Advanced MRI in inflammatory arthritis

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Chapter 9

Summary, general discussion and future perspectives

Summary of findings

This thesis describes the application of advanced imaging tools in patients with inflammatory joint diseases. The first part describes the first steps in the evaluation of time-intensity curve (TIC)-shape analysis as a new post-processing technique for dynamic contrast material enhanced-magnetic resonance imaging (DCE-MRI) scans in patients with inflammatory joint diseases. The second part encompasses various (DCE-)MRI studies that focus on understanding the preclinical and early phases of arthritis and on whether these advanced imaging techniques can be helpful in the early differentiation of inflammatory joint diseases and the predicting of outcomes.

Part I

As an explorative test, we tested the diagnostic ability of the TIC-shape analysis in arthritis by applying it to a group of patients with clear symptoms and to a group of healthy volunteers. Should this simple test applied to the two opposite ends of a disease spectrum fail, the method probably will never have sufficient discriminative power to differentiate inflammatory joint diseases in an early stage and be of use in disease course prediction. To do this, in **chapter 2** we described the results of DCE-MRI TIC-shape analysis in 5 healthy volunteers and 5 full-blown rheumatoid arthritis (RA) patients. In this small group we observed a significant higher relative number of type 4 TIC-shapes in the RA patients. This result supports the further evaluation of the technique as a discriminator of early disease. We also showed that TIC-shape analysis allows for the evaluation of enhancement heterogeneity in patients and healthy subjects.

The introduction of a new post-processing option for DCE-MRI scans requires a test of reliability and a comparison to the existing post-processing options such as Pharmacokinetic modeling (PKM). The latter is widely considered to be the gold standard in DCE-MRI analysis and therefore the yardstick by which other analysis techniques should be measured.
In **Chapter 3** we evaluated the within-scanner reproducibility of DCE-MRI combined with the TIC-shape analysis, a qualitative analysis and PKM in 10 early arthritis patients. The results showed that, in this setting, the TIC-shape analysis is a robust post-processing method, with reproducibility measures comparable to those of the qualitative analysis. Of the three tested methods, PKM showed the lowest within-scanner reproducibility. We also showed that the between-scanner reproducibility of the most relevant TIC-shapes (type 2 and 4) outperforms the reproducibility of qualitative analysis in 6 patients. While we could not evaluate the between-scanner reproducibility of PKM, we showed that the within-scanner reproducibility of this method is inferior to the between-scanner reproducibility of the TIC-shape analysis.

PKM post-processing is more difficult and more time consuming compared to TIC-shape analysis, which makes the latter method an attractive post-processing option in clinical practice. However, little is known about the relationship of outcomes of both techniques. In **chapter 4** we related the outcomes of the PKM and of the TIC-shape analysis to each other and of both techniques to relevant clinical parameters in 44 early arthritis patients. We showed that parameter outcomes of both techniques are closely related and that both techniques show significant correlations to clinical parameters. This finding, in combination with the observed higher reproducibility of TIC-shape analysis as observed in chapter 3 led us to the conclusion that the TIC-shape analysis is the preferred post-processing method for DCE-MRI data in patients with inflammatory joint diseases.

Part II

In **chapter 5** we tested the pivotal hypothesis whether the primary feature of patients with spondyloarthropathy (SpA) is enthesitis while synovitis is the primary feature in patients with RA. We therefore applied a newly developed knee and ankle arthritis MRI scoring system to a group of 41 patients, 28 with knee arthritis and 13 with ankle arthritis. Using this scoring system, we scored the frequency, localization and extent of synovial and enthesial inflammation in different locations across the joints. Besides the MRI acquisitions, biopsies were taken of the inflamed synovium in all patients. We measured the degree of inflammation in these specimens by the infiltration of inflammatory cells in the synovium. We compared these outcomes to the DCE-MRI outcomes. After 2 years of follow-up, 20 patients were classified as having RA, 13 as having SpA and 8 as having crystal arthritis (CA). We observed no significant differences in frequency, localization and extent of enthesitis between the SpA and RA group. We observed a tendency towards a higher synovitis score in the SpA group, however this difference was not significant. Besides, we observed a similar histological degree of synovitis in both patient groups; only the number of CD163 macrophages was significantly increased in the synovial sublining of SpA vs. RA patients. The number of these macrophages correlated positively with the synovitis score. In this study, we showed that inflammation of the enthesis is comparable in both RA and SpA patients. The tested hypothesis was therefore not confirmed in our MRI/histology study.

The etiology of RA is still poorly understood. As features of synovial inflammation, such as cell infiltration, expression of cytokines and other inflammatory mediators are similar in early arthritis patients compared to patients with long standing disease, it is hypothesized that early arthritis already represents a chronic form of arthritis that is preceded by a subclinical stage. In **Chapter 6** we examined the synovium of 13 individuals that were autoantibody (IgM-RF and/or ACPA) positive but did not show clinical signs of arthritis, both histologically and using DCE-MRI combined with the qualitative analysis and TIC-shape analysis. We compared synovial cell infiltration in

autoantibody positive individuals to 10 individuals that underwent knee arthroscopy and synovial biopsy for unexplained knee pain and DCE-MRI data to data of 6 healthy volunteers. During follow-up, 4 autoantibody positive individuals developed arthritis after a median period of 3 months. Both histologically and on DCE-MRI we observed no significant differences between the autoantibody positive individuals and healthy volunteers, even for the individuals that developed arthritis. This led to the hypothesis that the subclinical stage that precedes the development of clinical signs of synovitis is relatively short and that this stage is preceded by a pre-clinical phase of several years or moths without any signs of synovial inflammation. Possibly, a second trigger (e.g. a minor trauma or viral infection) is required to initiate the development of clinical arthritis.

In chapter 2 we showed that DCE-MRI combined with TIC-shape analysis is able to differentiate healthy volunteers from RA patients based on the relative number of type 4 TIC-shapes. In **chapter 7** we investigated the inflamed synovium of 28 early knee arthritis patients using this technique. After 2 years of follow up, 7 patients were classified as having RA and 21 as non-RA. We observed s significantly higher number of type 4 TIC-shapes in the RA patient group compared to the non-RA group while no other DCE-MRI parameters showed significant differences. Some clinical and laboratory parameters (swollen and tender joint counts, CRP level and percentage of ACPA positive patients) in the RA group were higher compared to the non-RA group. This finding provides the rationale for further investigating the potential discriminative power of the TIC-shape analysis in early arthritis patients.

The PKM analysis of DCE-MRI data should provide quantitative values that represent tissue perfusion and therefore density and permeability of small vessels. As neoangiogenesis, the formation of new vessels, is a feature of inflamed synovium, this post-processing method could be used as a marker of synovial inflammation. In **chapter 8** we applied this method in 54 early arthritis patients with different diagnoses. We compared the DCE-MRI parameters between the different diagnosis groups and different disease outcomes and related DCE-MRI parameters to clinical parameters in all patients and histologic data in 18 patients. We excluded 7 patients due to problems with PKM analysis. After 2 years of follow up, 18 patients were classified as having RA, 8 as having SpA, 5 as having another form of arthritis and 16 as having unclassified arthritis. We observed significant differences of the value of the parameter K^{trans} and K_{ep} with the highest values in in the SpA patient group and the lowest value in the group with other forms of arthritis. When looking at disease outcome (self-limiting, persistent non-erosive, erosive) we observed the highest K^{trans} value in the persistent non-erosive group and the lowest value in the self-limiting group, however differences were not significant. We observed significant correlations between the three PKM parameters and the disease activity parameter local swelling and the laboratory marker CRP and between the PKM parameter v_e and ESR. We also observed significant correlations

between both K^{trans} and K_{ep} and synovial expression of von Willebrand factor (vWF). The results indicated that the PKM parameters provide absolute measures of micro vessel integrity and that these parameters may be used as diagnostic biomarkers in early inflammatory joint disease.

General discussion and future perspectives

Imaging plays a substantial role in the diagnosis and management of patients with inflammatory joint diseases. It is an objective, non-invasive manner of evaluating the extent of disease and is used to monitor disease progression and assess treatment effect.

Inflammatory joint diseases primarily affect soft tissues such as the synovium and enthesis. It is therefore natural to focus imaging research in this patient group on the method that most reliably enables the evaluation of soft tissues, namely MRI. MRI can reliably depict the bony structures, cartilage, ligaments, muscles and other surrounding structures around the joint. Besides, when present, involvement of bone in inflammatory joint diseases is seen earlier on MRI than on plain radiography.

Rationale for using TIC-shape analysis in DCE-MRI

MRI has assumed an established role in the differentiation of benign vs. malignant disease in many fields of oncology. There are some general imaging features that help the radiologist in differentiating benign from malignant lesions and even characterize the lesion, such as T1/T2 signal intensity, signal homogeneity across the lesion, lesion border evaluation, enhancement and the presence or absence of ingrowth in surrounding structures.

DCE-MRI represents an additional tool at the radiologist's disposal to further characterize lesions. It highlights the physiological, time-dependent tissue behavior information into the whole picture, making some time dependent processes such as perfusion visible.

The method requires either a direct evaluation of the time changes by the radiologist, of some post-processing in order to transform the time information into parametric images.

Importantly, DCE-MRI in oncology is only an additional tool to the "standard" imaging diagnostic routine, and so far never used as the sole determining modality in differentiating benign from malignant disease.

It has, however, the potential to discriminate malignant from benign lesions and can supply the radiologist with more evidence to confidently characterize the lesion. In many fields of oncology, this technique has shown its added value.[1] In breast imaging, for example, the sensitivity and specificity for the detection of breast cancer increases from 93% and 60% respectively for morphological features alone, to 95% and 86% when a DCE-MRI is added,[2] and another study by Tuncbilec et al. showed that DCE-MRI parameters might predict survival.[3]

In breast cancer, as well as in other solid (primary) tumors a time intensity curve (TIC) type characterized by early enhancement followed by washout (in TIC-shape analysis the type 4 TIC) is often associated with malignancy. This behavior is thought to be a reflection of the increased perfusion and increased vessel permeability characteristic of

neo-angiogenesis. In some solid tumors differentiation of a malignant from a benign form most often occurs by only looking at the form of the TIC rather than using the rate of early enhancement or the amount of washout. The use of a technique that automatically analyses the shape of the TIC in every pixel, classifies them to a certain form category and displays this in maps represents therefore a very valuable tool for the radiologist and treating physician. This technique helps to detect the presence and the spatial distribution of enhancement patterns not only in small, localized regions, but also in large areas where a priori ROI selection is challenging.

Rationale for using DCE-MRI in inflammatory joint diseases

The use of DCE-MRI in arthritis is not new. As described in chapter 1, several studies in this patient group have investigated the use of this technique, where the DCE-MRI data were analyzed with a qualitative or PKM approach. Results of these studies have shown the potential of this approach in diagnostic classification, predicting disease outcome and evaluating the response to therapy.
Malignant cancer lesions and arthritis share some features of malignancy. An example is the neo-angiogenesis which leads to increased tissue perfusion and vessel permeability, and to the presence of invasive growth. This suggests that the technique would be also helpful in this pathology. Based on the above facts, we decided to pursue the following aims:

1. To evaluate whether DCE-MRI combined with the TIC-shape analysis is a viable method that can be used to evaluate joint inflammation in the earliest phases of arthritis.
2. To assess the robustness and reproducibility of the TIC-shape analysis, and to compare it with other existing post-processing methods.
3. To assess whether advanced MR imaging can provide insight in the pathophysiology of the 2 most common forms of arthritis: RA and SpA.
4. To assess whether DCE-MRI in combination with the TIC-shape analysis, PKM or both could be helpful in the differentiation between various inflammatory joint diseases arthritis types in the earliest phases of disease and predicting outcome.

AIM 1 – DCE-MRI and TIC-shape analysis in early arthritis

In the first part of this thesis we showed that DCE-MRI combined with a pixel-by pixel TIC-shape analysis in arthritis patients is technically feasible and that it has diagnostic potential. We also highlighted the advantages in whole synovium analysis and that the technique allows for the evaluation of heterogeneity within the synovium.
It is common radiological practice when using DCE-MRI in malignancy that the evaluation of the presence or absence of the “malignant” TIC in a lesion is often applied as single point evaluation or in one (ore some) region(s) of interest (ROI(s)). Data within this ROI is then averaged to create a single TIC.

Selecting a single point or selecting a ROI both have their own risks. Most malignant lesions are known to show heterogeneity of enhancement, a feature that is shared by synovitis. A single point evaluation of the enhancement might lead to a selection bias and wrongful determination of the form of the TIC of the lesion or synovium. On the other side, the selection of a ROI will lead to averaging of the enhancement data within the ROI, which also might lead to misclassification of the TIC.
The pixel-by-pixel classification of the form of the TIC and the rendering of the distribution of these TIC-shapes in a map leads to a direct visualization of the presence and distribution of the various TIC types within the lesion, removing any user-dependent sampling error.
It is therefore a logical choice to apply the TIC-shape analysis in arthritis, where sampling is difficult due to the large extent of the affected areas.
Because the TIC-shape analysis offers the evaluation of the whole synovium, and is able to highlight the heterogeneity of disease activity within the joint, we postulated that this pixel-by-pixel TIC shape approach would offer a better, more reliable outcome compared to analysis based on a selected ROI in one or few slices.
The extent of the imaging volume has effects on the results. Larger acquired volumes mean longer MRI acquisitions, leading to reduced temporal resolution of the DCEMRI scan. When only one or a few slices have to be analyzed, as while imaging smaller joints, the spatial resolution can be increased while keeping a high temporal resolution increasing the quality of the TICs, and, when applied, result in more reliable outcomes of PKM measurements. Choosing the best compromise between volume size and temporal resolution is still an unsolved problem. In synovitis, where the extent of the lesion is large, it might probably not be necessary to image the whole joint. So far, there is no data on the minimal or optimal number of slices that must be analyzed in order to obtain sufficient diagnostic information. This might be an interesting subject for further study.

AIM 2 – Reproducibility of DCE-MRI

In the literature, it is in fact proposed that post-processing using PKM should provide absolute, scanner independent, reproducible results. In our study we were not able to confirm this theory. The most reproducible post-processing method in the within-scanner analysis was found to be the qualitative analysis producing descriptive parameters (e.g. ME), followed by the TIC-shape analysis and lastly the PKM as least reproducible technique.
The reproducibility of the descriptive parameters in the between-scanner analysis, however, was worse compared to the reproducibility of the two most relevant TIC shapes (type 2 and 4 shapes).
In chapter 4 we showed that the outcomes of the TIC-shape analysis are closely related to the outcomes of the PKM analysis, as we observed a clear relation between the two methods. This raises the question whether the “true”, most objective parameters,

which at this moment are thought to be parameters obtained with the PKM analysis (the most challenging and error-prone method), are also the most suitable. A simpler post-processing method, more robust and reproducible might represent a more viable and meaningful option. As the TIC-shape analysis is computationally straightforward and provides relevant information about the enhancement and heterogeneity of enhancement, it might be the ideal post-processing method to study DCE-MRI data in patients with inflammatory joint diseases.

AIM 3- Advanced MR imaging and the pathophysiology of RA and SpA

In chapter 5 we tested the hypothesis that there is a difference in primary localization of inflammation between RA and SpA patients. As we could not find any differences between the two patient groups we could not confirm this hypothesis. This finding adds to the understanding of disease pathophysiology of SpA and can have impact on guiding research and treatment in this patient group. In chapter 6 we observed no differences in DCE-MRI parameters and histology between individuals in the preclinical phase of rheumatoid arthritis and healthy subjects. This underlines that the initial immune response in RA does not start in the joint. It is hypothesized that a second event may be required to trigger the development of clinical signs of arthritis.
Difference in locations of the heterogeneity of enhancement patterns of the (inflamed) synovium has been shown both in RA patients and healthy subjects (chapter 2). We showed that there is a difference in the location of the TIC shape expression between these groups. We also showed that there seems to be a tendency towards a higher synovitis score in SpA vs. RA patients (chapter 5) and in another study we observed a significantly higher K^{trans} and K_{ep} in the SpA group vs. the other forms of arthritis (chapter 7). The finding of higher vascularity is consistent with histology, where a higher micro vessel density was observed in SpA patients.[4–6] The combination of these findings with the observed difference in locations of the enhancement heterogeneity between healthy subjects and RA patients (chapter 2) suggests that differences in the localization of TIC-shape expression might also be observed between different patient groups. While this hypothesis has not yet been tested, if proven, it might further assist in understanding the pathophysiology of different forms of arthritis and might add to the diagnostic capabilities of the TIC-shape analysis.

AIM 4 – DCE-MRI and diagnostic classification

In Chapter 2 we showed the potential of DCE-MRI to detect inflammatory synovial tissue changes in early arthritis patients by demonstrating a pronounced difference in the number of type 4 (“aggressive”) TIC-shapes between RA patients and healthy volunteers, and in chapter 6 we observed a significantly higher number of type 4 TIC-shapes in patients with RA compared to non-RA. In a larger patient cohort with larger subgroups (chapter 7) we observed a significant difference in the PKM parameters K^{trans} and K_{ep} between SpA and other inflammatory joint diseases. As we showed a significant

correlation between the PKM parameters and the number of TIC type 2-4 in chapter 4, we expect to find a significant difference in number of TIC-shapes between different inflammatory joint diseases when performing TIC-shape analysis in larger, more differentiated cohorts.
We were not able to find differences in the PKM parameters that might predict disease outcome.
In these three studies we demonstrated the diagnostic capabilities of DCE-MRI combined with different post-processing options. More research is needed to further elucidate the use of DCE-MRI (combined with TIC-shape analysis) in diagnosing patients with inflammatory joint diseases before it can become of standard use in patient care.
We were unable to find differences in imaging parameters between patients with a different disease course. The fact that we did not find any difference might be due to the small number of patients that developed erosions (in chapter 7, three patients), so further follow up in larger patients group could help elucidate whether this lack of sensitivity is only related to the small cohort. We did not look at the TIC shape expression at specific sites where erosions develop. As type 4 is the “aggressive” TIC type, it can be postulated that at sites where the type 4 TIC shape (or the other fast-enhancing types 3 and 5) is predominant, erosions will develop. This will help to understand the process that leads to erosion formation and might have impact on treatment strategy.

Future research

In most of our studies, we used a 1.5 Tesla cylindrical bore scanner from GE (GE SIGNA Echospeed). This was a relatively old scanner without parallel imaging capabilities that was replaced during one of our studies (chapter 3). The other scanner we used was a 1.0 Tesla open MRI scanner (Philips Panorama), which provided sufficient imaging quality to study the large joint (such as the knee). Higher field strength (e.g. 3.0 Tesla) scanners currently available at our institution but not used at the time of the study provide more signal, and, with addition of parallel imaging, a better spatial and/or temporal resolution can be achieved. At our institution we are working at the development of improved sequences that will result in an even higher temporal and spatial resolution, even on lower field strengths. This could open new possibilities to increase field of view (FOV) and spatial resolution, eventually increasing the precision of the DCE measurements.
Reliable differentiation between joint fluid and synovium, and reliable determination of all aspects of enthesitis, however, still needs the intravenous injection of a contrast agent, which makes this technique still (slightly) invasive. To achieve a totally non-invasive biomarker, more research is needed to refine the technique and develop new options. New imaging sequences or techniques (such as diffusion and tensor weighted imaging (DWI/TWI)) might be helpful to achieve this goal.

Another interesting future application would be the study of DCE-MRI combined with TIC-shape analysis in the investigation of disease activity before and after treatment.
Previous work has shown significant reduction of the descriptive parameter early enhancement rate/initial rate of enhancement ((E)ER/IRE) has been observed after the intra-articular injection of corticosteroids[7–9] and treatment with disease modifying anti rheumatic drugs (DMARDS)[10–12] or anti-TNF.[12–14] Besides, a significant reduction of the PKM parameter K^{trans} has been observed in patients treated with anti-TNF.[15–17] As we showed that the number of TIC-shapes is significantly related to the PKM parameters K^{trans}, K_{ep} and v_e (chapter 4), and that the TIC shape classification depends on the IRE/(E)ER (differentiation between fast and slow enhancing TIC-shapes), we expect a change of TIC shape expression after treatment, namely a drop in the relative number of fast enhancing TICs (type 4) and an increase in the number of slow enhancing TICs (type 2). As these descriptive parameters cannot be compared between various centers in a multicenter study as these descriptive parameters are not quantitative. TIC shape analysis might provide an easy post processing method that can be easily used in a multicenter research setting.
Besides, changes in the distribution and heterogeneity of TIC shapes within the synovium change after treatment might bring new insight in the effectiveness of the treatment in an even earlier stage.

The application of the pixel-by pixel TIC-shape analysis outside of the field of inflammatory joint diseases is also of interest. In many fields DCE-MRI is already being used in conjunction with other post-processing methods.[1] The TIC-shape analysis might offer a faster and more robust quantification method for tumor staging. Among the possible, still unexplored fields, in interventional radiology, the evaluation of treatment effect after vascular arterial and venous revascularization of limbs might be investigated using DCE-MRI. In the assessment of liver function using liver specific contrast agents, DCE-MRI could be used to assess liver function after portal venous embolization. Another interesting option could be to transpose the TIC-shape analysis to DCE-CT acquisitions and focus on patients with acute brain infarction to evaluate the vitality of the involved brain and help guiding treatment.

Clinical relevance and final remarks

In this thesis we provided evidence for the technical feasibility and good reproducibility of DCE-MRI combined with TIC-shape analysis in arthritis patients, especially in inter-scanner comparisons. We also demonstrated the close relationship of TIC-shape analysis and PKM. Combining these facts, we can confidently suggest that TIC-shape analysis should be the preferred method for post-processing DCE-MRI data in arthritis patients, especially in multicenter studies.
In the second part we showed the potential role of (DCE-)MRI (combined with TIC-shape analysis) in understanding disease pathophysiology, establishing diagnosis and

predicting disease outcome. Whether the technique will become of significant value in the early differentiation of disease, however, is difficult to predict, because a significant overlap of TIC-shape numbers and PKM values between the different types of inflammatory joint diseases is a consistent finding, also in the larger patient groups. More research on this topic is therefore needed.

It will probably take a long time before we can establish the diagnosis or extent of disease using imaging as the sole (totally non-invasive) biomarker. However, a position of (DCE-)MRI as an imaging diagnostic and prognostic biomarker, besides clinical and laboratory markers might become a point on the horizon in the nearer future.

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