Evaluation of an equilibrium phase free-breathing dynamic contrast-enhanced MRI prototype sequence compared to traditional breath-held MRI acquisition in liver oncology patients

Introduction

Within oncology, it is essential that the imaging achieved is of the highest quality possible to ensure effective management and treatment options can be applied. The liver is the second most common site of metastatic disease from a primary breast, lung or a colorectal tumour.[1] The use of Magnetic Resonance Imaging (MRI) in hepatic metastatic disease has been evidenced in the United Kingdom (UK) by the Royal College of Radiologists[2] (RCR) and National Institute for Clinical Excellence[1] (NICE) guidelines as the reference standard examination to characterise small malignant liver lesions. Identifying or excluding malignancy is the primary aim, while the distinction between benign and malignant lesions contributes in determining disease severity/staging, and monitoring therapy/recurrence. If a malignant lesion is identified, it is important to distinguish between primary and secondary cancers as this will determine patient treatment options,[1] and establish the distribution of malignant lesions to adjacent vascular anatomy (for resection, radiofrequency ablation, or biopsy).[3-5]

The RCR guidelines[2] recommend contrast MRI oncology liver imaging with T1 and T2 weighted (W) sequences, in and out of phase for fatty tissue and focal lesion location, with diffusion-weighted imaging (DWI) to aid differential diagnosis of haemangiomas and benign cysts. The application of dynamic contrast-enhanced MRI (DCE-MRI) imaging can be a challenge in practice, as the duration of the scan is long compared to the physiological processes of heart rate, blood flow rate and respiration cycles.[6] This may reduce temporal resolution and increases motion and reconstruction artefacts. Strategies such as breath-holding or respiratory compensation are routinely employed to reduce breathing artefacts.[7] Applying technological developments, such as parallel imaging, respiratory

triggering, and partial-Fourier techniques to accelerate examinations, and allow periods of arrested respiration during the unenhanced, arterial, portal venous and equilibrium phases of DCE-MRI. With the potential to reduce each breath-hold examination to 23 seconds. This can be helpful when imaging children and adults with diminished respiratory capacity, or whose compliance may be complicated by communication difficulties (deafness or language barriers), or diminished cognitive ability.[7] Furthermore, protocols which employ hepato-biliary specific contrast can accentuate the number of breath holds required[8] increasing breathing artefacts resulting in repeat imaging and further intravenous (IV) contrast agents.

This study aimed to investigate whether a prototype (non-product) free-breathing DCE-MRI radial VIBE sequence could provide comparable diagnostic quality to a traditional arrested-respiration DCE-MRI sequence in patients who have difficulty in following breath-holding instructions. Comparing the equilibrium phase of imaging which is considered to be the 'standard' sequence for assessing metastatic pathology within the field of oncology imaging in the UK.[2]

Literature Review

A literature search was performed to identify studies reporting performance data on MRI imaging (index test) and liver lesions (target conditions). The search used MEDLINE, PUBMED, Biomed Central databases, subject-specific electronic databases (Elsevier, ScienceDirect, Wiley, Springer and Sage), and manufacturer literature from 2005 to present. Manufacturer materials may introduce bias to the evidence, but it was also a source of technical data explaining pertinent physics, protocols, and data from early implementer sites.

Found literature evidenced improved quality using free-breathing DCE-MRI[9-11] and controlled aliasing DCE-MRI[12] in 3T[7-11] imaging. The novelty of this study is the application of a 1.5T MRI scanner, which due to the lower field strength than the published studies would gain new clinical results. Previous

studies applied 3T[7-11] strength which would inherently result in different data due to different signal to noise ratios, contrast to noise ratios, spatial and temporal resolution quality.[13] Furthermore, the published studies concentrated on arterial and portal-venous sequences acquired with a high IV flow rate (2ml/second[7,9,10]). This study will review data acquired post contrast after a lower IV flow rate (1ml/second) in the equilibrium phase, potentially resulting in different imaging outcomes.

Methods

The institutional ethics board approved this study. The sample population were selected from the prospective worklist of the MRI department within the study setting (specialist oncology centre). The eligibility criteria consisted of adults (>18 years) referred with known secondary liver malignancy to assess on-going treatment and management. All patients recruited from the prospective worklist demonstrated difficulty complying with pre-MRI examination breath hold instructions and pre-scan arrested respiration exercises. All patients provided informed consent to participate in the study. The minimum recruitment sample size required was calculated using a priori power analysis to allow reasonable detection of effect using G-power (v.3.1.9.2, Universität Kiel, Deutschland) software. Applying a *t*-test (two-tails) of difference between two independent means (two groups), with an error probability (α) of 0.05, power (1-β probability of error) of 0.80, and an effect size (ρ) of 0.8 (large). The sample size calculated required *n*=26 participants (Table 1).

The DCE-MRI protocol consisted of an unenhanced, arterial, portal venous (using a liver-specific contrast agent) and equilibrium phases (Table 2). The department's protocol contra-indicated IV contrast more than once within 24 hours due to documented risks associated in patients with healthy and impaired renal function.[14-16] Furthermore, it would be unethical to delay patient's treatment to undertake additional imaging on two separate occasions. Likewise, it is unrealistic to compare the new technique with standard historical imaging as the patient condition can change between attendances. In this study, a compromise was reached by obtaining imaging with a prototype T1W 3D radial (non-

product) free-breathing work-in-progress (WIP) novel sequence and a breath-held T1W Volumetric Interpolated Breath-hold Examination (VIBE) sequence in the equilibrium (contrast washout) phase of imaging. The investigation employed the free-breathing sequence (#528 radial VIBE WIP sequence, Siemens Healthineers, Erlangen, Deutschland), similar to the commercially available StarVIBE sequence (FREEZEit package, Siemens Healthineers, Erlangen, Deutschland). This sequence allows DCE-MRI of the liver to be acquired during free respiration, which was achieved by filing k-space in a radial stack of stars sampling fashion with 2016 radial views, to reduce the susceptibility of breathing motion artefacts.[17] Additionally, K-space weighted image contrast (KWIC, Siemens Healthineers, Erlangen, Deutschland), and golden angle view-sharing reconstruction were applied to make further use of redundant data and thereby increase the temporal resolution. The view angle was incremented by the golden angle (111.246°) after all partitions of a particular view were measured and view sharing reconstruction applied.[18] The view sharing used with golden angle sampling is most similar (but not identical) with the work of Winkelmann et al.[18] The interventional free-breathing sequence took approximately 6 minutes 30 seconds to acquire data, with a temporal spacing of 4.2 seconds with 21 spokes on the inner k-space ring. The traditional breath-held imaging took approximately 23 seconds; both sequences were acquired on a Siemens MAGNETOM Aera1.5T (Siemens Healthineers, Erlangen, Deutschland, Table 2 and 3).

Both imaging datasets were reviewed using a Likert scale questionnaire. A bias of using Likert scoring is the subjective nature of the scoring. This study adopted a forced choice method as 'undecided' and 'neutral' options were removed[19] to reduce central tendency and acquiescence bias. Both sequences were reviewed by two Consultant Radiologists specialising in both MRI and liver oncology on Picture Archiving and Communications (PACs) workstations (Sectra, Linköping, Sweden). The datasets were separated, anonymised and presented in a randomised order. The Radiologists (blinded to the original results) graded both sequences against diagnostic image quality criteria that were considered essential by the Radiologists. The study reviewed sharpness of the liver capsule; visibility of the intra-

hepatic vessels; and conspicuity of lesions smaller than 1cm and larger than 1cm. Against grading of (1) major blurring, not clearly visible; (2) some blurring, visible but not clear; and (3) no blurring, visible and clear. Additionally, the presence of artefacts were graded with a scale of (1) major artefact, non-diagnostic; (2) some artefact, remains diagnostic; or (3) no artefact, and diagnostic.

This study represented a two-sample comparison with the null hypothesis of no statistical difference between the two samples (equal). The alternative hypothesis was the free-breathing sequence is inferior/or superior in diagnostic quality to the breath-held phase. Statistical analysis applied a paired two sample *t*-test (VassarStats.net. Vassar College, New York, United States of America), checked with a degrees of freedom (df) chart (StatPrimer (c) v7.0 Gerstman B. 2016). For this study, a *p*-value <0.05 was considered statistically significant. Additional statistical comparison applied Cohen's weighted (Linear) Kappa coefficients for agreement between both data sets graded by the radiologists (IBM Corp. 2016. IBM SPSS Statistics, Version 24.0.0.2, New York, USA; applying IBM Weighted Kappa Extension for SPSS).

Results

The sample size calculation recommended a minimum *n*=26 particpants; the final study group comprised *n*=30 patients (*n*=60 free breath and arrested respiration sequences in total). This oversampling increased the statistical power to 0.85 (1-β probability of error). Data analysis applying the two-tailed *t*-test demonstrated a rejection of the null hypothesis ($p< 0.001$ Table 4). The *t*-value ($t=13.31$) was above the critical *t*-value ($t=2.045$ Table 1), and the two groups were significantly different. Kappa agreement between imaging techniques for all criteria was poor (*k*-0.023; *p*-0.050). The free-breathing sequence scored consistently higher (13.5 ± 1.94) compared to the breath-held technique (8.1 ± 2.06; $p<0.0001$) at equilibrium phase imaging, with an improvement of more than a third in image quality (Table 5 and figure 1).

Sharpness of the liver capsule

The findings demonstrated the sharpness of the liver capsule was improved (2.9 ± 0.30; p<0.0001; Table 4 and 5) using the free-breathing sequence (*K*-0.012; *p-0*.626). The contour and shape of the liver capsule can be indicative of both malignant and benign pathology, and it is essential that it can be assessed adequately.[20]

Visibility of intra-hepatic vessels

The free-breathing sequence imaging demonstrated improved vessel conspicuity (2.8 ± 0.37; p<0.0001) compared to the breath-held acquisition (1.7 ± 0.54; Figure 2a and 2b). The free-breathing sequence imaging scored a higher mean score overall (Table 5), kappa agreement was poor (*k*-0.009; *p*-0.649), concurring with studies of pancreatic vessel sharpness.[21]

Lesion Conspicuity

Although the conspicuity of sub-centimetre lesions scored slightly lower (2.8 ± 0.5; p<0.0001) than for larger lesions (2.9 ± 0.35; p<0.0001, Table 5). Lesion conspicuity improved within the free-breathing sequence concerning both sub-centimetre and larger lesions (41% for sub-centimetre lesions and 39% for larger lesions) compared to the breath-held acquisition (*k*-0.035; *p*-0.250 and *k*-0.000; *p*-1.000, respectively). The free-breathing sequence demonstrated two discreet large lesions which were difficult to delineate on the breath-held imaging (Figure 3a and 3b). A further example illustrated in Figure 4a and 4b of a sub-centimetre lesion on the free-breathing sequence imaging which was subtle in the breath-held imaging.

Artefacts

The breath-held imaging received a mean lower score (1.6 ± 0.49) compared to the free-breathing sequence images, which displayed an improvement of 31% in image quality (2.6 ± 0.57; p<0.0001; Table 5), and reflected in agreement between imaging techniques (*k*-0.043; *p*-0.181). The ghosting

artefact demonstrated in Figures 5a and 5b in the breath-holding technique, exacerbated towards the dome of the liver where motion from respiration and the diaphragm made it difficult to detect some lesions compared to the free-breathing acquisitions (Figure 5c).

Discussion

A disadvantage of radial k-space sampling is the presence of streaking artefact (Figure 5d) which was not observed on the conventional breath-held Cartesian imaging. The streaking artefact may be amplified from tissue outside of the field of view creating artefacts in radial imaging unlike Cartesian k-space filing.[22] In the case of liver imaging in the axial plane, the arms are by the patient's side. One possible solution would be to raise the patient's arms above their head to eliminate them from the field. However, this artefact only had a mild detrimental effect on image quality and was easily identifiable due to its characteristic 'straight-line' appearance. As this artefact appears mainly as a texture over the underlying detail, the likelihood of obscuring lesions is lower than for the Cartesian respiratory based ghosting artefact.[17]

An additional advantage of using the free-breathing sequence can be to reduce artefacts related to patient anxiety following respiration instructions.[23-25] Datendorfer et al[26] proposed 70% of patients who reported anxiety before breath-held MRI scanning, had impaired imaging (motion artefact) which could not be attributed to unavoidable physiological causes such as pulse or flow. Traditional MRI sequences collect data in a 'Cartesian' (line-by-line format), with the acquired parallel lines differing by a fixed difference in phase.[16] If a patient moves during the examination, phase offsets are created that disturb the phase-encoding scheme, resulting in artefacts in the phase-encoding direction. However, compensation for patients who were unable to achieve breath-holding imaging sequences (increased by high anxiety levels) may benefit from data acquisition in a radial or 'propeller' format. By applying rotating spokes that overlap in the centre of k-space, this artefact cannot occur in the same way, and there is increased motion-averaging effect due to the overlap.[17]

In considering potential image quality improvements in abdominal MRI, one potential is the trade-off between spatial versus temporal resolution. Hirokawa et al[27] demonstrated radial sequences were of superior quality and showed less physiologically-induced artefacts than a sequence acquired using Cartesian k-space filling and gated to the patient's breathing. These findings were repeated by Chandarana et al,[11] in the investigation of liver MRI at 3T, comparing a breath-hold standard Cartesian T1 3D imaging sequence against the same Cartesian T1 3D imaging sequence adapted for free-breathing (by increasing the number of averages in an attempt to reduce breathing artefact), and a free-breathing radial fill of K-space in a 'stack of stars' scheme.[11] Bamrungchart et al[12] further established that despite some streaking artefact that is inevitable with a radial k-space filling technique, it could be superior for imaging patients who were unable to achieve periods of arrested respiration.

An alternative approach to increase temporal resolution in the DCE-MRI data set would be to reduce the amount of data sampled by skipping some of the data that is typically acquired.[6] Due to the predictable nature of some of the acquired DCE-MRI data, the missing information can be recovered by 'undersampling'. However, the further apart the actual measured data, the greater the likelihood of misrepresentation and it is therefore important to recognise the trade-off between acceleration and error.[6] Potentially applying radial k-space filling to decrease motion artefact with under-sampled datasets allows for a reduction in the number of projections and a resulting reduction in acquisition time.[7,28-30] Exploring other novel data reconstruction methods, both golden angle and KWIC (applied in this study) enhance spatial and temporal resolution. KWIC is a view sharing technique using radial data acquisition, exploiting the fact that the centre of k-space is oversampled to reduce the number of views that contribute to lower resolution areas of k-space.[30,31] Although this technique can reduce streaking artefact caused by under-sampling of k-space by combining data from neighbouring segments in the outer k-space,[28] there is an issue with the fidelity of the temporal profile. By making

use of data from neighbouring areas of k-space, the wider temporal window in the outer edges of k-space can cause pixels near the edges of the lesions to be less accurate where a tumour 'ends' and the healthy tissue 'begins'. Obtaining images in this way means that any number of consecutive views will provide an even sampling of k-space which has the advantage that the temporal resolution can be arbitrarily selected and optimised.[30] A possible alternative (although not applied in this study) would be to decrease or avoid these limitations by adopting advanced compressed sensing based reconstruction techniques like Golden angle RAdial Sparse Parallel (GRASP, Siemens Healthineers, Erlangen, Deutschland). Applying an extension of the StarVIBE sequence, through a time incoherent golden angle stack of stars ordering and time-resolved compression reconstruction techniques.

A limitation of the study to acquire full DCE-MRI data in both (breath held and free breathing) sequences meant we were was unable to explore the enhancement characteristics and pharmacokinetics during the arterial and venous phases. Likewise, the application of the KWIC reconstruction technique has potential inherent issues with signal intensity at the periphery of lesions[28] the impact of which could also not be assessed in this study due to the constraint of arterial and venous phase data. Increased streaking artefact was noted during the arterial phase which could be a potential risk to image quality (noted in previous studies at 3T MRI in higher IV flow rates of 2mls[7,32]) but could not be compared, as this sequence at the time of study was only available on 1.5T MRI. Additionally, the effect of a delayed washout equilibrium phase[2] of imaging characteristics using different IV flow rates (1ml or 2ml/second) has yet to be explored in detail. Future work would also need to consider the evaluation of this novel sequence in comparison to respiratory triggered sequences, or post-processing image registration and motion correction algorithms in this patient group.

Conclusion

The study data demonstrated that there is a potentially viable alternative for patients who find breath hold instructions difficult in MRI of the liver. The diagnostic quality of the temporal and spatial resolution produced in the T1W 3D prototype free-breathing radial VIBE sequence imaging of the liver was rated higher than the traditional T1W FatSat VIBE imaging sequence. The results of this study have the potential to influence the way DCE-MRI is acquired in 1.5T oncology imaging. Whilst improving the examination experience for these patients, and detection of their hepatic metastases.

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