ROI or Voxel DCE Analysis in Clinical Applications

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, and it is widely applicable in management of various cancers. It is the current standard for breast MR imaging; also many research studies have been conducted to evaluate its application for other cancers. This tutorial is focused on the analysis of DCE-MRI data, and how the analyzed parameters are used in clinical diagnosis and therapy monitoring. Since DCE-MRI is the most established for breast imaging, I will use breast cancer as examples. 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 is commonly used; but for therapy response monitoring, the whole tumor should be analyzed. The commercial software that is available for quantitative analysis of DCE-MRI will be described.

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 x 100%. 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. 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 increased R1 is then converted 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 wash-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. 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.

ROI-based analysis and pixel-by-pixel analysis

The choice of the Region of interest (ROI) based or pixel-by-pixel based analysis is usually dependent on the application. For diagnostic purpose the hot spot ROI approach is commonly 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.

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 [3-4]. 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, and the optimal approach is to generate pixel-by-pixel maps of DCE parameters, and the operator can choose a hot spot to evaluate the DCE kinetics. The final diagnosis will be made based on the hot spot data as well as the spatial distribution pattern within the lesion.

Three dedicated analysis software for breast MRI are commercially available, including CADstream (by Merge CAD Inc. Bellevue, WA), DynaCAD (by Invivo Corp. Orlando, FL) and CADvue (by iCAD, Inc. Nashua, NH). The approach is similar. The identification of suspicious tissues is based on the choice of a pre-set threshold enhancement to show color-coding. The DCE pattern is determined based on the signal intensities on two selected post-contrast frames. 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 measured from the hot spot or the selected ROI can be obtained for further analysis. The percentage of voxels within the lesion that show wash-out, plateau and persistent enhancing pattern can be calculated.

The diagnostic breast MRI research obtained to date provide strong evidence suggesting that a higher spatial resolution to reveal the morphology of the lesion in greater details has a better diagnostic value [5]. 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 8 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 5-8 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. Although the current analysis software is

named as CAD (computer-aided diagnosis) system, however, it does not provide diagnostic information. A current research area is to integrate the quantitative morphological and DCE parameters to give diagnostic impression [6]. As we have shown, compared to the whole tumor ROI, the hot spot ROI DCE analysis yields a higher diagnostic accuracy. However, the DCE pattern analysis is only good for diagnosis of lesions that present as masses with well-defined boundaries, not for diagnosis of lesions that present as non-mass like enhancements [6]. Whether the distribution of DCE parameters has a diagnostic value needs to be further investigated.

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). 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) [7-9] or other heuristic parameters (such as wash-in, wash-out slope, maximum % enhancement, initial area under the enhancement curve) [10-11] 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. Since pixel-by-pixel analysis is performed, a wealth of information can be extracted. One current research area is to evaluate which DCE parameter(s) is the best predictor of final pathologic response. In a multi-center study sponsored by American College of Radiology Imaging Network (ACRIN 6657), signal enhancement ratio (SER) was analyzed. SER was defined as the signal enhancement ratio between two time points t1 (e.g. 2.5 minutes) and t2 (e.g. 7.5 minutes) as [(S1-S0)/(S2-S0)]. It has been shown that this ratio is approximately proportional to the kep within a wide kep range commonly seen in breast cancer [10]. Due to the nature of multi-center study, variations in the imaging protocol at different sites are expected, and using a heuristic parameter is more likely to guarantee that a reliable parameter can be obtained. Once a parameter map, such as SER, is available, many parameters may be analyzed. For example, the number of pixels above a certain threshold, the percentile value (10%, 25%, 50%-median, 80%, etc.) of pixels within the lesion, or the distribution of these pixel values (e.g. kurtosis [12]) can be measured. If a parameter measured at an early time after starting of the therapy can differentiate between good responders vs. poor responders at completion of therapy, it may serve as an early indicator to predict therapeutic efficacy. This is particularly helpful to spare patients from unnecessary toxicity of ineffective therapy. It has also been shown that DCE parameters may be combined with morphological parameters of the lesion to improve the prediction accuracy [13]. For prediction of patient's prognosis after therapy, DCE parameters are often combined with other clinical characteristics (tumor size, volume, biomarker, and other clinical prognostic factors) for combined analysis [10-11].

Another 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. 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. Since the parameters measured in different studies during therapy 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 [14]. However, the subsequently published studies revealed great difficulty in obtaining the AIF reliably and consistently [15]. If the measured AIF were problematic, using that to serve as reference would lead to an even higher error in fitted parameters compared to those analyzed using the AIF of the general population. One alternative solution is to measure the hemodynamics of individual patients as references instead of measuring the AIF. Although progress in this research area is slow due to the complexity of the problem, it is needed to provide a detailed account of the drug induced vascular changes during the developmental phase of the drug.

V. Quantitative DCE Analysis Software

Quantitative analysis of DCE data reported in the literature was generally performed using in-house software developed by individual research groups. With the maturity of the DCE analysis in the breast and prostate, the MRI CAD companies are developing commercial product for performing quantitative, pixel-by-pixel, analysis. The first well-established product was Tissue 4D®, developed by Siemens for DCE analysis in the prostate. 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. The three companies developing CAD systems for breast MRI (Merge CAD, In vivo, and iCAD) are also working in this field. In addition to specific software for the breast and prostate, it is highly anticipated that DCE tools for other organs will become available in the near future.

Given that pixel-by-pixel analysis will yield much more information compared to the ROI-based analysis, and that the analysis software has become more and more widely available, voxel-based analysis will become the standard in the future. It is highly anticipated that integrated research combining DCE and morphological analysis will be the main focus in either diagnosis or therapy monitoring for management of cancer. In addition to the breast and prostate, this analysis approach may be extended to cancers in other organs as well.

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