Development and clinical applications of the time intensity curve shape analysis in dynamic contrast enhanced MRI: a pixel-by-pixel approach
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Citation for published version (APA):
CHAPTER 1

General introduction and outline of the thesis
INTRODUCTION

For as long as it has been available to radiologists, MRI has always represented a mainstay in diagnostic imaging, not only for its non-invasiveness, but also for its extraordinary flexibility and versatility. From imaging pathology, it has moved steadily towards imaging pathophysiology, opening therefore new frontiers in the monitoring and prediction of treatment response in various diseases such as cancer, and inflammatory disease. Here MRI does not rely on rather coarse measures such as tumour diameter but on changes in tumour architecture such as tumour blood supply.

In order to grow beyond a few hundreds micrometres, tumours require adequate oxygen and nutrient supply, as well as the removal of waste product. To achieve these requirements, tumours create their blood supply by developing a system of newly formed, functionally abnormal vascular networks in a process called angiogenesis (or neoangiogenesis) [1-3].

Targeting angiogenesis represents a recent strategy in the development of anti cancer therapies, and in the last decade two new major classes of anti cancer drugs have been introduced: antivascular or vascular disrupting agents (acting on the vascular endothelium, resulting in the collapse of the tumour vasculature, e.g combretastatin) [4], and anti-angiogenic agents (preventing the process of angiogenesis, e.g. vatalanib and bevacizumab) [5].

These two classes of drugs target the signal pathways responsible for the growth of the new blood vessels or the factors required for the survival and structural integrity of the immature endothelium. More than a dozen endogenous proteins have been identified that act as positive regulators or activators of angiogenesis. These include, among others, the cytokine (signal protein) VEGF (vascular endothelial growth factor) and TNF (Tumour Necrosis Factor) -α.

Angiogenesis is a critical process not only in cancer, but also in inflammatory disorders. It is also present in rheumatoid arthritis where VEGF is released in response to TNF-α, increasing endothelial permeability and swelling, and stimulating angiogenesis. Angiogenesis, increased leakiness and cytokine expression is known to occur also in Crohn’s disease [6, 7]. The enhancement in angiogenesis in Crohn’s disease highlights neovascularisation as a major contributor to the initiation and perpetuation of chronic intestinal inflammation [8].

Antivascular and antiangiogenic agents reduce tumour growth (or prevent metastases) [1] through primarily cytostatic modes of action, such as selectively
inhibiting membrane receptors, cell cycle regulators or other signalling pathways. Since these agents affect the tissue physiology long before they result in a morphological change (volume, shape) of the targeted lesion, conventional imaging endpoints based on reduction of tumour size are inadequate for evaluating clinical response.

The ability of an imaging technique to highlight physiological changes when no anatomical changes have occurred has therefore become more and more important since the introduction of these new drugs, and in this framework Dynamic Contrast Enhanced (DCE) MRI has assumed an important role.

**DCE-MRI**

Dynamic Contrast Enhanced magnetic resonance imaging (DCE-MRI) is an important imaging technique that can be used in radiology as an additional tool in the diagnosis and staging of cancer. It is repeatable, does not involve ionising radiation, has an excellent spatial resolution and can be performed on clinical MR scanners with standard specifications. DCE-MRI consists of a series of fast MRI scans that are acquired for a time typically varying between 3 to 10 minutes while a contrast agent is injected intravenously. The time-dependent signal intensity or Time Intensity Curve (TIC) in the tissues changes due to the inflow of the contrast agent, and this change is recorded and further analysed to provide several parameters useful for the diagnosis. Because of its relatively simple implementation, DCE-MRI can be applied both in the daily clinical routine and in research settings. The additional value of this technique with respect to conventional static MR imaging sequences lies in its ability to identify changes in the tissue physiology.

The idea of measuring physiological tissue properties by measuring the temporal change of the concentration of an injected exogenous contrast agent is not recent. In 1948 Kety proposed a pharmacokinetic model [9], the first of its kind, in which he showed that it was possible to understand the exchange process of a contrast agent between blood and tissue by repetitively measuring the contrast agent concentration (in that context, an inert gas) in blood samples. In the 70s and 80s the advent of imaging techniques such as computed tomography (CT) and MRI has allowed the localised measurement of contrast agent concentration, therefore broadening the scope of the technique, as well as its accuracy. This has prompted the development of new dynamic contrast enhanced techniques, adapted to the
particular imaging modality, such as CT, PET (Positron Emission Tomography) and MRI. With the introduction of MRI, and especially since fast MRI based imaging strategies became available in the late 80s, dynamic contrast enhanced MR imaging has gained wider application in radiology.

The value of DCE-MRI in the diagnosis of cancer and inflammatory diseases derives from its sensitivity to changes in vessel permeability.

A characteristic of the newly formed vessels in angiogenesis is their abnormally high wall permeability, which results in the easier access of macromolecules to the extravascular space (extravasation). In regions where angiogenesis occurs, the increased leakage rate of medium-sized molecules outside the capillary walls can be seen with imaging techniques that make use of contrast media of the appropriate size, such as those used in DCE-MRI (Gd chelates, i.e. Gd$^{3+}$ “encapsulated” in a cage, size < 1 KDalton). In the case of increased permeability, the contrast medium exits the vascular space at an increased rate, quickly filling the extravascular space and resulting in fast signal enhancement. It also reaches saturation of the extra vascular space earlier than in normal tissue, resulting in the contrast agent quickly leaving this compartment. The presence of abnormal permeability is therefore indicated by fast enhancing, quickly washing out TICs.

**DCE-MRI analysis**

In contrast to other MRI sequences, images generated by DCE-MRI are not immediately processed and displayed. The 4-dimensional data (3D image repeated in time) need to be post-processed to produce parametric images.

Another way of looking at data generated by DCE-MRI is to select a region of interest (ROI) in the lesion and observe how the average signal intensity of the ROI varies in time. Radiologists search for “abnormal” TICs, i.e. TICs that present a quick rise in signal, followed by an early signal decrease. This approach, though operator dependent, is widely used in routine clinical practice and it is today an established method in breast cancer diagnosis (three point measurement) [10].

Radiologists have observed and classified a number of enhancement types in various pathologies (Figure 1), and this classification is often used nowadays in clinical research studies. This straightforward approach, sometimes described as heuristic (i.e. obtained by exploration of possibilities, rather then by following set rules) lacks precision and is not a quantitative measure of physiological properties.
In the early 90s, three researchers [12, 13, 14] independently developed a modification of Kety’s pharmacokinetic model, adapted to the small low-molecular weight paramagnetic Gd-chelate based contrast agents used in MRI, to produce the first DCE-MRI based pharmacokinetic models. These models were later shown to fall under the same umbrella known as “Tofts generalised model”.

Briefly, the model is a mathematical simplification of the structure of the tissue, which is divided into two main interfaced spaces: the plasma volume, through which the contrast agent is carried, and the extravascular extracellular space, where the contrast agent diffuses into (MRI contrast media cannot penetrate the cell). The rate at which the contrast agent crosses the capillary membrane, the plasma volume and the volume in the extravascular extracellular space determines the signal pattern of the DCE-MRI measured data. The application of the theoretical pharmacokinetic model to the DCE-MRI data (through parameter fitting) permits the extraction of physiologically relevant quantities that reflect intrinsic properties of the tissue, such as vascular permeability, blood flow, extracellular extravascular and vascular volume. The main difference with the original Kety model lies in the fact that MR contrast agents are not freely diffusible (Kety used gaseous tracers), and that MRI does not measure the contrast medium itself, but the indirect effect of the contrast medium on the magnetic state of the many hydrogen atoms in the direct neighbourhood, hereby amplifying the effect of each molecule of contrast agent [15]. This approach, known in the literature with different names such as model-based approach, quantitative or pharmacokinetic model analysis, is acknowledged to produce the best DCE-MRI endpoint for measuring changes of intrinsic tissue properties in disease [15].

DCE-MRI is therefore considered a suitable candidate to become a biomarker of drug efficacy, and has gained in popularity. It is now used as a marker of the expression of VEGF, but also the effect of anti-TNF agents, currently used in the therapy of rheumatoid arthritis [16] and Crohn’s disease [17].
However, despite the proven advantages, pharmacokinetic modelling, even 20 years after its introduction, is still only applied in research settings, and is not yet used in the broader clinical routine. The accuracy and rigour of the method come at a price, and a number of unsolved issues limit its application in daily practice: among others these include the difficulty of correctly obtaining all the data needed for the modelling. For a correct implementation of the model, the absolute contrast agent concentrations must first be calculated from the MR signal, requiring the – non-straightforward – calculation of the native tissue relaxation time $T_1$ (an intrinsic property of the nuclear spins). The choice of the arterial input function or AIF, (i.e. the function describing the time-dependent concentration of the contrast agent in the capillaries feeding the tissue described by the model) is pivotal along with a number of other parameters used in the model. These are however very difficult to accurately measure, and sometimes they are not measurable at all. Furthermore, several pharmacokinetic models exist, and in different flavours; the model which should be applied to a certain patient or patient population can be more or less complex, depending on the pathology, way of delivery of the contrast agent and dosage, and there is no agreement yet on which model is the most suited in the various pathologies. Some models pose some quite stringent requirements on the quality of the data, in terms of sampling rate and Signal to Noise Ratio (SNR), which can severely limit the robustness of the (non linear) fitting process. Most importantly, though Tofts’ model has been largely used, its ability to correctly describe low molecular weight contrast kinetics in most tumours has been questioned [18, 19]. In addition to being technically too demanding, the pharmacokinetic model was shown to be not as robust as the semi-quantitative methods [20].

Alternative ways are therefore still being sought. Whereas a lot of effort is put into improving the pharmacokinetic models, or the way the data are acquired and analysed, others focus on semi-quantitative models. Some authors have taken a step back and re-evaluated the simple, heuristic, straightforward, by-eye analysis of the TICs. The simple approach of looking at the shape of the original TIC has some obvious advantages, which make this method of analysis worth further investigation. It is easily understood, it is robust, and it can be applied in the daily clinical routine. The cumbersome pharmacokinetic modelling has not reached this level yet.
AIM
The main line of this thesis is about a new approach to the simple look-at-the-TIC method: instead of individually looking at averaged TICs, these are analysed in a pixel-by-pixel fashion, i.e. in every single voxel acquired by the DCE-MRI scan sequence. This method is proposed to overcome the intrinsic insensitivity to spatial heterogeneity of the ROI-based analysis: because large lesions, whether cancerous or inflammatory, are not homogeneous, sampling and averaging signal from the ROIs to look at the dynamic course of the TIC misses important characteristics of the lesion. One of the aims of this thesis was to determine if introducing this spatial dimension would effectively improve the robustness of the heuristic analysis.

A second aim was to introduce the method in the daily clinical routine, to see how radiologists received the new method. This was achieved by rendering the TIC shapes, automatically calculated in each voxel in the field of view, in colour coded maps which can be easily read by a radiologist and by creating a Graphical User Interface (GUI) where the classification algorithm was implementd, so that it was made available to radiologists and researchers.

The third aim was to apply the pixel-by-pixel TIC analysis in clinical research studies. We investigated whether the TIC was able to differentiate diseased from healthy tissue, and if it was sensitive to the effect of antiangiogenic or anti-TNF drugs.

The last, not less important aim was to investigate the relation between the parameters created by the pixel-by-pixel TIC shape analysis and the parameters of other methods such as the semi-quantitative analysis and the traditional reference standard, i.e. the Tofts pharmacokinetic model based analysis.

OUTLINE OF THE THESIS:
In chapter 2, a novel approach to the analysis of DCE-MRI data is presented where the classification of lesions in terms of shape of the Time Intensity Curve is performed in a pixel-by-pixel fashion. For this purpose an algorithm was developed that automatically detects the shape of the TIC and renders them in colour coded images, giving the radiologist a bird’s eye view of the behaviour of the TIC in the lesion. This algorithm is initially applied to a range of patients with arthritis, soft tissue sarcomas, osteosarcomas, and chondrosarcomas.
In chapter 3, an overview is given of the application of the pixel-by-pixel TIC shape analysis method in patients with chondrosarcoma. We investigate how the different shape types are distributed in this pathology, and look for the heterogeneity of the pathology in terms of TIC shape. Furthermore, the relationship between the TIC shape analysis and the semi-quantitative parameters $ME$ (Maximum Enhancement) and $ISI$ (Initial Slope of Increase) is investigated.

In chapter 4, an application of the TIC shape analysis is presented in a study investigating fistulising Crohn’s disease. In this work we looked at how the relative amounts of each shape type can be related to disease activity.

In chapter 5, the pixel-by-pixel TIC shape analysis is applied to rheumatoid arthritis in a feasibility study. A small cohort of patients with active disease is compared with matched healthy controls, and the capability of the TIC-shape analysis is tested for its ability to discriminate disease activity.

As we were interested in the correlation between the TIC Shape analysis technique and Tofts’ pharmacokinetic model, a preliminary study was performed to make sure that we could provide the best quality pharmacokinetic modelling from our data. In particular, we focussed on the Arterial Input Function, a key element of Tofts’ model and today still an object of investigation, and on how to improve its calculation in the data obtained in our study.

In chapter 6, a reproducibility study is described, where the suitability of the signal arising from the sagittal sinus as input for the AIF was investigated. A correction algorithm was introduced which was developed to improve the calculation of the AIF in case of low temporal resolution of the DCE-MRI scan. This study was preliminary to the study presented in chapter 7, where we performed DCE-MRI in a brain cancer study.

In chapter 7, we present a phase I-II clinical trial investigating the effect of the combination of the antiangiogenic treatment (bevacizumab, an antibody against VEGF) and chemotherapy (continuous dose-intense temozolomide) in patients with a recurrent high grade glioma after first- or second-line treatment. We applied DCE-MRI to evaluate the effect of the treatment and to investigate the possible prognostic value of the parameters extracted by Tofts’ pharmacokinetic model.

In chapter 8, the relationship between the TIC shape analysis and the extended (Tofts) pharmacokinetic model is investigated, by applying both methods to the DCE-MRI data acquired for the glioma study in chapter 7. Furthermore the
predictive value of the TIC shape analysis for the effect of the antiangiogenic drug is investigated.

In chapter 9, we investigate the usefulness of DCE-MRI in fistulising Crohn’s disease on a 3.0 Tesla scanner, in a pixel-by-pixel TIC analysis fashion as well as using extended pharmacokinetic modelling.

In the Summary and Discussion, we summarise the results and present future applications and challenges.

In Appendix 1, new software is presented, which was developed to make the TIC-classification algorithm as well as the pharmacokinetic model available to researchers and radiologist. The software consists of a graphical user interface (GUI), in which the algorithms developed in Chapter 2 and 3 are implemented, as well as the analysis according to Tofts’ pharmacokinetic model.

In Appendix 2, a detailed description is given of the Tofts Pharmacokinetic model. This was used in this thesis as a “reference standard” against which to compare the newly developed pixel-by-pixel TIC shape analysis. The limitations and problems of the model are described here in detail.

REFERENCES

CHAPTER 1


