Background: Assessment of tissue perfusion by means of model-based dynamic contrast-enhanced MRI (DCE-MRI) with derivation of quantitative (K único, k ep, V e) and semi-quantitative (IAUGC) pharmacokinetic (pk) parameters was introduced 20 years ago. Since then, the potential of this concept to serve as a non-invasive biomarker has been shown by various preclinical and clinical studies. Many efforts are currently underway to establish the accuracy and precision of this approach to enable comparison of pk parameters across imaging platforms, clinical sites and time. Although many factors contributing to overall measurement error have been identified, the effect of commercially available DCE-MRI post-processing solutions on pk measurement derivation has yet to be defined.

Purpose: To test the reproducibility of model-derived quantitative and semi-quantitative pk parameters between various commercially available post-processing solutions for DCE-MRI.

Material and Methods: Uterine fibroids were considered as perfusion model because lesions are well delineated and reside in a low motion environment. The 15 largest uterine fibroids in 15 randomly selected female patients (mean age 44 years, range 28-60 years) were defined as the study group. All DCE-MRI studies were performed at 1.5T (Avanto, Siemens, Erlangen, Germany), using variable flip angle T1 mapping (flip angles: 2, 8, and 20 degrees) and a 4D, time resolved MR angiography sequence with interleaved stochastic trajectories (TWIST) after the injection of 0.1 mmol/kg gadobenate dimeglumine (Bracco Diagnostics, Princeton, NJ). DCE-MRI studies were post-processed on four unique commercially available workstations using a Tofts model paradigm: Tissue4D™ (Siemens, Erlangen, Germany), DynaCAD™ (Invivo, Gainesville, Florida, USA), Aegis™ (Sentinelle Medical, Toronto, Ontario, Canada) and CADvue™ (iCAD, Inc. Nashua, NH, USA). Subject-related settings for DCE-MRI post-processing (e.g., height, contrast type & volume, T1 mapping, contrast arrival time, arterial input function [AIF]) were specified if requested by the software. If T1 mapping was not an available parameter (DynaCAD™, Aegis™) an average T1 time of 1043 ms was used based on T1 map calculations from all datasets. Five readers prospectively measured K único, k ep, V e, and IAUGC by placing two unique regions of interest (ROI), user defined vs. targeted placement) within a single previously selected uterine fibroid. Measurement was done on each workstation in random order and repeated 3 times for each study, resulting in 7200 data points. Mean comparison (ANOVA), intraclass-correlation coefficient (ICC), root mean square coefficient of variation (RMSCoV) to estimate within subject coefficient of variation (wCV) and Bland-Altman limits of agreement were calculated.

Results: Initial median comparison (Figure 1) revealed a difference of pk data output from two workstations by a magnitude of 10 (CADvue™, K único, k ep, DynaCAD™, K único, k ep, V e) or 100 (DynaCAD™, V e) compared to the other. Figure 2 demonstrates the wCV for each workstation combination by pk parameter (range: 25.1 to 74.1%), calculated by RMSCoV. Figure 3 demonstrates Bland-Altman limits of agreement for each workstation combination by pk parameter output following rescaling to account for magnitude differences in pk expression between workstations. Table 1 illustrates which workstation combinations there was no significant difference for each rescaled pk parameter. ICCs showed a strong correlation between readers significantly >0.9 (p<0.05; range 0.95-0.98). Pharmacokinetic measurements were not significantly different between the two ROI methods (p>0.05; mean ICC 0.85; range 0.58-0.95). The range of ICCs for each workstation combination by pk parameter were: K único: 0.33-0.68, k ep: 0.02-0.81, V e: -0.03-0.72, and IAUGC 0.47-0.78.

Conclusion: There is substantial variability for DCE-MRI pharmacokinetic parameters (K único, k ep, V e, IAUGC) across different commercially available DCE-MRI post-processing solutions. Although the Tofts and Kermode model is fairly standardized, there are many parameters (T1 map, AIF type, subject specific data, model goodness of fit) that can affect the pk output. If DCE-MRI is to succeed as a widely incorporated biomarker, the industry must agree on a post-processing standard.

References:

Table 1: Workstation combinations producing no significant difference in output by pk parameter

<table>
<thead>
<tr>
<th>pk parameter</th>
<th>workstation combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>K único</td>
<td>Aegis™ - DynaCAD™</td>
</tr>
<tr>
<td>k ep</td>
<td>Tissue4D™ - DynaCAD™</td>
</tr>
<tr>
<td>V e</td>
<td>DynaCAD™ - CADvue™</td>
</tr>
<tr>
<td>IAUGC</td>
<td>Tissue4D™ - CADvue™</td>
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</tbody>
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Figure 1: Median comparison of raw pk outpur by workstation

Figure 2: wCV for each workstation combination by pk parameter

Figure 3: Bland-Altman mean difference and limits of agreement for each workstation combination by pk output