that the therapy also causes vascular damage, and the enhancement kinetic pattern will change from the wash-out pattern to a less aggressive pattern of plateau or persistent

enhancement. Many studies have investigated whether the change of enhancement kinetics is associated with the final treatment outcome, and hence may serve as an early response predictor. Although some encouraging results have demonstrated that the changes in the exchange rates (Ktrans, kep) or other heuristic parameters (such as wash-in slope, maximum % enhancement, initial area under the enhancement curve) showed significant differences between good responders versus poor responders, yet they could not reliably predict the treatment outcome. Furthermore, when compared to the early changes in tumor size, most published studies reported that these kinetic parameters are inferior to the size changes for predicting the final treatment outcome using the standard chemotherapy regimens.

The more attractive role of DCE-MRI is to evaluate the response of anti-angiogenic or anti-vascular therapy, particularly in early clinical trails during the drug development phase [11-12]. To date, Trastuzumab (Avastin®, an antibody targeting VEGF) is the only clinically approved anti-angiogenic agent for treating metastatic breast cancer, through neutralization of vascular endothelial growth factor (VEGF). DCE-MRI provides a means for assessing the treatment-induced vascular changes, preferably before the size change occur, to better understand the therapeutic mechanism of the drugs. It may provide insightful information to evaluate the efficacy of drugs in clinical trial phases, and to guide the design for future studies. For this purpose, the changes in the entire tumor need to be evaluated, in contrast to the hot-spot approach used for diagnosis. The most useful analysis method is to perform pixel-by-pixel analysis of the enhancement kinetics from the entire tumor, and the histograms of the analyzed parameters can be compared between studies performed before and after therapy to evaluate changes. Since the parameters measured in different studies will be compared, other confounding factors that may affect the changes need to be considered. One most important factor is the difference in the arterial input function. An international consensus panel for application of DCE-MRI in drug trials recommended that the arterial input function be measured on individual basis, and used as reference to obtain quantitative parameters such as Ktrans and kep, or at least to provide a reference for normalization of lesion enhancements for evaluating changes [3]. However, the subsequently published studies revealed great difficulty in obtaining the AIF reliably and consistently [4]. If the measured AIF were problematic, using that to serve as reference would lead to an even higher error in fitted parameters compared to using the AIF of the general population.

V. Application of DCE-MRI in Other Organs

DCE-MRI has been extensively applied in other organs in addition to the breast. It is a suitable technique for studying solid tumors (or, any mass lesions) in any organ in the body, including brain, lung, liver, spinal cord, vertebrate, kidney, prostate, ovary, cervix, and musculoskeletal systems. The DCE kinetic parameters from the lesion and the adjacent normal tissues can be characterized according to methods described above. In the liver, it has been shown that the dual vascular supply from the hepatic artery and the portal vein can be modeled appropriately [13]. Since the normal tissue parenchyma in the liver and kidney shows early and strong enhancements, another very important application of DCE-MRI is to provide multiple sets of post-contrast images, to allow for the capture of the arterial phase image without having to time the acquisition based on contrast arrival time. Several examples will be shown.

VI. Analysis Tools of DCE-MRI Provided by Major Scanner Manufactures and Commercial Venders

Currently there are two main software dedicated for analysis of breast DCE-MRI, CADstream® by Confirma Inc. (Bellevue, WA) and DynaCAD® by Invivo corp. (Orlando, FL). Although the CAD (computer-aided diagnosis) system is mainly designed for analysis of breast DCE study, it can be used to analyze any DCE data. The features provided by these two systems are similar. The tools provided by CADstream and DynaCAD systems will be illustrated. The software detects the DCE sequence and imports all images for analysis. The typical display includes rendering maximum intensity projection (MIP) and the corresponding view from 3 planes (axial, sagittal, coronal)- one acquired and two reformatted. The color-coding to label the suspicious enhancements can be turned on based on the choice of the threshold enhancement to show color-coding, and the two post-contrast frames selected for determining the wash-out pattern. Typically the red color is used to label the voxel showing wash-out, green to label plateau, and blue to label persistent enhancing pattern. The preferred color can be changed. The DCE kinetics from the hot spot or the selected ROI is displayed on the screen, and the enhancement threshold and the selected frames for analysis of wash-out can be easily changed by moving the cursor. The percentage of voxels within the lesion that show wash-out, plateau and persistent enhancing pattern is calculated. The program also provides the lesion segmentation tool based on connectivity of enhanced tissues. A square can be placed over the enhanced lesion, and the 3D view of the lesion can be displayed. The 3 dimensional size, as well as the total volume of the lesion, is given. The morphology of the lesion has to be interpreted by the radiologist and recorded. Finally a report summarizing all key findings will be generated for each case. Based on all presented information, a final diagnostic impression or the BI-RADS score can be given. While these two systems can be purchased as standing-alone off-line systems for any scanners, the three major MRI scanner manufactures are working to integrate the CAD systems to the scanner for on-line analysis. The capability for on-line processing is mostly useful for planning MR-guided biopsy. Philips owns Invivo and has integrated DynaCAD into their scanner for guiding biopsy. GE owns Confirma and offers CADstream. Siemens is currently developing their own CAD system (Brevis®) for breast diagnosis. They are planning to apply for FDA approval after the biopsy guiding capability

has been implemented. Another major manufacture, Aurora Imaging Technology Inc., which makes breast specific MRI systems, has their own on-line CAD and biopsy-guiding systems.

Siemens is currently developing another software (Tissue 4D®) for quantitative analysis of DCE data. The program analyzes the two pharmacokinetic parameters, Ktrans and kep, pixel-by-pixel within the selected ROI. The increased T1 relaxivity is converted to the concentration using an estimated proportional constant provided by the software. Three blood kinetic curves (fast, medium, and slow flow) are built-in and can be selected based on the organ of interest. Two fitting models are provided, the Tofts model (ignoring the vascular space) and Tofts+vp (considering the vascular space). The obtained fitting parameters from the pixel-by-pixel analysis within the selected ROI can be displayed as overlaying color-maps and histograms, also the data can be exported for further analysis. This is the only software provided by the major scanner manufacture that offers the capability for quantitative analysis of Ktrans and kep. This program is expected to be released during the first quarter in 2009. It is highly anticipated that the availability of this standard analysis tool will facilitate comparison of quantitative DCE studies, which could not be done before due to many various approaches taken by different research groups.

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