The Effect of Registration on Voxel-Wise Tofts Model Parameters and Uncertainties from DCE-MRI of Early-Stage Breast Cancer Patients Using 3DSlicer

Matthew Mouawad¹ · Heather Biernaski² · Muriel Brackstone^{3,4} · Michael Lock^{4,5} · Anat Kornecki^{6,7} · Olga Shmuilovich^{6,7} · Ilanit Ben-Nachum^{6,7} · Frank S. Prato^{1,2,6} · R. Terry Thompson^{1,2,6} · Stewart Gaede^{1,2,8} · Neil Gelman^{1,2,6}

Received: 18 December 2018 / Revised: 15 June 2020 / Accepted: 23 July 2020 / Published online: 3 August 2020
© Society for Imaging Informatics in Medicine 2020

Abstract

We quantitatively investigate the influence of image registration, using open-source software (3DSlicer), on kinetic analysis (Tofts model) of dynamic contrast enhanced MRI of early-stage breast cancer patients. We also show that registration computation time can be reduced by reducing the percent sampling (PS) of voxels used for estimation of the cost function. DCE-MRI breast images were acquired on a 3T-PET/MRI system in 13 patients with early-stage breast cancer who were scanned in a prone radiotherapy position. Images were registered using a BSpline transformation with a 2 cm isotropic grid at 100, 20, 5, 1, and 0.5PS (BRAINSFit in 3DSlicer). Signal enhancement curves were analyzed voxel-by-voxel using the Tofts kinetic model. Comparing unregistered with registered groups, we found a significant change in the 90th percentile of the voxel-wise distribution of K^{trans} . We also found a significant reduction in the following: (1) in the standard error (uncertainty) of the parameter value estimation, (2) the number of voxel fits providing unphysical values for the extracellular-extravascular volume fraction ($v_e > 1$), and (3) goodness of fit. We found no significant differences in the median of parameter value distributions (K^{trans} , v_e) between unregistered and registered images. Differences between parameters and uncertainties obtained using 100PS versus 20PS were small and statistically insignificant. As such, computation time can be reduced by a factor of 2, on average, by using 20PS while not affecting the kinetic fit. The methods outlined here are important for studies including a large number of post-contrast images or number of patient images.

Keywords Breast DCE-MRI · Deformable registration · Percent sampling · Imaging biomarkers · 3DSlicer · Computation time

Background

Dynamic contrast enhanced (DCE) MRI is a valuable tool for aiding clinical diagnosis and treatment monitoring of breast cancer. A series of T1 weighted images are acquired with at least one image prior to the injection of a contrast agent and several images following the injection. From these images, signal enhancement curves are generated either voxel-by-voxel or using the average signals over regions of interest. These curves can be analyzed using pharmacokinetic models, empirical models, or qualitative methods [1]. Pharmacokinetic model analysis can provide physiological information and has many advantages over using empirical models or qualitative methods [1]. Pharmacokinetic models have been applied extensively in studies evaluating image-based measures for monitoring breast cancer therapies. One of the most popular models in breast cancer is the Tofts model [2]. From this model, one can extract two parameters referred to as v_e and

✉ Matthew Mouawad
mmouawad@uwo.ca

¹ Medical Biophysics, Western University, London, ON, Canada

² Lawson Imaging, Lawson Health Research Institute, London, ON, Canada

³ Surgical Oncology, London Regional Cancer Program, London, ON, Canada

⁴ Oncology, Western University, London, ON, Canada

⁵ Radiation Oncology, London Regional Cancer Program, London, ON, Canada

⁶ Medical Imaging, Western University, London, ON, Canada

⁷ Diagnostic Imaging, St. Joseph's Health Center, London, ON, Canada

⁸ Physics and Engineering, London Regional Cancer Program, London, ON, Canada

K^{trans} , where v_e is the fraction of tissue volume occupied by the extra-cellular, extra-vascular space (EES) and K^{trans} is the extravasation rate of contrast from the vasculature to the EES. To be physically realistic, measured v_e values must be < 1 .

Inter-scan patient movement during the DCE image series can degrade pharmacokinetic analysis of the curves unless image registration is applied [3, 4]. While several papers [5–10] have reported on image registration in breast imaging, very little information has been provided on the influence of registration in pharmacokinetic analysis, particularly the Tofts model. Shafer et al. [9], using in-house developed software, investigated the influence of registration on the root-mean-square-error (RMSE) of the data around a fitted curve. For this study, the analysis was based on an early version of the Tofts model using an analytic arterial input function (AIF) that has shown poor performance compared with more contemporary AIFs [11]. In addition, the assessment of the kinetic fit was based on a voxel averaging method rather than voxel-by-voxel, the registration was only in two dimensions through a single slice of the tumor, and their data set only had 5–6 images with a time resolution of > 60 s on a 1.5 T MRI scanner. To our knowledge, the influence of registration on measured pharmacokinetic parameters and their uncertainties has not been investigated and not with more recently measured arterial input functions.

While image registration is an important step in pharmacokinetic analysis, the computation time can be quite long. This is especially true for deformable registration based on mutual information which is a cost function known to be robust in the presence of local contrast changes such as in the case of DCE [6, 7, 9, 12–14]. Long computation times could be a burden particularly for large clinical studies. For example, our analysis procedure is presently applied for the SIGNAL trial [15] in which registration of 29 DCE images will be performed for each of more than 100 patients. To reduce computation time for registration, it is possible to use a random subset of the image voxels rather than the full image [16]. Here we use the term percent sampling (PS) to refer to the fraction of voxels sampled within the region of interest. To our knowledge, the effect of under-sampling the image for estimation of the cost metric and its effect on the performance of the kinetic model analysis has not previously been explored quantitatively in the context of DCE-MRI.

In this paper, we consider the influence of fully 3D deformable registration on voxel-by-voxel analysis using the Tofts model and the AIF from Parker et al. [17] in the context of breast DCE-MRI. In particular, we assess the influence of this registration on parameter values and their uncertainties and on the extent of physically reasonable values for v_e . We also investigate the efficacy of reduced percent sampling as a means of reducing computation time. Our study demonstrates the importance of registration on pharmacokinetic analysis in breast DCE and the efficacy of reduced sampling. In addition,

our results provide the reader with estimates of parameter precision for voxel-by-voxel analysis that can be achieved at 3 T with moderate spatial resolution and typical acquisition times. Finally, we specifically chose an open-source program (3DSlicer) that can be applied for image registration with only minimal time and resource investment for implementation.

Materials and Methods

DCE-MRI breast images were acquired from 13 patients with early-stage breast cancer [15]. The median (range) of patient ages was 60 (52–77). The studies were performed on a 3T-PET/MRI system (Siemens Biograph mMR) with a four-channel breast coil [18]. Patients were positioned prone to mimic the radiotherapy delivery position with the ipsilateral arm above their head and the contralateral arm at their side.

Figure 1 shows a timing diagram for the image acquisition. Three-dimensional fat-suppressed fast low-angle shot (FLASH) images were acquired with $TR = 4.1$ ms, $TE = 1.5$ ms, and flip angle $= 15^\circ$. The images had a spatial resolution of $1.0 \times 2.1 \times 2.1$ mm interpolated to $1.0 \times 1.0 \times 1.2$ mm, a field of view of 38×38 cm, and a slab thickness of 13.4 cm. Using 6/8 Partial Fourier in two directions and an acceleration factor of two of the acquisition time per image was 18–20 s. Each DCE series included one pre-contrast image and 28 post-contrast images following Gadovist (0.1 mMol/kg) injection. Single-slice half-Fourier acquisition single-shot turbo spin echo (HASTE) images positioned at the arch of the aorta were acquired. The HASTE acquisition had a temporal resolution of 0.37 s (nine patients) or 0.42 s (four patients), and a duration of 18.5 s (nine patients) or 15.5 s (four patients), respectively.

Images were registered using the BRAINSFit module [19] of 3DSlicer (<https://www.slicer.org/>) v4.5.1 [20–22] on a PC running windows 10 (16 GB ram, intel i7–4790 3.6 GHz CPU). Unless otherwise specified, default values for this version were used for other parameters related to the registration as these have been tuned by the authors of the BRAINSFit over the course of development and generally provide good registrations [19].

Fig. 1 Timing diagram for the image acquisition. Following contrast injection (t_0) a HASTE series is acquired for 15.5 or 18.5 s (t_1) which is immediately followed by the post-contrast dynamic contrast enhanced series until approximately 10 min has elapsed (t_2)

The key steps in the registration process are as follows: A mask was defined over the affected breast, extending to approximately the pectoral muscle and dilated to include air around the skin. This mask defined the region from where voxels were sampled for estimation of the cost function. The interpolator used for the registration and for final generation of the image output was a windowed sinc. All images were registered to the middle post-contrast image (i.e., the 14th time point) [9, 23]. To correct for gross movement, we performed a sequential affine registration, i.e., a rigid, a rigid + scale, a rigid + scale + skew, and finally an affine registration. Finally, the deformable registration was performed using the output images from the sequential affine registration as the input. The deformable registration was performed using a BSplines interpolation scheme approximately 2 cm isotropic grid spacing as we were not expecting large deformations.

Registrations were performed using each of the following values of percent sampling (PS): 100%, 20%, 5%, 1%, and 0.5%. The percent sampling here refers to the percentage of voxels within the mask used for determination of the cost function and were sampled randomly. (Within the BRAINSFit module in 3DSlicer, this is referred to as the “percentage of samples”.) The computation time was recorded for each registration procedure applied to each patient. This investigation was performed to determine if registration performance could be maintained while decreasing computation time.

Analysis of the unregistered and registered DCE-MRI data was performed with MATLAB 2016b using in-house code. Otsu’s segmentation method [24] was applied to automatically segment the tumor using the last post-contrast image. Voxels included in the contour were fit, voxel by voxel, using the Tofts kinetic model [25] and a population-derived arterial input function (AIF) [17]. The time at which the contrast agent arrived at the arch of the aorta on the HASTE images was considered lower bound on the time of arrival of the contrast bolus to the tumor. Model fitting was applied to voxels that met the following conditions: (1) the signal enhancement was 1.5 times that of the pre-contrast value at any point in the time series and (2) the maximum value of the signal curve did not occur at the last time point. Parameter values of K^{trans} (forward rate constant) and v_e (fractional volume of extracellular, extravascular space) were generated for each voxel within the segmented region of each patient and each registration condition. In addition, the uncertainties for K^{trans} and v_e (σK^{trans} and σv_e) and the root-mean-square-error (RMSE) of the fit were determined for each voxel, where the uncertainty here refers to $\frac{1}{2}$ of the 68% confidence interval width.

Statistical analysis of parameters included the following: for K^{trans} , σK^{trans} , and the RMSE, the median and 90th percentile over all voxels in each of the segmented tumors was calculated for unregistered images and registered images at each PS level. For v_e and σv_e , we also computed the median values but did not consider 90th percentile metric because for

some voxels the extracted values were extremely high. Instead, we determined the number of voxels with $v_e > 1$ (unphysical) and the number of voxels with $\sigma v_e > 4$ four threshold values (0.1, 0.2, 0.5, and 1.0). A Wilcoxon sign-rank test was used to compare the values of each parameter obtained from unregistered images with those obtained from registered images. A comparison of values obtained using PS = 100% to values obtained with the lower percent sampling (PS) was also carried out with this test. Theoretically, 100PS should result in the best registration performance.

Results

Figure 2 shows the mean and standard deviation of the total computation time across patients. Using a lower PS values (≤ 20 PS) lead to a dramatic reduction in the computation times compared with 100PS, as well as a large reduction in the standard deviation. However, using 1 or 0.5PS did not further decrease computation time compared with 5PS and so they were omitted from further analysis.

For the following paragraphs, Table 1 shows a summary of the comparisons of each PS case to the unregistered data.

Figure 3 illustrates values of K^{trans} and its uncertainty (σK^{trans}) extracted from unregistered and registered images from all PS groups. Comparing unregistered images with registered images (all PS), differences in the uncertainty metrics (median and 90th percentile σK^{trans}) and in the 90th percentile K^{trans} are large for some patients and were found to be statistically significant (Table 1). However, the differences in the median value of K^{trans} between unregistered and registered images (all PS) were not significant, though a relatively large difference can be seen for one subject. Any variations in these metrics (Fig. 3) between PS groups appear to be small. The only difference that was significantly worse than 100PS (but small) was between the median of σK^{trans} for 5PS.

Fig. 2 Computation times for all PS cases for registering the series of 29 images (1 pre-contrast and 28 post-contrast). The bar represents the mean and the whiskers represent the standard deviation. Each point represents a patient

Table 1 Results of statistical comparisons between parameters obtained with unregistered images versus registered images (at any PS level). SR represents a significant reduction, SC a significant change, and NS means no significant difference ($p < 0.05$). Dashed lines indicate where comparison metrics were not assessed

	Median	90th percentile	Number of voxels above threshold
K^{trans}	NS	SC	-
σK^{trans}	SR	SR	-
v_e	NS	-	SR ($v_e > 1.0$)
σv_e	SR	-	SR for median and $\sigma v_e > 0.1, 0.2, 0.5, 1.0$
RMSE	SR	SR	-

Figure 4 illustrates differences in v_e and its uncertainty (σv_e) extracted from unregistered versus registered images from all PS groups. Comparing unregistered images with registered images (all PS), differences in the uncertainty metrics (median σv_e ; number of voxels with $\sigma v_e > 0.2$) and in the percentage of unphysical voxels ($v_e > 1$) are large for some patients and were found to be statistically significant (Table 1). Significant differences were also found between the number of voxels with $\sigma v_e >$ other thresholds tested (Table 1, Fig. 5). However, any difference of the median value of v_e between unregistered and registered images (all PS) was not significant. Any variations in these metrics (Fig. 4)

between PS cases appear to be small, and none was statistically significant.

For the RMSE, the median (Fig. 6a) and 90th percentile (Fig. 6b) of all PS cases were significantly reduced compared with the unregistered data (Table 1). There were no significant differences between 20 and 5PS compared with 100PS but there was a trend to significance in both the median ($p = 0.07$) and 90th percentile ($p = 0.08$) when comparing 5PS with 100PS.

The results presented above indicate that changes in parameters between PS levels are small even when changes between unregistered images and registered images are large. This is demonstrated in Fig. 7 which illustrates parametric color images of K^{trans} and v_e from a single slice of the images from one patient (P11). This figure includes parametric images obtained without registration and following registration with three different levels of percent sampling (100PS, 20PS, and 5PS). Although differences in the parametric images between the unregistered versus registered cases are clearly obvious, any differences between the parametric images obtained with different PS levels are subtle, especially in comparing 100PS with 20PS.

Discussion

In this study, we investigated the influence of registration on DCE-MRI kinetic parameters in the context of breast imaging

Fig. 3 Median and 90th percentile of K^{trans} (a, b) and σK^{trans} (c, d) for unregistered and registered images (all PS cases). Median and 90th percentile was determined over all voxels in the segmented region for each patient. P# represents patient number

Fig. 4 Median v_e (a), percentage of voxels with $v_e > 1$ (b), median σv_e (c), and percentage of voxels where σv_e exceeded 0.2 (d) for unregistered and registered images (all PS). P# represents patient number. The median values were determined over all voxels in the segmented region for each patient

using freely available and well-tested open source software (3DSlicer and BRAINSFit). We are the first to show how registration can reduce the number of unphysical voxel fits and improve the precision of voxel-wise parameter estimates which is important in the context of assessing response to therapy using these kinetic parameters. In addition, we showed how registration time can be reduced by a factor of two using a smaller sampling of voxels (20PS). To our knowledge, no other publication has quantitatively explored the influence of registration or of reduced PS on the parameter

values (K^{trans} , v_e) or their associated uncertainties (σK^{trans} , σv_e) in DCE-MRI of breast cancer.

The methods presented here are being implemented in the SIGNAL clinical trial as mentioned in the introduction [15]. The DCE-MRI imaging protocol has a relatively high time resolution compared with many previous studies [2] that investigate DCE-MRI of breast cancer, with full breast coverage. For our clinical trial, registration of 29 DCE images will be performed for each of more than 100 patients and in some cases twice per patient as they will be receiving DCE-MRI both before and after radiotherapy. As such, reducing the computation time for registration will be important for maintaining timely assessment of images and data. As DCE-MRI improves and 3D images can be acquired faster (which results in more images), ways to mitigate registration time will become even more important. PS reduction is one strategy; however, reducing PS below 5PS did not appear to have little if any effect on computation time.

In this study, we found that registration reduced the number of voxels for which the fitting with the Tofts model led to an unphysical value for v_e ($v_e > 1$). This has not been widely considered. However, even with registration, the number of such voxels was still substantial (Fig. 4b) for some patient image sets. From our observation and a previous report [26], this tends to occur for signal enhancement curves that have not reached the washout phase by the end of the dynamic series. For this study, post-contrast imaging covered a time period of approximately 10 min, but this may not be sufficient for estimating v_e of voxels near the edges of the tumor which were typically still enhancing by the end of the series. It is unclear

Fig. 5 Percentage of voxels having σv_e above four different thresholds for different registration cases (PS values). The bar presents the mean across patients and the error bars represent the standard deviation

Fig. 6 The median (a) and 90th percentile (b) of the model fit RMSE for unregistered and all PS cases for each patient. Median and 90th percentile were determined over all voxels in the segmented region for each patient. P# represents patient number

how these unphysical voxels affect K^{trans} estimation, particularly since the fitting procedure is highly non-linear.

Previous studies investigating DCE-MRI registration have not typically reported the effect of registration on model fit parameter outputs and associated uncertainties for the Tofts model. Interestingly, the median values of the parameter values (K^{trans} and v_e) seemed relatively insensitive to slight misalignment of images as indicated by the lack of significant difference comparing unregistered and registered data. In voxel-by-voxel analysis, which has the potential to show the spatial heterogeneity of the tumor, we can see that there is a significant effect of registration on the overall distribution of parameter values as indicated by the significant change in the 90th percentile of K^{trans} and the reduction of unphysical voxels. Furthermore, we can significantly reduce the uncertainty in the parameter values (σK^{trans} , σv_e), increasing confidence in voxel-wise analysis without a large cost in computation time when a lower PS is used.

Interestingly, there was a large amount of variation in K^{trans} (Fig. 4a, b) and v_e (Fig. 5a) across patients even though all patients were early-stage breast cancer patients with a similar age [15]. However, this is most likely reflective of the highly heterogeneous nature of tumors. In comparison with reported ranges in the literature for studies that used the Tofts model, it is not uncommon for there to be variability between patients [27, 28].

Our data also demonstrates a large variation between patients regarding the extent to which the RMSE (Fig. 6), uncertainty metrics (σK^{trans} , σv_e , Figs. 2c, d, and 3c, d), and number of voxels with unphysical values of v_e (Fig. 4b) were reduced by image registration. In fact, there are some patients for which any such changes are quite small, suggesting that these patients are able to remain essentially motionless during the 10-min DCE acquisition. It may be that the uncertainty values obtained for these patients might represent an estimate of the

Fig. 7 Parametric color images of K^{trans} and v_e obtained without registration (Unreg) and following registration with three different levels of percent sampling (100PS, 20PS, 5PS). The images correspond to a single slice obtained from one patient (P11). The parametric color images are overlaid on the last post-contrast gray level image. Differences in the

spatial distribution of parameters between the unregistered versus registered images are clearly obvious. However, any differences between the images obtained with different PS levels are subtle, especially in comparing 100PS with 20PS

potentially achievable fit uncertainties with our protocol (3 T, four channel breast coil, 4.4 μL voxel volume, full breast coverage in approximately 20 s). There are several potential factors that could influence the extent to which patients can remain motionless, including level of comfort in this radiotherapy position (one arm overhead), a position that could be challenging for older patients, as those in our study (median (range) of age 60 (52–77)).

One limitation of our study was the relatively small number of patients. However, we detected statistically significant reductions in the standard error of the parameters and in the goodness of fit. Also, the percentage of voxels with unphysical values of v_e decreased dramatically for several patients. Nevertheless, the small sample size required the use of nonparametric statistics. In particular, we applied a rank-based test which is not sensitive to the amount of difference in parameters between registered and unregistered cases. Thus, data points (Figs. 3, 4, 6) showing small changes in a parameter could be subject to some uncertainty in direction of change. In addition, a larger sample size would have greater statistical power and might have led to additional significant differences between 100PS and lower PS cases. However, these differences appear to be small.

In this study, we did not exhaustively investigate all registration parameters. In addition, there may be ways to further reduce computation time, such as removing parts of the registration steps before the BSpline, i.e., it may only be necessary to perform a rigid and affine before the BSpline without any intermediate steps.

A further limitation of the present work was the lack of a gold standard to which the values of K^{trans} and v_e could be compared. However, we have provided metrics that strongly suggest better efficacy of the Tofts model analysis post-registration and therefore provide more confidence in the post-registration values compared with unregistered values. These metrics include the number of voxels with unphysical values of v_e , the goodness of fit (RMSE), and the uncertainties (σK^{trans} and σv_e). All of these metrics showed statistically significant improvement following registration. For some patients the improvement was quite large.

Finally, we would like to highlight the fact that patients included were imaged prone with their ipsilateral arm raised above their head to mimic the radiotherapy position. Typical breast MR imaging studies are performed with the patient prone with both arms at their side. This difference may affect the extent of patient motion compared with our study. However, the application of MRI for image guidance and treatment monitoring of radiotherapy for breast cancer treatment is growing. Thus, there is a need for MRI studies involving breast patients imaged in the radiotherapy delivery position to assess ways to mitigate motion as well as quantify the optimal imaging and analysis techniques.

Conclusion

In this paper, we investigated the influence of registration using 3DSlicer and percent sampling on extracted kinetic parameters and their uncertainties. Registration resulted in significant reductions in the number of unphysical fits ($v_e > 1$), the standard error (uncertainty) of parameter estimation, as well as the root-mean-square error of the model fit. We also found that computation time could be reduced by a factor of two by using reduced sampling (20PS) without detectable changes in these measures. This computation time reduction will help to improve the practicality of analyzing DCE images with high time resolution for large clinical studies and for studies that include a large number of post-contrast injection images.

Acknowledgments The authors would like to thank Siemens Canada for supplying the breast coil used in this study.

Funding Information The authors would also like to acknowledge grant funding from the Ontario Research Fund–Research Excellence (OCAIRO Project RE-04-026), the Canadian institutes of Health Research (149080), and the Breast Cancer Society of Canada for funding support.

References

1. Khalifa F, Soliman A, El-Baz A, Abou El-Ghar M, El-Diasty T, Gimel'farb G, et al: Models and methods for analyzing DCE-MRI: A review. *Med Phys* 41:124301,2014. <https://doi.org/10.1118/1.4898202>
2. Wang C-H: Review of treatment assessment using DCE-MRI in breast cancer radiation therapy. *World J Methodol* 4:46,2014. <https://doi.org/10.5662/wjm.v4.i2.46>
3. O'Connor J, Jackson A, Parker G, Jayson GC: DCE-MRI biomarkers in the clinical evaluation of antiangiogenic and vascular disrupting agents ANGIOGENESIS: A TARGET FOR ANTICANCER THERAPY. *Br J Cancer* 96:189–95,2007. <https://doi.org/10.1038/sj.bjc.6603515>
4. Giger ML, Karssemeijer N, Schnabel JA. Breast Image Analysis for Risk Assessment, Detection, Diagnosis, and Treatment of Cancer. *Annu Rev Biomed Eng* 15:327–57,2013. <https://doi.org/10.1146/annurev-bioeng-071812-152416>
5. Dmitriev ID, Loo CE, Vogel W V, Pengel KE, Gilhuijs AKG: Fully automated deformable registration of breast DCE-MRI and PET/CT. *Phys Med Biol* 58:1221–33,2013. <https://doi.org/10.1088/0031-9155/58/4/1221>
6. Denton ER, Sonoda LI, Rueckert D, Rankin SC, Hayes C, Leach MO, et al: Comparison and evaluation of rigid, affine, and nonrigid registration of breast MR images. *J Comput Assist Tomogr* 23:800–5,1999. <https://doi.org/10.1097/00004728-199909000-00031>
7. Hill A, Mehnert A, Crozier S, McMahon K: Evaluating the accuracy and impact of registration in dynamic contrast-enhanced breast MRI. *Concepts Magn Reson Part B Magn Reson Eng* 35:106–20, 2009. <https://doi.org/10.1002/cmr.b.20133>
8. Rueckert D, Sonodaa LI, Denton E, Rankina S, Hayesc C, Leach M, et al: Comparison and evaluation of rigid and non-rigid registration of breast MR images. *Med Imaging* 99:3661,1999, p. 78–88

9. Schäfer S, Preim U, Glaßer S, Preim B, Tönnies K: Local similarity measures for lesion registration in DCE - MRI of the breast. *Ann BMVA* 2011:1–13,2011
10. Martel AL, Froh MS, Brock KK, Plewes DB, Barber DC: Evaluating an optical-flow-based registration algorithm for contrast-enhanced magnetic resonance imaging of the breast. *Phys Med Biol* 52:3803–16,2007. <https://doi.org/10.1088/0031-9155/52/13/010>.
11. Woolf DK, Taylor NJ, Makris A, Tunariu N, Collins DJ, Li SP, et al: Arterial input functions in dynamic contrast-enhanced magnetic resonance imaging: which model performs best when assessing breast cancer response? *Br J Radiol* 89:20150961,2016. <https://doi.org/10.1259/bjr.20150961>
12. Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ: Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging* 18:712–21,1999. <https://doi.org/10.1109/42.796284>
13. Tanner C, Schnabel JA., Hill DLG, Hawkes DJ, Degenhard A, Leach MO, et al: Quantitative evaluation of free-form deformation registration for dynamic contrast-enhanced MR mammography. *Med Phys* 34:1221,2007. <https://doi.org/10.1118/1.2712040>
14. Chebrolu VV, Shanbhag D, Bedair R, Gupta S, Hervio P, Reid S, et al: Impact of non-rigid motion correction on pharmacokinetic analysis for breast dynamic contrast-enhanced MRI. *Proc 23rd Sci Meet Int Soc Magn Reson Med* 2015:668
15. Guidolin K, Lock M, Yaremko B, Gelman N, Gaede S, Kornecki A, et al: A phase II trial to evaluate single-dose stereotactic body radiation therapy (SBRT) prior to surgery for early-stage breast carcinoma: SIGNAL (stereotactic image-guided neoadjuvant ablative radiation then lumpectomy) trial. *J Radiat Oncol* 4:423–30, 2015. <https://doi.org/10.1007/s13566-015-0227-2>.
16. Johnson HJ, McCormick MM, Ibanez L: The ITK Software Guide Book 1: Introduction and Development Guidelines Fourth Edition Updated for ITK version 4. 8 2015. <https://itk.org/>
17. Parker GJM, Roberts C, Macdonald A, Buonaccorsi GA, Cheung S, Buckley DL, et al: Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI. *Magn Reson Med* 56: 993–1000,2006. <https://doi.org/10.1002/mrm.21066>
18. Patrick JC, Terry Thompson R, So A, Butler J, Faul D, Stodilka RZ, et al: Technical Note: Comparison of megavoltage, dual-energy, and single-energy CT-based μ -maps for a four-channel breast coil in PET/MRI. *Med Phys* 44:4758–65,2017. <https://doi.org/10.1002/mp.12407>
19. Johnson HJ, Harris G, Williams K, Williams NK, Williams K: BRAINSFit: Mutual Information Rigid Registrations of Whole-Brain 3D Images, Using the Insight Toolkit. 2007.
20. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin J-C, Pujol S, et al: 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging* 30:1323–41, 2012. <https://doi.org/10.1016/j.mri.2012.05.001>
21. Kikinis R, Pieper SD, Vosburgh KG: 3D Slicer: A Platform for Subject-Specific Image Analysis, Visualization, and Clinical Support. *Intraoperative Imaging Image-Guided Ther* 2014. https://doi.org/10.1007/978-1-4614-7657-3_19
22. Kapur T, Pieper S, Fedorov A, Fillion-Robin JC, Halle M, O'Donnell L, et al: Increasing the impact of medical image computing using community-based open-access hackathons: The NAMIC and 3D Slicer experience. *Med Image Anal* 2016. <https://doi.org/10.1016/j.media.2016.06.035>
23. Melbourne A, Hipwell J, Modat M, Mertzaniadou T, Huisman H, Ourselin S, et al: The effect of motion correction on pharmacokinetic parameter estimation in dynamic-contrast-enhanced MRI. *Phys Med Biol* 56:7693–708,2011. <https://doi.org/10.1088/0031-9155/56/24/001>
24. Otsu N: A Threshold Selection Method from Gray-Level Histograms. *IEEE Trans Syst Man Cybern* 9:62–6,1979. <https://doi.org/10.1109/TSMC.1979.4310076>
25. Tofts P, Gunnar B, Buckley DL, Evelhoch JL, Henderson E, Knopp M V, et al: Estimating kinetic parameters from dynamic contrast-enhanced T1-weighted MRI of a diffusable tracer: Standardized quantities and symbols. *J Magn Reson Imaging* 10:223–32,1999
26. Tofts PS, Parker GJM: DCE-MRI: Acquisition and analysis techniques. In: Barker P, Golay X, Zaharchuk G, Eds. *Clin. Perfus. MRI Tech. Appl.*, vol. 9781107013, Cambridge: Cambridge University Press, 2010, pp 58–74. <https://doi.org/10.1017/CBO9781139004053.006>
27. Hayes C, Padhani AR, Leach MO: Assessing changes in tumour vascular function using dynamic contrast-enhanced magnetic resonance imaging. *NMR Biomed* 15:154–63,2002. <https://doi.org/10.1002/nbm.756>
28. Yankeelov TE, Lepage M, Chakravarthy A, Broome EE, Niemann KJ, Kelley MC, et al: Integration of quantitative DCE-MRI and ADC mapping to monitor treatment response in human breast cancer : initial results. *Magn Reson Imaging* 25:1–13,2007. <https://doi.org/10.1016/j.mri.2006.09.006>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.