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Ultrashort Echo Time (UTE) Imaging for Contrast Agent Deposition Measurement: A Review

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Abstract. The deposition of Gadolinium-based contrast agents (GBCAs) has become a growing concern in the field of enhanced Magnetic Resonance Imaging (MRI). GBCAs have been found to be accumulate in various tissues, including the brain and bone, leading to potential long-term health risks, even in patients with normal renal function. Conventional MRI sequences are often limited in detecting Gd deposition in tissues like cortical bone due to their extremely short transverse relaxation times. Ultrashort Echo Time (UTE) MRI sequences offer a promising solution to this challenge by capturing signals from tissues with short relaxation times, enabling more accurate assessment of Gd deposition. This review provides a comprehensive overview of the application of UTE sequences in the measurement of Gd deposition, highlighting key advancements in the applications of UTE technique. It also explores the use of UTE imaging in combination with other methods. This review also discusses potential future directions and give some possible solutions.

Keywords: Ultrashort Echo Time (UTE) Imaging, Contrast Agent Deposition.

1. Introduction

The deposition of contrast agents, particularly Gadolinium (Gd)-based contrast agents (GBCAs), is an increasingly important issue in diagnostic imaging. GBCAs are extensively used to enhance image contrast, allowing for the clear differentiation between abnormal and normal tissues. Despite their widespread use, recent studies have raised concerns about the potential long-term effects of GBCAs, particularly their tendency to accumulate in various tissues, including the brain, bones, and skin. Such accumulations can pose significant health risks, with Nephrogenic Systemic Fibrosis (NSF) being one of the most severe complications linked to GBCAs [1]. NSF is a debilitating and potentially life-threatening condition characterized by fibrosis of the skin, joints, and internal organs, particularly affecting patients with impaired kidney function.

Given the potential risks associated with GBCA deposition, there is an urgent need for advanced imaging techniques that can precisely assess these depositions within the body. Traditional MRI techniques, while non-invasive and effective for a wide range of applications, often fall short when it comes to detecting signals from tissues like cortical bone, which have very short transverse relaxation times. These tissues typically produce signals that decay too quickly for conventional MRI sequences to capture effectively. This limitation hampers the ability to accurately assess the extent and distribution of GBCA deposition, particularly in tissues with rapid signal decay. Ultrashort Echo Time (UTE) MRI sequences have emerged as a powerful tool to overcome these limitations. UTE sequences are specifically designed to capture signals with extremely short transverse relaxation time, making them uniquely capable of imaging tissues like cortical bone [2, 3], tendons, and other areas where conventional MRI sequences struggle. By enabling the detection of these otherwise elusive signals, UTE sequences offer a more comprehensive assessment of contrast agent deposition [4]. This capability is particularly valuable for monitoring the safety and long-term effects of GBCAs in patients, especially those with compromised renal function or other risk factors.

This review aims to provide a thorough exploration of the applications of UTE sequences in the measurement of MR contrast agents, particularly GBCAs. It will delve into the latest technological advancements that have enhanced the sensitivity and accuracy of UTE MRI, such as improvements in hardware, pulse sequence design, and post-processing techniques. Additionally, the review will discuss the current challenges faced by this technology, including issues related to image resolution, acquisition time, and the need for specialized equipment.

2. Literature Statistics

Figure 1 presents the annual count of research papers retrieved from Google Scholar using the search terms "Ultrashort Echo Time" and "Contrast Agent Deposition" from 2010 to 2023. The data indicate a consistent increase in the volume of relevant literature over this period, with the number of publications rising from 130 in 2010 to a peak of 442 in 2023. This upward trend suggests an expanding research focus on the application of UTE Imaging in the quantification of contrast agent deposition.

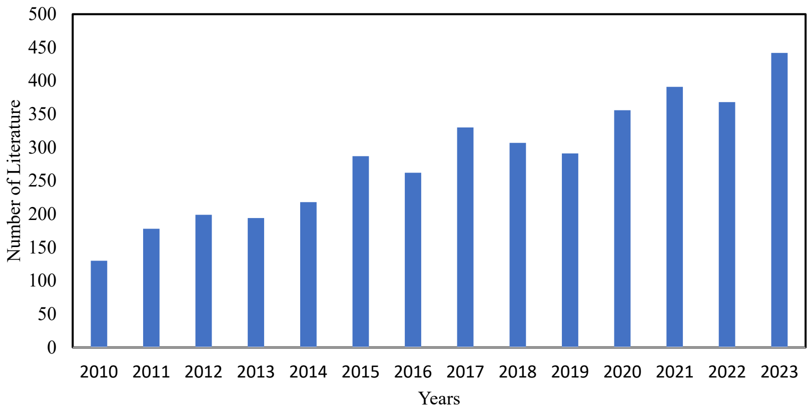

Figure 1. The number of papers searched using “Ultrashort Echo Time” and “Contrast Agent Deposition” per year in Google Scholar

3. Application in Contrast Agent Deposition Measurement

3.1. Mechanisms of Contrast Agent Deposition

Contrast agents in Magnetic Resonance (MR) Imaging are used to enhance the contrast of MR images by making changes on the relaxation times T1 and T2, so as to magnify the difference between the targeted tissues and the surrounding tissues. Most contrast agents use the lanthanide ion gadolinium (III) due to its high magnetic moment as well as its ability to remain stable with unpaired electrons [5]. Contrast agents can be applied intravenously or orally, and the method of administration depends on the subject and the specific imaging requirements.

Gadolinium-based contrast agents (GBCAs) are classified into two main categories: linear and macrocyclic. Linear GBCAs are known to be less stable and more prone to releasing free gadolinium ions, while macrocyclic GBCAs are generally considered more stable and safer [9]. The choice between these types can impact the risk of gadolinium retention in the body.

Recent studies have revealed the mechanisms of how gadolinium enters and deposits in the human body, especially in the brain and bone. Rasschaert et al. [6] proposed that GBCAs enter brain

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parenchyma by first entering the cerebrospinal fluid (CSF) and then passing through the wall of ventricles into the brain. This finding has significant implications for understanding the potential long-term effects of gadolinium retention in neural tissues. In another study, researchers applied several types of GBCAs to decedents and measured the deposition of Gd in different tissues. The results indicate that the level of deposition in bone tissues is higher than in any other tissues, including brain tissues, among all the contrast agents tested [7]. This discovery has led to increased interest in bone tissue as a potential biomarker for gadolinium retention.

Further research revealed a moderately good correlation between Gd deposition in bone and in brain tissue [8]. Therefore, measuring the Gd deposition in bone tissues can also provide relative information concerning Gd deposition in the brain. This correlation opens up new possibilities for non-invasive monitoring of gadolinium retention over time. The potential health implications of gadolinium retention have become a topic of significant concern in the medical imaging community. While the majority of patients who receive GBCAs do not experience adverse effects, there have been reports of a condition known as gadolinium deposition disease (GDD) in some individuals [10]. Symptoms of GDD can include pain, cognitive changes, and skin thickening, although the causal relationship between gadolinium retention and these symptoms remains a subject of ongoing research. In response to these concerns, regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidelines and restrictions on the use of certain GBCAs, particularly linear agents [11]. These actions have led to changes in clinical practice, with a shift towards using macrocyclic agents when possible and a more cautious approach to administering contrast agents, especially in patients who may require multiple enhanced MRI scans over their lifetime.

The development of gadolinium-free contrast agents has also gained momentum in recent years. Researchers are exploring alternative paramagnetic ions, such as manganese and iron, as well as non-metallic contrast agents that work through different mechanisms [12]. These efforts aim to maintain or improve upon the diagnostic capabilities of current GBCAs while minimizing the potential risks associated with gadolinium retention. As our understanding of gadolinium pharmacokinetics and its long-term effects in the body continues to evolve, it is crucial for radiologists and other healthcare providers to stay informed about the latest research and guidelines. Balancing the diagnostic benefits of contrast-enhanced MRI with the potential risks of gadolinium retention remains a key consideration in clinical decision-making.

3.2. UTE Imaging for measurement

Tedesch et al. [9] proposed that the administrations of Gadolinium-Based Contrast Agents (GBCAs) correlate with T1 relaxometry. They observed that R1, the reciprocal of T1, increases linearly with the deposition of gadolinium, indicating that MRI T1 mapping can be used as a tool for Gd concentration measurement. This finding is significant as it provides a potential non-invasive method for monitoring gadolinium retention in tissues over time. However, conventional MRI methods face limitations when it comes to detecting signals from certain tissues, particularly cortical bone. This is due to the low proton density of cortical bone as well as its extremely short transverse relaxation time (T2) [10]. These characteristics make it challenging to capture meaningful signals using standard MRI sequences, which typically require longer echo times.

To address this shortcoming, a new method named ultrashort echo time (UTE) imaging was introduced. The UTE sequence employs a novel approach to RF pulse design and signal acquisition. It makes use of half-pulses to create echo times (TE) that are extremely short. This is achieved by dividing a conventional RF pulse at its peak into two separate excitations [2]. By doing so, UTE allows for signal acquisition to begin almost immediately after excitation, capturing rapidly decaying signals that would be lost in conventional sequences.

The advent of UTE imaging has opened up new possibilities for visualizing and quantifying tissues with very short T2 relaxation times, such as cortical bone, tendons, and ligaments. This technique has found applications not only in musculoskeletal imaging but also in neuroimaging and cardiovascular imaging. Furthermore, the UTE imaging method can be combined with other advanced MRI techniques

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to enhance its diagnostic capabilities. One such combination is with T1 mapping [4]. By integrating UTE with T1 mapping, researchers and clinicians can more accurately assess gadolinium deposition in tissues with extremely short transverse relaxation times, like cortical bones.

4. Recent Advances and Innovations

In recent years, researchers have proposed various techniques for measuring gadolinium (Gd) deposition. Initially, an x-ray fluorescence technique was proposed to measure Gd deposition [11]; however, this technique presents the risk of ionizing radiation and cannot differentiate the distribution of deposition across different bone regions [12].

In contrast, MRI has become an ideal alternative due to its non-invasive and radiation-free nature. Nevertheless, the transverse relaxation time of cortical bone is extremely short, making it difficult for traditional MRI sequences to capture its signal. To address this issue, Zhao et al. proposed a T_1 mapping method based on ultrashort echo time (UTE) sequences, which is UTE-T_1 which can detect Gd signals [4]. Although UTE-T_1 mapping offers this advantage, it faces the challenge of prolonged scan times. To overcome this, researchers further developed three-dimensional ultrashort echo time quantitative susceptibility mapping (3D UTE-QSM), which combines the strengths of UTE sequences and conventional QSM, successfully addressing the issue of Gd's extremely short echo time while reducing scan time [13]. However, despite the progress made in measuring Gd deposition in cortical bone with 3D UTE-QSM, its application in trabecular bone remains challenging. Recently researchers have developed a three-dimensional adiabatic inversion recovery prepared ultrashort echo time Cones (3D IR-UTE-Cones) for the selective imaging of trabecular bone [14], which indicates the potential for measuring Gd deposition in trabecular bone.

5. Future Directions

There are two directions that need further study. One of the directions is that there are still few studies concerning Gd concentration in trabecular bone. A research has proposed that the level of gadolinium accumulation in trabecular bone is significantly higher than in cortical bone[15]; however, the imaging of trabecular bone has been a technique challenge. One possible way to overcome this limitation is to combine UTE imaging with 3D IR-UTE-Cones. Another direction will be that 3D UTE-QSM can also be used to detect other substances whose transverse times are extremely short and magnetic susceptibility are strong. There are some existing studies that apply UTE-QSM technique for the detection of mineral density in human femur as well as tibia cortical bone specimens [16, 17].

6. Conclusion

This review provides a complete explanation of the applications of UTE in contrast agents (particularly GBCAs) measurement. It highlights the advancement in UTE imaging. Despite that, some limitations still exist, including the lack of studies concerning the technique for Gd concentration assessment in trabecular bone. Further studies are needed for developing such techniques to overcome these limitations.

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