SAHLGRENSKA ACADEMY

Optimization of MP2RAGE sequence parameters for head and neck T1-mapping and OE-MRI

Ellen Börjesson

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Sahlgrenska Academy
University of Gothenburg
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Supervisors: Emilia Palmér, Department of Medical Radiation Sciences.
Maja Sohlin, Department of Medical Radiation Sciences.
Examiner: Magnus Båth, Department of Medical Radiation Sciences.

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University of Gothenburg

Abstract

Cancer is the collective name for more than 200 types of diseases that annually causes the death of 8.8 million people, cancer in the head and neck (H&N) accounts for 330.000 of these. It has been shown that hypoxic tumors are more resistant to treatment than well oxygenated tumors. The possibility to examine hypoxia in a tumor could be used for predicting external radiation treatment response, and hence enable adaptive treatment. Today, there is no standardized method to examine hypoxia. Oxygen Enhanced Magnetic Resonance Imaging (OE-MRI) is an in-vivo technique that evaluates the change in T1-value when breathing oxygen compared to when breating air. While breathing oxygen, if the excess oxygen does not bind to hemoglobin molecules, inhomogeneities will occur since oxygen is paramagnetic which shortens the T1-value of the tissue. T1-mapping is a technique where T1-values of tissues are calculated, and by combining OE-MRI and T1-mapping the change of T1-value caused by the excess oxygen can be detected. By using the pulse sequence *Magnetization Prepared 2 Rapid Acquistition Gradient Echoes* (MP2RAGE), the measured signal will be T1-weighted and independent of M_0, T_2^* and $B1^-$, which is desirable for T1-mapping.

The aim of the study was to find the optimal MP2RAGE parameters in order to create a Signal-to-T1 calibration curve to be used for T1-mapping and OE-MRI. To establish the optimal MP2RAGE parameters, the inversion times, repetition time and flip angles were optimized in three subsequent steps in order to find a combination parameters that gave rise to a high signal difference for T1-values in the H&N area. The optimized parameters were validated via phantom measurements by comparing the calculated T1-values with the specified T1-values in the phantom. In addition, the MP2RAGE sequence was used for OE-MRI on a patient with H&N cancer.

In this study the optimization of MP2RAGE sequence was successful. The phantom validation showed that several combinations of MP2RAGE parameters resulted in accurate T1-maps. It was also shown that MP2RAGE parameters resulting in the largest difference in signal did not necessarily produce the most accurate T1-map.

Keywords: MRI, OE-MRI, MP2RAGE, T1-mapping.

Sammanfattning

Cancer är samlingsnamnet för över 200 sjukdomar som årligen orsakar 8.8 miljorner dödsfall. Cancer i huvud-hals området står för 330,000 av dessa dödsfall. Det är visat att hypoxiska tumörer är mer resistanta mot behandling än väl syresatta tumörer. Att kunna utvärdera hur utbredd hypoxin är i en tumör innan och under behandling skulle kunna användas för att ge patienten en mer anpassad behandling. Idag finns det inget standardiserat sätt att göra detta. Syreförstärkt MR (Oxygen enhanced MRI (OE-MRI)) är en metod för att undersöka hur kroppens T1-värden ändras om patienten andas ren syrgas jämfört med luft. Om överskottet av syre inte binder till hemoglobin kommer det skapa magnetfältsinhomogeniteter i kroppen eftersom syre är paramagnetiskt, vilket förkortar vävnadernas T1-värde. Genom att använda OE-MRI i kombination med T1-mapping, där varje pixelvärde översätts till motsvarande T1-värde, kan ändringen i T1-värde orsakat av överskottet av syre utvärderas på pixelnivå. Med bildtagningssekvensen *Magnetization Prepared 2 Rapid Acquistition Gradient Echoes* (MP2RAGE) kommer den uppmätta signalen vara T1-viktad och oberoende av M_0, T_2^* och $B1^-$ vilket är önskvärt för T1-mappning.

Syftet med studien var att finna de optimala bildtagningsparametrarna för MP2RAGE-sekvensen för att skapa en signal-till-T1 kalibreringskurva att använda för T1-mappning vid OE-MRI. För att fastställa de optimala MP2RAGE parametrarna ändrades inversionstiderna, repetitionstiden och flipvinklarna i tre steg för att finna en kombination av parametrar som ger stor signalskillnad mellan T1-värden för vävnader i huvud-hals området. Bildtagningsparametrarna validerades för ett fantom genom att undersöka hur väl de uppmätta T1-värdena stämde överens med fantomets kända T1-värden. Utöver det användes MP2RAGE-sekvensen för OE-MRI på en patient med huvud-hals cancer. Det visades att flera olika kombinationer av parametrar gav bra resultat och kan användas för T1-mapping, så länge bildtagnignsparameterarna var optimerade för rätt T1-intervall. Det visades även att en stor signalskillnad inte nödvändigtvis gav bäst resultat, utan att signalskillnaden kan tillåtas vara lägre för att korta ner scantiden.

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Abbreviations

AMD - Absolute mean difference
B_0 - External magnetic field
$B1^+$ - Transmit field
$B1^-$ - Receiver field
FOV - Field of view
GRE - Gradient echo
Hb - Hemoglobin
Hz/px - Hertz/pixel
H&N - Head and neck
IR - Inversion recovery
MP2RAGE - Magnetization Prepared 2 Rapid Acquisition Gradient Echoes
MRI - Magnetic resonance imaging
M_0 - Proton density
M_{xy} - Transverse magnetization
M_z - Longitudinal magnetization
NZ - slices per slab / number of slices in the longitudinal direction (z)
OE-MRI - Oxygen Enhanced MRI
ROI - Region of interest
RF pulse - Radiofrequency pulse
R1 - Longitudinal relaxation rate
SNR - Signal to Noise Ratio
TOLD - Tissue oxygenation level dependent
TI - Inversion time
TR - Repetition time
TRflash - Echo spacing in the MP2RAGE pulse sequence
T1 - Longitudinal relaxation time
$T2^*$ - Apparent spin-spin relaxation time
α - Flip angle

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A Appendix 1 **I**

1 | Introduction

Cancer is the collective name of more than 200 types of diseases, annually causing the death of 8.8 million people world while [1] where cancer in the head and neck (H&N) accounts for 330.000 of these [2]. All types of cancer cells share six hallmarks:

- inability to undergo apoptosis,
- cell growth and division independently of external signals,
- continuous growth regardless of external signals,
- ability to a limitless number of cell divisions,
- ability to spread to other tissues and form metastases,
- promote the construction of blood vessels [3].

The fast growing blood vessels are often irregular, disorganized and dysfunctional which leads to hypoxic areas in the tumor [4].

Hypoxic tumors are more resistant to treatment compared to non-hypoxic tumors [5]. One reason for this is that the cells are further away from blood vessels, making them less exposed to e.g. the chemotherapy drugs [6]. Another reason is given by the oxygen fixation hypothesis that states that the probability of permanent DNA damage is higher in the presence of oxygen than in the absence [4].

The level of hypoxia in a tumor is not dependent on the tumor size [7] and the hypoxia is not necessarily homogenely distributed in the tumor, making it hard to predict how the tumor will respond to treatment [8]. The possibility to examine hypoxia in a tumor could be used for predicting external radiation treatment response, allowing adaptive radiation treatment. One way of estimating hypoxia could be with Oxygen Enhanced Magnetic resonance imaging (OE-MRI).

OE-MRI is a non-gadolinium based in-vivo technique to assesses tumor oxygenation. Tissue oxygenation level dependent (TOLD) MRI is one type of OE-MRI that evaluates changes of T1-value in tissue when breathing oxygen compared to when breathing air. The measured change in T1-value within tumor tissue between breathing oxygen and air is theoretically proportional to the level of tissue oxygenation and thus has the potential of being an indicator of hypoxia [5].

Different tissues have different T1-values that can be estimated by using T1-mapping, where signal in an T1 weighted image are translated voxel-wise into T1-values and displayed as a parametric map (T1-map). T1-mapping is often used for imaging of the heart [9] and has been used for imaging of the brain where T1-values for white matter, gray matter and cerebrospinal fluid are well established [10]. T1-mapping of

the H&N area however, is relatively unexplored. Multiple inversion recovery pulse (IR) sequences can be used for T1 mapping, resulting in a relatively long scan time. The T1-values in the T1-map is also affected by $B1^-$-inhomogenites, since it causes the signal to decrease, which will be perceived as a shorter T1-value.

Magnetization-Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) is a pulse sequence starting with an 180 inversion pulse followed by two gradient echo (GRE) readouts. Using the the complex signals from each GRE, the MP2RAGE images can be can be computed by calculating the ration of the two images . The signal strength in each MP2RAGE voxel is independent of receiver field $B1^-$-inhomogenites, proton density M_0 and the T_2^*-value (apparent spin-spin relaxation time) making the acquired image purely T1-weighted [11]. By Bloch simulation of the sequence, the signal each T1-value gives rise to can be estimated, i.e., a Signal-to-T1 calibration curve can be obtained. This calibration curve can then be used for T1-mapping, and TOLD.

The aim of this project was to optimize the parameters of the MP2RAGE sequence to obtain minimized deviations and fluctuations in the estimated T1-maps used for OE-MRI in H&N cancer.

2 | Theory

2.1 Oxygen enhanced MRI (OE-MRI)

OE-MRI is a method that is sensitive to how the level of oxygen (O_2) in blood plasma and interstitial tissue fluid changes when breathing hyperoxic gas [12]. Oxygen, which is paramagnetic, will cause inhomogeneities in the magnetic field that shortens the T1, or equivalently increases the longitudinal relaxation rate R1 = 1/T1. [8].

Since healthy tissue already is well oxygenated, breathing oxygen will cause the hemoglobin (Hb) molecules to be fully saturated, and the residual O_2 will remain dissolved in the blood plasma and interstitial tissue fluid. As O_2 is paramagnetic, the inhomogenities in the magnetic field will increase leading to a decrease in T1-value and an increase in R1. In hypoxic areas, most O_2 will bind to the hemoglobin, leaving few, or non, O_2 molecules free and there will be no change in T1-value or R1 (figure 2.1).

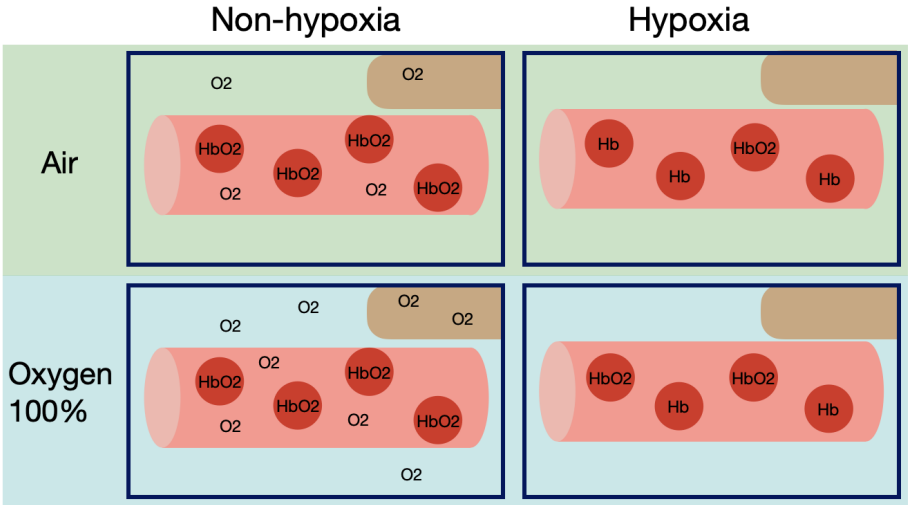


Figure 2.1: In non hypoxic tissue the hemoglobin molecules are well saturated while breathing air, and breathing hyperoxic gas will increases the amount of O_2 molecules in the plasma and interstitial fluid. Since O_2 is paramagnetic, the inhomogenities in the magnetic field will increase. In hypoxic tissues the will O_2 molecules bind to the hemoglobin, and the amount of O_2 in the plasma is negligable. Adapted from reference [12]

The change in R1 caused by breathing oxygen can be describes as ΔR1,

$$\Delta R1 = R1(O_2) - R1(air) \tag{2.1}$$

where R1(O_2) and R1(air) are while breathing oxygen or air, respectively. Theoretically ΔR1 is proportional to the change in dissolved oxygen for a given voxel [8]. A positive ΔR1 is an indication that the area is non-hypoxic, while no change, or a negative ΔR1, could indicate that the area is hypoxic [8].

2.2 Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE)

MP2RAGE is a 3D pulse sequence starting with an 180°-inversion pulse, and after a time TA, the first GRE block is acquired by application of n excitation pulses with a small flip angle (α_1). After the first GRE readout, a second delay TB is introduced before starting the second GRE readout, that is identical to the first GRE except for the flip angle (α_2) (figure 2.2). The two gradient echo images are acquired at inversion times TI_1 and TI_2 respectively, defined as the time from the inversion pulse to the center of k-space in each GRE. After the second GRE readout, a third delay time TC is introduced followed by reapplication of the inversion pulse. This procedure is repeated n_{PE} times in order to sample the k-space in three dimensions. From this data two images, GRE_{TI1} and GRE_{TI2}, with inversion timed TI_1 and TI_2 can be reconstructed. The two images are then combined to the so called MP2RAGE image as

$$MP2RAGE = \frac{GRE_{TI1} \cdot GRE_{TI2}}{GRE_{TI1}^2 + GRE_{TI2}^2} \tag{2.2}$$

where GRE_{TI1} is the signal value acquired at TI_1 and GRE_{TI2} the image acquired at TI_2. Accordingly, the MP2RAGE images will have signal values between -0.5 to 0.5.

One major advantage of calculating the MP2RAGE image as per equation 2.2, the effects of T_2^*, M_0 and $B1^-$-inhomogenites are removed, indicating that small changes in T1 should be easier to detect [11] (for more details on the calculation of the MP2RAGE image, see appendix A).

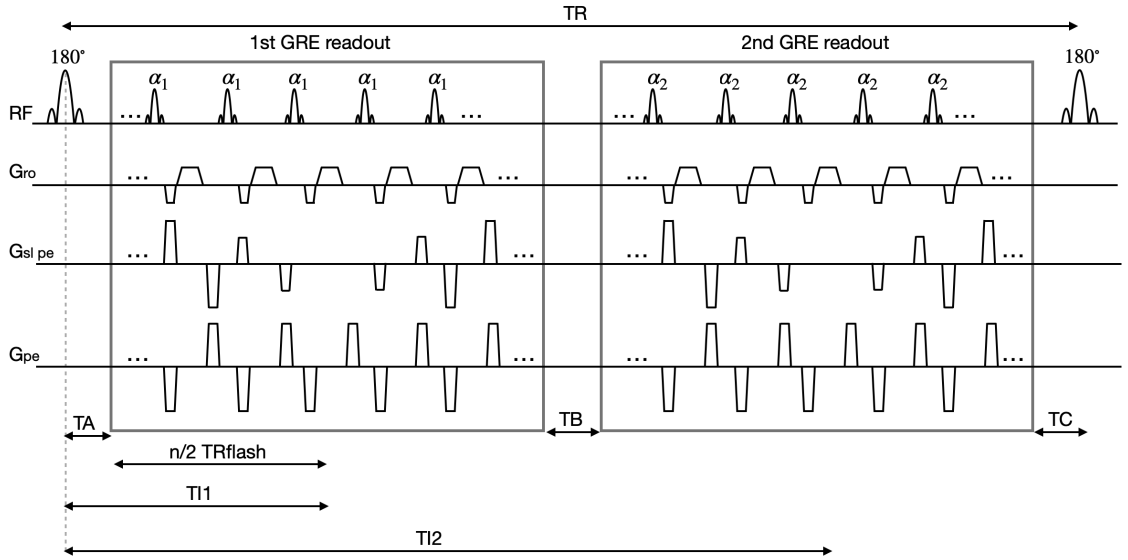


Figure 2.2: Scheme of the MP2RAGE pulse sequence. The inversion times TI_1 and TI_2 are the times from the inversion pulse to the center of k-space in each GRE readout. TRflash is the time between successive excitation pulses in the GRE kernel. TR is the time between two successive inversion pulses. n is the number of excitation pulses. α_1 and α_2 is the flipangles. TA, TB and TC are delay times. Adapted from reference [11].

2.2.1 T1-mapping using the MP2RAGE sequence

As mentioned in the introduction, Bloch simulations of the MR2RAGE pulse sequence can be used to estimate the signal each T1-value gives rise to, resulting in a Signal-to-T1 calibration curve (figure 2.3) [13]. The Signal-to-T1 calibration curve is dependent on MP2RAGE sequence parameters repetition time TR, inversion times TI_1 and TI_2, flip angles α_1 and α_2, echo spacing TRflash and number of excitations n per GRE block (slices per slab (NZ) for Siemens).

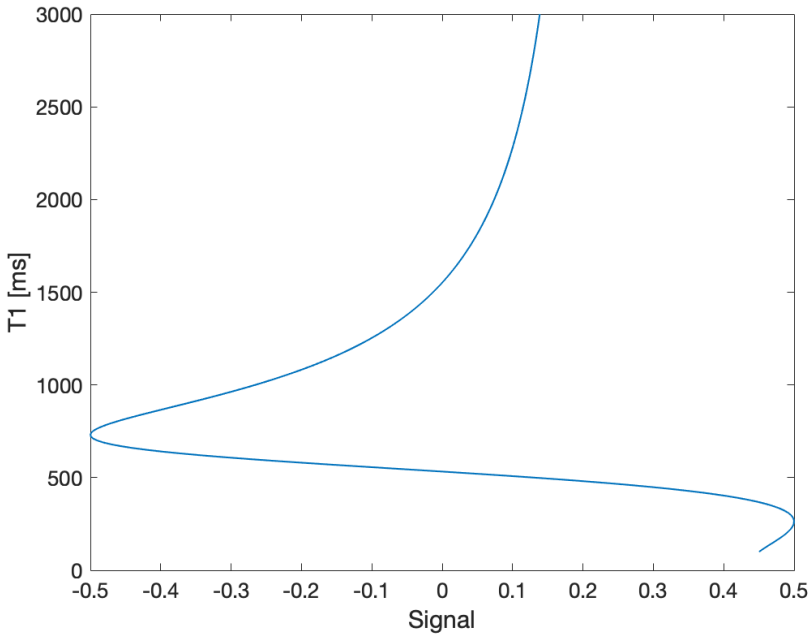
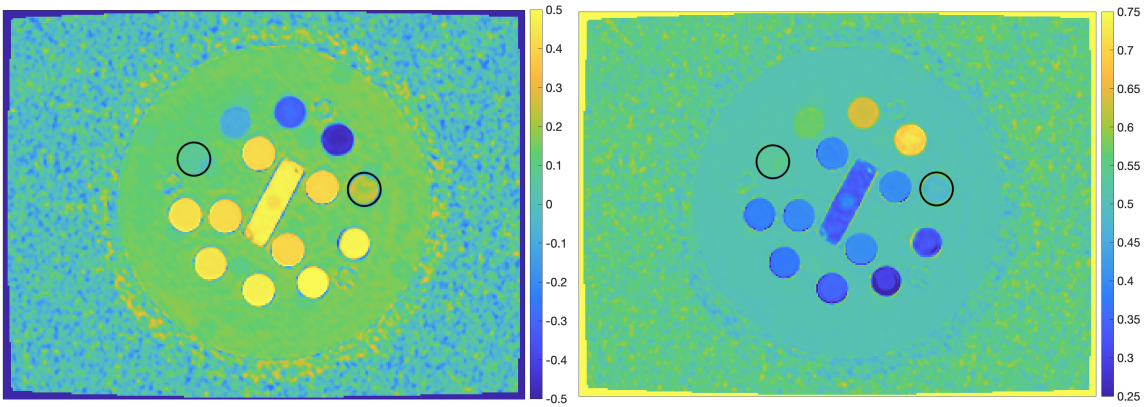


Figure 2.3: Exampel of the Signal-to-T1 calibration curve, obtained from Bloch simulations of the MP2RAGE sequence.

This means that the correspondence between T1-value and signal is known, but several T1-values can give rise to the same signal (see figure 2.3), which means that converting the signal to T1 is not always possible.

An MP2RAGE image of a phantom is seen in figure 2.4a. The image has been acquired with the same MP2RAGE sequence parameters used when simulating the Signal-to-T1 calibration curve in figure 2.3. Since the same sequence parameters have been used, a T1-map seen in figure 4.5b can be calculated by voxel-vise application of the Signal-to-T1 calibration curve to the MP2RAGE image, translating the signal of each voxel into a T1-value.



(a) The MP2RAGE image where the signal only can assume values between -0.5 to 0.5.

(b) T1-map of the MP2RAGE image. The pixels are presented in T1-values [s]. The colorbar shows that there is only T1-values in the range from 250 ms to 750 ms.

Figure 2.4: Illustrations of an MP2RAGE-image and corresponding T1map

Depending on the optimization of the MP2RAGE sequence parameters, several T1-values can give rise to the same signal. For example, as seen in figure 2.3, T1 values of 2033 ms and 514 ms have a signal of approximately 0.1. The code used for the T1-mapping ([13]) can only convert the signal to T1-values which is in the interval with a negative slope. For figure 2.3, this means that the signal will only be converted to T1-values between 250–750 ms.

If T1-mapping were to be performed using the example sequence parameters and T1-values of 514 ms and 2033 ms (right and left encircled area, respectively, figure 2.4) were of interest, the problem becomes apparent. The different encircled areas should represent different T1-values, but they have almost equal values since the sequence parameters was inaccurately optimized for these T1-values. By changing the MP2RAGE sequence parameters to cover a larger T1-interval, accurate T1-maps could be calculated.

3 | Method

To optimize the parameters of the MP2RAGE sequence to obtain minimized deviations and fluctuations in the estimated T1-maps, the signal obtained from each T1-value was simulated. The simulated optimized parameters were validated by phantom T1-mapping. Additionally was a proof of concept of OE-MRI conducted for patient data.

All experiments were preformed on a wide-bore Siemens Aera 1.5T MRI scanner (Siemens Healthcare, Erlangen, Germany) dedicated for radiation therapy purposes, with a 32-channel head coil distributed from the same manufacturer.

3.1 Estimating T1 relaxation times in the head and neck area

To optimize the parameters of the MP2RAGE sequence for the range of T1-values expected in OE-MRI of the H&N, T1-values for different type of tissues in the anatomical area are required. For a healthy volunteer, images were acquired at different inversion times (TI) using an inversion recovery pulse sequence (IR) with the following measurement parameters; TI = 50, 100, 150, 250, 625, 1500, 2250 and 3000 ms, TR = 4500 ms, FOV = 256×256 pixels, slice thickness = 5 mm, and reconstructed pixel spacing = 0.98×0.98 mm^2. Images were also acquired for one H&N cancer patient to investigate T1-values of H&N tumor pre- and mid-treatment (2.5 weeks external radiation treated). The TIs pre-treatment were 50, 250, 625, 1000 and 2250 ms and the TIs mid-treatment were 50, 1000 and 2250 ms. FOV were 96×128, slice thickness 5 mm, and reconstructed pixel spacing 1.96×1.96 mm^2.

For five different tissues (i.e., tumor, parotid, muscle, tongue, and fat), the mean signal value in a region of interest (ROI) in respective tissue was calculated for each TI. The T1-values for the tissues were estimated by curve fitting of the mean signal values using the following equation:

$$M_Z = M_0(1 - 2e^{TI/T1}) \tag{3.1}$$

where M_Z is the net magnetization , M_0 is the magnetization immediately after the inversion pulse and TI is the inversion time.

3.2 Optimization of MP2RAGE parameters

In order to perform T1-mapping to be used for OE-MRI the deviation and fluctuation in the estimated T1-value has to be minimized. To establish optimal MP2RAGE parameters, simulations of the pulse sequence (appendix A) were conducted (MATLAB R2021b, The MathWorks, Inc., Natick, Massachusetts, United States) given certain criteria. The criteria were;

- the Signal-to-T1 calibration curve should enclose, i.e. the slop should be negative within the T1-interval for parotid to hypoxic tumor in order for the T1-mapping to be performed correctly for these H&N tissues,
- the difference in signal for the optimized extreme T1-interval should be $\geq$0.9,
- the calibration curve should be relatively linear between the two extreme T1-values, $T1_{min}$ and $T1_{max}$, so that the conversion from signal in the MP2RAGE image to T1 would be as insensitive to signal fluctuations as possible.

3.2.1 The optimization steps

To easily keep track of which parameter was varied the following sequence parameters were optimized in three subsequent steps: Inversion times (TI_1 and TI_2), repetition time (TR) and Flip angles (α_1 and α_2).

In order to optimize an MP2RAGE sequence, estimated intervals of optimization parameter were given, i.e T1-interval of interest, TR-interval, and flip angle-interval. Additional parameters needed to be known were echo spacing (TRflash), the number of excitations within a single GRE block (NZ (slices per slab for Siemens)), inversion efficiency, and $B1^+$-values. The inversion efficiency was assumed to be 100% and the spatial inhomogeneity in transmit field ($B1^+$) was assumed to be negligible due to 1.5T system.

In the first step, potential TI_1- and TI_2-values were varied from n·TRflash/2 to TR - n·TRflash/2 in steps of 100 ms and with the condition that TI_2-TI_1>n·TRflash [11]. The interim input values was TR = 2500 ms and flipangles = 3/3 degrees, as well as the estimated T1-interval for the H&N are that went from $T1_{min}$ to $T1_{max}$ in steps of 50 ms. For every combination of TI-values, the signal of the MP2RAGE-sequence and Signal-to-T1 calibration curve were simulated. The slope between each adjacent T1 value was calculated, and if the entire slop within the estimated T1-interval was negative, the inversion time TI_1 was saved and used in the next step. Since only TI_1 would be transferred to step two, the interim input value of TR and flip angles was assumed to have low significance, as they were to be altered in later steps. The only condition was that TR had to be longer than the expected TI_2-value.

In the second step, the same interim flip angles as in the first step were used but TR was varied within the given TR-interval in steps of 100 ms. Since the TI-values depend on TR, all the TI_1-values from the first step were used to calculate new TI_2-values for every TR-value. For each TR-value and its associated TI-values, the

signal from the MP2RAGE-sequence and Signal-to-T1 calibration curve were simulated. Once again the slope between each adjacent T1 value were calculated, and if the entire slope was negative within the T1-interval, the TR-value and TI-values was saved and used in the last step.

In the last step of the simulation, all combinations of TR- and TI-values distributed from the first and second step were used and the flip angles were varied from 1-5 degrees independently of each other. For the combinations of variables that gave a negative slope between each adjacent T1 value of the Signal-to-T1 calibration curve within the T1-interval, the slope k between each adjacent T1 value was evaluated. The slope k had to be steeper than $0.8 \cdot K$, were K is the slope of the linear function defined as

$$K = \frac{\mathrm{T1}_{max} - \mathrm{T1}_{min}}{\mathrm{Signal}_{max} - \mathrm{Signal}_{min}} \tag{3.2}$$

where $\mathrm{T1}_{min}$ and $\mathrm{T1}_{max}$ are the starting and end point of the given T1-interval, and Signal_{max} and Signal_{min} are the maximum (0.5) and minimum (-0.5) signal-values. By constraining the slope k to constantly be steeper than $0.8 \cdot K$ and at the same time have a signal difference $\geq$0.9 between $\mathrm{T1}_{min}$ and $\mathrm{T1}_{max}$, the curve will be relatively linear over the entire T1-interval, if the step length between the T1-values is small enough. In this case the step length was 50 ms, which was assumed to be small enough. This means that the end tails of the calibration curve cannot become excessively steep.

3.2.2 The dependence of different T1-interval

To examine if the range of the T1-interval had significance for the accuracy of the T1-values, optimization of MP2RAGE parameters and phantom measurements were made for three different T1-intervals: 200–2100 ms, 300–2100 ms, and 300–800 ms. The intervals were chosen to cover the T1-values in the H&N area and as many of the phantom's T1-values as possible.

The optimization input values were TRflash = 2.7 ms, n = 36 and TR was varied from 2000 to 3500 ms. For each interval, the combination of variables that gave the greatest difference in signal between $\mathrm{T1}_{min}$ and $\mathrm{T1}_{max}$, hence the optimal parameters, were validated using phantom measurements. The acquisition parameters for phantom validation, besides the simulated optimal parameters, were; FOV = 320×224×36 pixels (i.e., slices per slab = 36), slice thickness = 5 mm, reconstructed pixel spacing 0.9×0.9 mm^2, and bandwidth 1560 Hz/px.

It was found that the parameters optimized for the T1-interval 300–2100 ms gave the most correct T1-values, and therefore this interval used for the remaining simulations and phantom measurements.

3.3 Simulation parameters and phantom validation

Phantom measurements were conducted with the MP2RAGE sequence to validate and compare different sets of MP2RAGE parameters. The validations were performed using a QalibreMD System Standard Model 130 phantom. The phantom contains compartments with known T1-values in the range from 22.859 ms to 2033 ms which allows it to be used for validation of the T1-map produced by the simulated Signal-to-T1 calibration curve. For every conducted measurement, the obtained MP2RAGE image was converted to a T1-map using a publicly available code in GitHub [13], and ROIs were drawn in the compartments with T1-values within the T1-interval. In each ROI, the mean T1-value and standard deviation were calculated as well as signal to noise ratio (SNR, equation 3.3). The mean measured T1-value was compared with the specified T1-value. Additionaly, the absolute mean difference (AMD) for all compartments from the specified T1-value was calculated.

$$\mathrm{SNR} = \frac{\mathrm{Signal}_{\mathrm{ROI}}}{\mathrm{Standard\ deviation}_{\mathrm{ROI}}} \tag{3.3}$$

3.3.1 The dependence of repetition time

Additional phantom measurements were made for the T1-interval 300–2100 ms using a shorter TR in order to reduce the acquisition time but with the cost of less signal difference. The simulated combination of parameters that gave a signal difference $\geq$0.9 between $T1_{min}$ = 300 and $T1_{max}$ = 2100, and had TR shorter than 3200 ms were selected, resulting in six combinations of parameters (hereinafter referred to as suboptimal parameters). For the suboptimal parameters, the difference in signal between T1 = 1800 ms and T1 = 2000 ms were calculated, as this is the area of the curve that often is steepest. Three combinations of parameters that gave the largest difference in signal, thus the flattest slope in the end tail area, were used for the phantom measurements (TR = 3100, 2800, and 2700). In addition to the three different sets of simulated suboptimal parameters was the acquisition parameters for phantom measurements: FOV = 240×320×36 mm^2, slice thickness = 5 mm, reconstructed pixel spacing 0.9×0.9 mm^2 and bandwidth 1560 Hz/px.

An additional optimization of MP2RAGE parameters and phantom measurement with the T1-interval of 300–2100 ms was performed in order to reduce the acquisition time even further. The optimization was performed with optimization input values of TRflash = 3 ms and a shorter TR-interval of 2000–3000 ms. The phantom acquisition parameters, besides the simulated optimal parameters, were: FOV = 240×320×36 mm^2, slice thickness = 5 mm, reconstructed pixel spacing 0.9×0.9 mm^2 and bandwidth 1010 Hz/px.

3.3.2 The dependence of number of slices, TRflash and bandwidth

In this section, NZ, TRflash, and/or bandwidth were changed without redoing the optimization. To examine if NZ had significance for the accuracy of the T1-values, an additional phantom measurement was performed using the combination of simulated suboptimal parameters resulting in TR = 3100 ms where NZ was set to 72 pixels, i.e. slice thickness = 2.5 mm. In order to obtain similar signal to noise ratio, the bandwidth was set to 920 Hz/px, resulting in a TRflash of 3 ms. No other parameters were changed.

For the combinations of simulated suboptimal parameters with TR = 2800 ms, an additional phantom measurement was made where TRflash was set to 3 ms (and following the bandwidth to 1010 Hz/px), no other parameters were changed. This was done to examine the T1-maps accuracy depending on TRflash (and following bandwidth).

To validate if bandwidth alters the T1-values, an additional phantom measurement was acquired with the simulated optimal parameters for T1-interval of 300–2100 ms and the shorter TR-interval of 2000–3000. The TRflash = 3 ms was kept constant, while the bandwidth was altered from 1010 Hz/px to 920 Hz/px, while all other parameters stayed constant.

3.4 OE-MRI on patient with MP2RAGE

OE-MRI was performed on one patient with H&N-cancer. Ethical approval was obtained from the Swedish Ethical Review Board (Dnr. 2021-03792). The tumor was located between the left parotid gland and left retromandibular vein and had a diameter of approximately 5 mm, see figure 3.1.

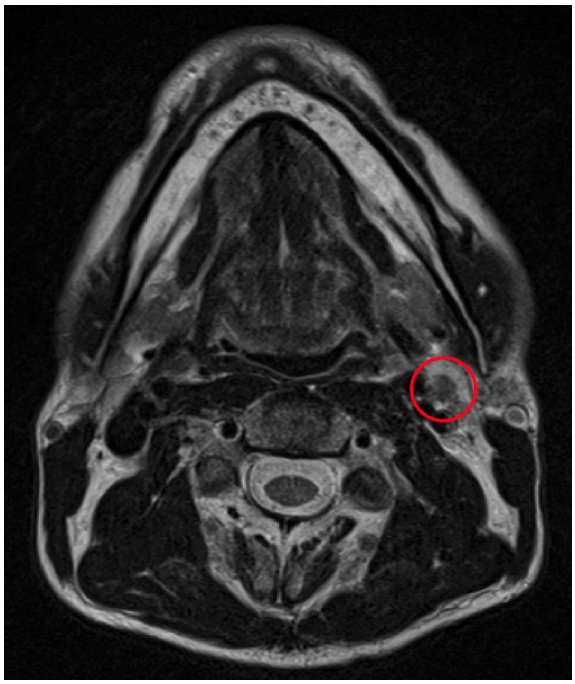


Figure 3.1: T2-weighted coronal slice of the patient that were used to delineate ROIs. The area with the tumor is encircled (not used for evaluation).

The patient (same as in section 3.1) was positioned head first supine. A T2-weighted image was acquired as anatomical reference. For the OE-MRI, the MP2RAGE sequence was utilized with unoptimized parameters, since the optimization code was not complete (TR = 3500, TI_1 = 746 ms, TI_2 = 1446 ms, flipangles = 5/5 degrees, FOV = 320×240 pixels, slice thickness = 5 mm, and pixel spacing 0.9×0.9 mm^2). Five MP2RAGE scans with an individual acquisition time of 2 minutes and 52 seconds were performed. For scan 1 and 5, respectively, the patient was breathing air. During scan 2-4, oxygen (15 l/min) was distributed via an oxygen mask, and the oxygen saturation of blood was simultaneously indirectly monitored using a pulse oximeter. There was a pause of approximately 2.5 minutes between scan 4 and 5 in order to allow the oxygen saturation to decrease before final image acquisition.

All five MP2RAGE images were voxel-wise converted to T1-maps using a simulated Signal-to-T1 calibration curve. ROIs were delinated (left and right masseter muscle, left and right palatine tonsil, tongue and tumor) using the T2 weighted anatomical image and subsequently transferred to the T1-maps. The mean T1-value was calculated for each ROI in each T1-map.

To verify that the unoptimized parameters translated the signal to T1-values correctly, i.e. that the simulation of the calibration curve was successful, the MP2RAGE parameters used in the OE-MRI of the H&N cancer patient were also verified using the T1 phantom (QalibreMD System Standard Model 130). For the image, a T1-map was produced, and the mean T1-value, for each sphere with T1-value in the interval 800-2000 ms, was calculated.

4 | Results

4.1 Estimating the T1 relaxation times in the head and neck area

The estimated T1-values for the different tissues in healthy volunteer, and patient pre-treatment and 2.5 weeks treated are shown in table 4.1. For healthy volunteer, tongue had the highest T1-value of 823.8 ms and fat the lowest of 298.6 ms. For patient, tumor had the highest T1-value of 1154.9 ms pre-treatment and 962.8 mid-treatment, and fat the lowest of 261.2 ms pre-treatment and 334.3 ms mid-treatment.

Table 4.1: T1-values [ms] for healty volunteer, and patient pre- and mid-treatment. The values were measured in the H&N region with an inversion recovery pulse sequence.

	Parotid L	**Parotid R**	**Muscle L**	**Muscle R**	**Tounge**	**Fat**	**Tumor**
Healthy volunteer	634	614	797	787	824	299	-
Patient pre-treatment	776	778	979	1027	905	261	1155
Patient mid-treatment	821	698	869	845	861	334	963

4.2 Simulation parameters of the MP2RAGE sequence

4.2.1 The dependence of different T1-interval

The optimal MP2RAGE parameters obtained from the optimization for the three different T1-intervals 200–2100, 300–2100 and 300–800 ms can be seen in table 4.2.

Table 4.2: The optimal parameters for the MP2RAGE sequence obtained from the optimization, for the three different T1-intervals: 200–2100 ms (A), 300–2100 ms (B) and 300–800 ms (C). NZ = 36, TRflash = 2.7 ms. TR = repetition time, TI_1/TI_2 = first and second inversion time, α_1/α_2 = flip angle one and two, Diff signal = Difference in signal between the endpoints of the optimized interval.

Simulation	**TR**	$\mathbf{TI_1}$	$\mathbf{TI_2}$	$\boldsymbol{\alpha_1}$	$\boldsymbol{\alpha_2}$	**Diff signal**
200–2100 ms (A)	3300	649	1549	2	3	0.93
300–2100 ms (B)	3200	749	1449	3	4	0.92
300–800 ms (C)	3200	349	1249	3	2	0.91

The Signal-to-T1 calibration curves for the optimized parameters of the three different intervals can be seen in figure 4.1. The calibration curve representing the interval 300–2100 ms (B) is less steep for T1-values higher than 1800 ms than the calibration curve representing the interval 200–2100 ms (A). The calibration curve representing the interval 300–800 ms (C) has approximately the same slope over the entire range.

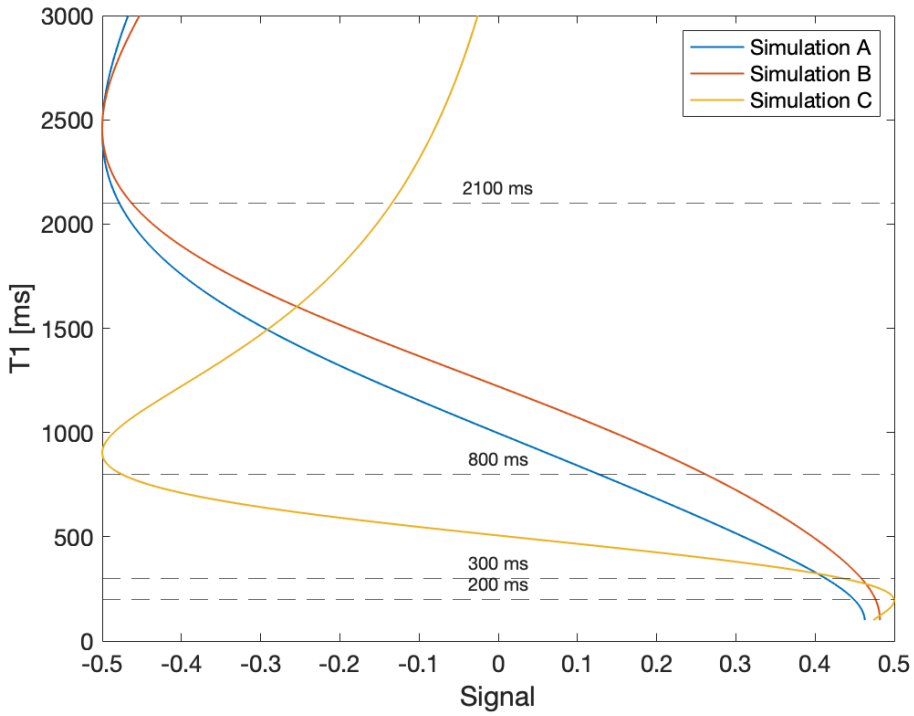


Figure 4.1: Signal-to-T1 calibration curves for optimized MP2RAGE parameters for T1-intervals 200–2100 ms (A), 300–2100 ms (B), and 300–800 ms (C). Except from the T1-interval, all the input values in the optimization were the same

4.2.2 The dependence of repetition time

The suboptimal MP2RAGE parameters for T1-interval 300–2100 ms when TR was shorter than 3200 ms, as well as the optimized parameters for TRflash = 3 ms with TR restricted to 3000 ms can be seen in table 4.3 as simulation 1, 2, 3 and 4. The corresponding Signal-to-T1 calibration curves for the parameters can be seen in in figure 4.2.

Table 4.3: Suboptimal parameters to be used for T1-mapping. The parameters for simulation 1, 2 and 3 were selected from the same optimization as simulation B, but had a shorter TR. Simulation 4 was optimized for TRflash = 3 ms and smaller TR-interval (2000–3000 ms). For simulation 1_{mod} both TRflash and NZ were changed without redoing the optimization, while simulation 2_{mod} only had a different TRflash. TR = repetition time, TI_1/TI_2 = first and second inversion time, α_1/α_2 = flip angle one and two, NZ = slices per slab, Acq time = Acquistition time, Diff signal = Difference in signal between the endpoints of the optimized interval, * = Modified NZ, TRflash and/or bandwidth

	Simulation	**TR**	**TI_1**	**TI_2**	**α_1**	**α_2**	**TRflash**	**NZ**	**Acq time**	**Diff signal**
Shorter TR	**1**	3100	749	1449	4	5	2.7	36	2min 54s	0.92
	2	2800	649	1449	4	5	2.7	36	2min 37s	0.90
	3	2700	649	1349	3	4	2.7	36	2min 31s	0.90
	4	2500	654	1245	4	5	3.0	36	2min 20s	0.91
Mod*	**1_{mod}**	3100	749	1449	4	5	3.0	72	2min 54s	0.92
	2_{mod}	2800	649	1449	4	5	3.0	36	2min 37s	0.90

The longest TR (simulation 1) gave the flattest curve for T1-values higher than 1800 ms but a more steep curve for T1-values shorter than 800 ms. The Signal-to-T1 calibration curve for simulation 1 (TR = 3100) is most similar to the curve with optimization B (TR = 3200 ms), which was the simulation that gave the greatest difference in signal (i.e. "optimal parameters"). The visual difference between calibration curve with TR = 2800 ms (simulation 2) and TR = 2700 ms (simulation 3) is minimal for most of the interval.

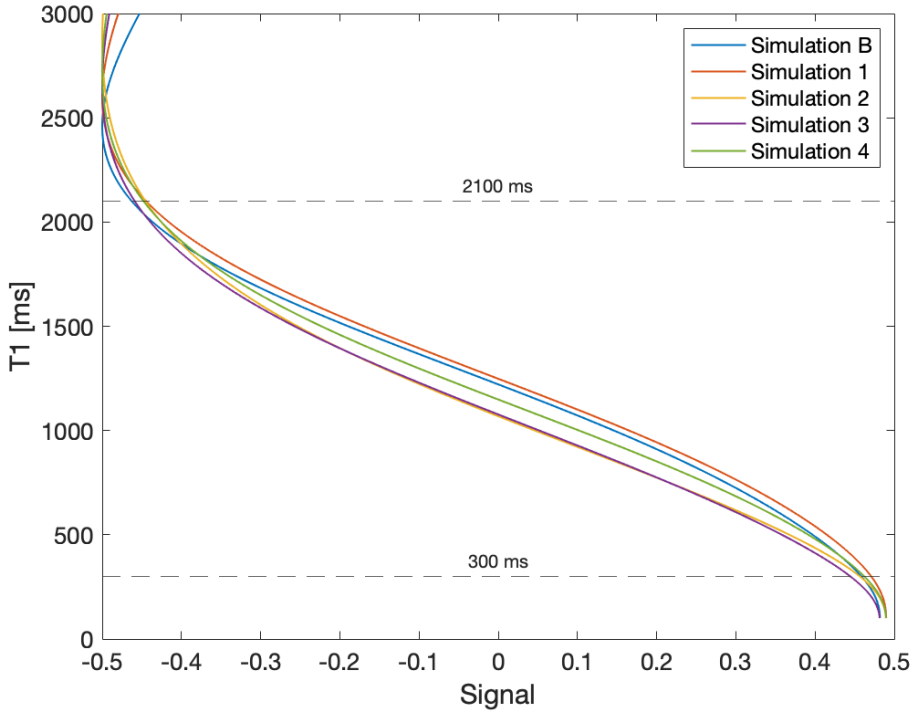


Figure 4.2: Signal-to-T1 calibration curves for the T1-interval 300–2100. Simulation B was the optimal curve, optimized with TRflash = 2.7 ms, while simulation 1, 2 and 3 were selected from the same optimization but shorter TR. Simulation 4 were optimized with TRflash = 3 ms.

4.2.3 The dependence of number of slices, TRflash and bandwidth

In the last simulations, NZ and/or TRflash were changed without redoing the optimization. The MP2RAGE parameters for simulation 1_{mod} and 2_{mod} can be seen in table 4.3. For simulation 1_{mod}, were the parameters from simulation 1 kept constant, only TRflash was changed to 3 ms and NZ to 72. For simulation 2_{mod} was only TRflash changed. The parameters for simulation 4_{mod} were exactly the same as for simulation 4, and is therefore not listed in the table, but during the phantom validation measurement 4_{mod} had a different bandwidth than measurement 4.

The Signal-to-T1 calibration curve for simulation 1_{mod} became steeper for T1-values shorter than 800 ms, compared to simulation 1, see figure 4.3.

There was insignificant difference between Signal-to-T1 calibration curves comparing simulation 2 and 2_{mod} (figure 4.3).

The Signal-to-T1 calibration curve for simulation 4_{mod} is exactly the same as for simulation 4 (figure 4.2) since no simulation parameters where change, only the bandwidth.

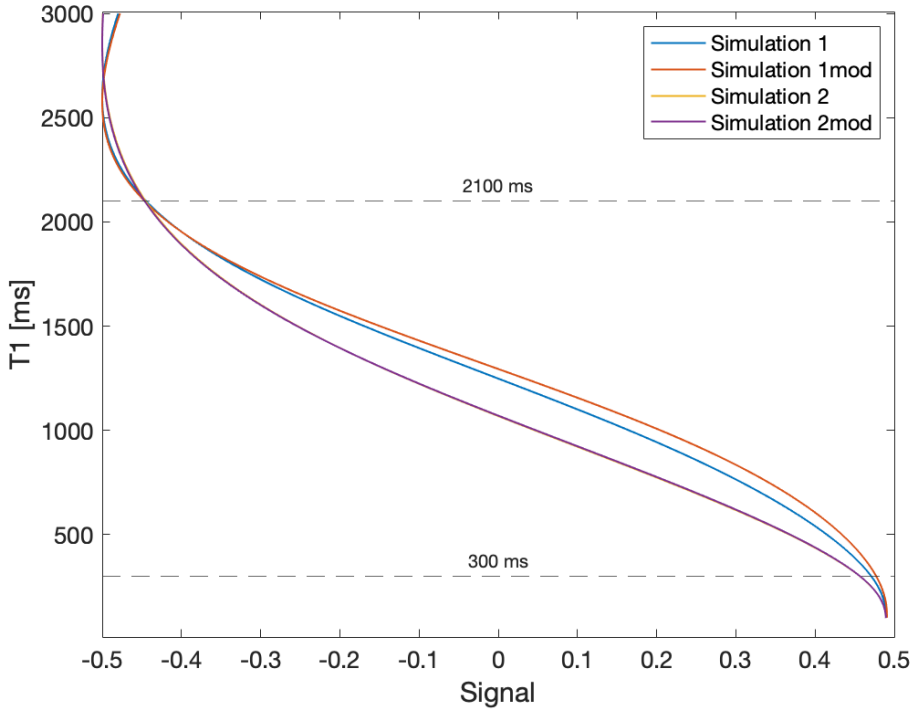


Figure 4.3: Signal-to-T1 calibration curves dependet on NZ and/or TRflash. The blue and yellow curve (simulation 1 and 2) were obtained with suboptimal parameters. For the red curve (simulation 1_{mod}) was TRflash set to 3 ms and NZ to 72, and for the purple curve (simulation 2_{mod}) was TRflash set to 3 ms, without without redoing the optimization.

4.3 Phantom validation

4.3.1 Different T1-intervals

Phantom measurements with MP2RAGE parameters from optimization A (T1 interval 200–2100 ms) and optimization B (T1 interval 300–2100 ms) showed that the measured T1-values that had the largest deviation from the specified T1-values were at the end points of the interval, see table 4.4. The measured T1 in the phantom compartment with specified T1 = 1489 ms had the largest deviation for both A and B.

For the measurement with MP2RAGE parameters from optimization C (T1 interval of 300–800 ms), the deviation in T1-value was a maximum of 6% at the end point of the interval. The AMD for the interval was 4%.

Table 4.4: Phantom measurements with parameters from simulation A, B and C. Simulation A were optimized to cover the T1-interval 200–2100 ms. Simulation B were optimized to cover the T1-interval 300–2100 ms. Simulation C were optimized to cover the T1-interval 300–800 ms. The specified T1 is the phantom compartments T1-value. The deviation in percentage between the specified T1 and measured T1 is denoted as "Difference". AMD is the absolute mean difference for all compartments.

	Specified T1 [ms]	**2033**	**1489**	**1012**	**730**	**514**	**368**	**260**	**AMD**
A	**Measured T1 [ms]**	1911	1374	979	710	503	351	246	-
	Standard deviation	99	40	33	24	23	16	20	-
	Difference [%]	6.0	7.7	3.2	2.7	2.1	4.7	5.5	4.6
	SNR	19	35	30	29	22	23	12	-
B	**Measured T1 [ms]**	1948	1383	992	716	499	353	245	-
	Standard deviation	65	30	27	22	16	16	23	-
	Difference [%]	4.2	7.1	2.0	2.0	3.0	4.2	5.7	4.0
	SNR	30	46	37	34	32	23	11	-
C	**Measured T1 [ms]**	-	-	-	705	502	353	244	-
	Standard deviation	-	-	-	15	16	10	11	-
	Difference [%]	-	-	-	3.4	2.3	4.1	6.0	4.0
	SNR	-	-	-	46	31	34	23	-

4.3.2 Acquisition time

For the following measurements suboptimal parameters were used where TR was shorter, without redoing the optimization.

For measurement 1 (TR = 3100 ms), 2 (TR = 2800 ms) and 3 (TR = 2700 ms) the maximal deviation between measured and theoretical T1-value was found for the phantom compartment with reference T1 = 1489 ms (table 4.5). Shorter TR gave a lower AMD and SNR.

In measurement 4, when the MP2RAGE parameters were optimized for TRflash = 3 ms with TR limited to 3000 ms, and the bandwidth was set to 1010 Hz/px, the maximal deviation in T1-value was found for the compartment with reference T1 = 1489 ms and was approximately 4.5 %. For the remaining compartments with T1-values within the optimization interval 300–2100 ms, the deviation was less then 2.5%.

Table 4.5: Phantom measurements with suboptimal parameters 1, 2, 3, as well as optimized parameters 4. The phantom measurements using modified simulations 1_{mod}, 2_{mod} and 4_{mod} are also presented. All simulations covered the T1-interval of 300–2100 ms. For measurement 1 to 3 the bandwidth was set to 1560 Hz/px, while measurement 1_{mod} and 2_{mod} had a bandwidth of 1010 Hz/px. Measurement 4 had a bandwidth of 1010 Hz/px while measurement 4_{mod} had a bandwidth of 920 Hz/px. The specified T1 is the T1-value in the phantom compartment. The deviation in percentage between the specified T1 and measured T1 is denoted as "Difference". AMD is the absolute mean difference for all compartments.

		Specified T1 [ms]	**2033**	**1489**	**1012**	**730**	**514**	**368**	**AMD**
Shorter TR	**1**	**Measured T1 [ms]**	2009	1386	994	710	506	356	-
		Standard deviation	68	37	25	20	13	10	-
		Difference in percent	1.2	7.0	1.8	2.8	1.6	3.4	3.0
		SNR	30	37	40	36	39	36	-
	2	**Measured T1 [ms]**	2015	1416	1006	715	507	355	-
		Standard deviation	96	35	21	21	15	12	-
		Difference in percent	0.9	4.9	0.6	2.0	1.4	3.5	2.2
		SNR	21	41	48	34	34	39	-
	3	**Measured T1 [ms]**	2019	1430	1008	715	507	358	-
		Standard deviation	107	43	23	23	17	17	-
		Difference in percent	0.7	4.0	0.4	2.1	1.3	2.8	1.9
		SNR	19	33	43	32	30	21	-
	4	**Measured T1 [ms]**	2012	1425	1024	724	514	360	-
		Standard deviation	90	32	17	16	13	10	-
		Difference in percent	1.0	4.3	-1.2	0.8	0.0	2.3	1.6
		SNR	22	45	60	45	40	38	-
Modified NZ, TRflash, BW	$\mathbf{1_{mod}}$	**Measured T1 [ms]**	2061	1444	1048	749	541	388	-
		Standard deviation	62	27	19	16	12	15	-
		Difference in percent	-1.4	3.1	-3.6	-2.6	-5.3	-5.5	3.7
		SNR	33	53	56	46	47	26	-
	$\mathbf{2_{mod}}$	**Measured T1 [ms]**	2031	1417	1008	719	508	355	-
		Standard deviation	89	22	13	14	10	7	-
		Difference in percent	0.1	4.8	0.4	1.5	1.2	3.6	1.9
		SNR	23	63	78	50	49	48	-
	$\mathbf{4_{mod}}$	**Measured T1 [ms]**	2035	1424	1010	722	509	359	-
		Standard deviation	95	29	19	16	10	8	-
		Difference in percent	-0.1	4.4	0.2	1.1	0.9	2.5	1.5
		SNR	21	50	54	46	52	48	-

4.3.3 Number of slices and TRflash

In measurement 1_{mod} (NZ = 72, TRflash = 3 ms, bandwidth = 920 Hz/px), the T1-values were measured higher than the reference value for all phantom compartments except the compartment with reference T1 = 1489 ms. Compared to measurement 1 there was a slightly higher difference in percentage from the specified T1-values.

For measurement 2_{mod} (TRflash = 3 ms, bandwidth = 1010 Hz/px), the maximal deviation in T1-value was approximately 5%, and found for the phantom compartment with a specified T1-value of 1489 ms. The deviation from the specified T1-value were slightly higher compared to measurement 2.

In measurement 4_{mod} (TR = 2500 ms, bandwidth = 920 Hz/px), the maximal deviation in T1-value was approximately 4.5 % for the phantom compartment with T1 = 1489 ms. For the remaining compartments with T1-values $\geq$ 514 ms the deviation in T1-value was 2.5 % or less. The mean difference in percentage were somewhat lower for measurement 4_{mod} compared to measurement 4.

4.4 OE-MRI of patient using MP2RAGE

The parameters used for the OE-MRI was not optimized but gave a sufficiently linear Signal-to-T1 calibration curve over the interval 800–2000 ms with a signal difference between $T1_{min}$ = 800 ms and $T1_{max}$ = 2000 ms of 0.82. The Signal-to-T1 calibration curve is shown in figure 4.4.

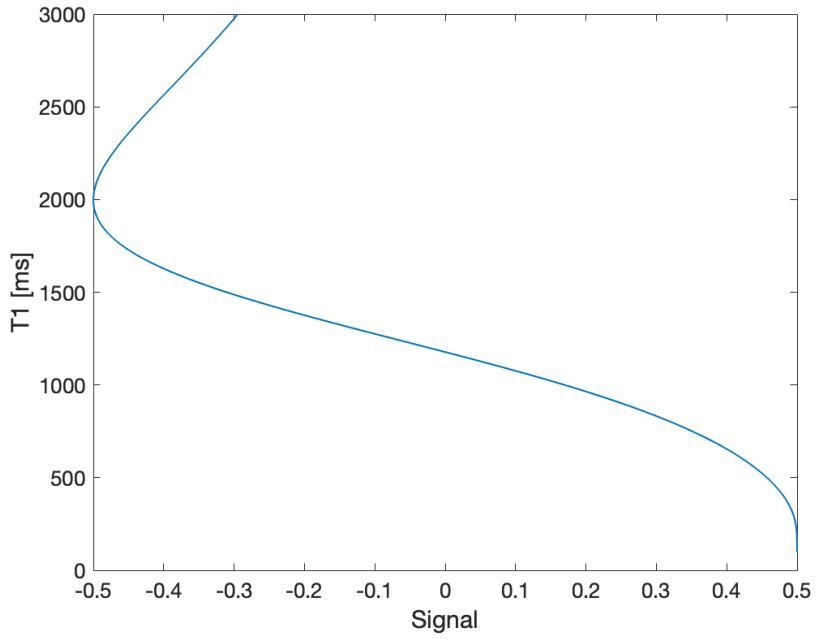


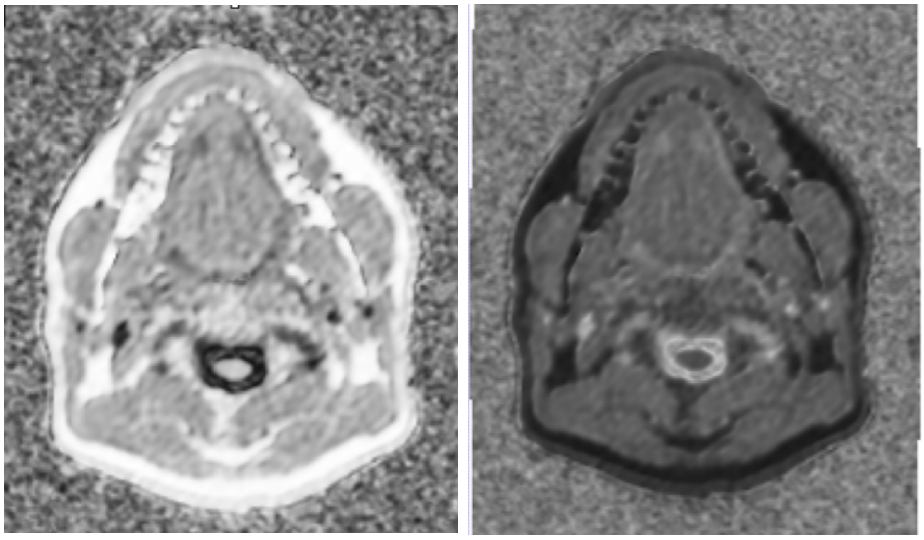
Figure 4.4: Signal-to-T1 calibration curve for the MP2RAGE sequence that were used for OE-MRI and T1-mapping on a patient. The parameters were: TR = 3500 ms, TI_1 = 746 ms, TI_2 = 1446 ms and flip angles = 5/5 degrees.

In the phantom validation the maximal percentage deviation in T1-value was 8.1% for the phantom compartment with T1 = 1489 ms. This was also the sphere with the maximal standard deviation of 27.8 ms. The AMD for the phantom measurement was 4.8%, which indicates that the parameters could be used for T1-mapping and OE-MRI.

Table 4.6: Phantom measurement for validation of the MP2RAGE sequence parameters that were used during OE-MRI.

Specified T1 [ms]	**2033**	**1489**	**1012**	**730.8**	**514.1**	**367.9**	**AMD**
Measured T1 [ms]	1977	1368	984	700	489	346	-
Standard deviation	27	28	22	14	16	13	-
Difference in percent	2.7	8.1	2.8	4.3	5.0	6.1	4.8
SNR	73	49	45	50	31	27	-

The T2-weighted anatomical image used for delineating of ROIs is shown in figure 3.1 and the MP2RAGE image with corresponding T1-map can be seen in figure 4.5.



(a) MP2RAGE image of the patient during OE-MRI.

(b) Corresponding T1-map of the patient.

Figure 4.5: Coronal slice of the patient pre-oxygen, acquired with the MP2RAGE sequence.

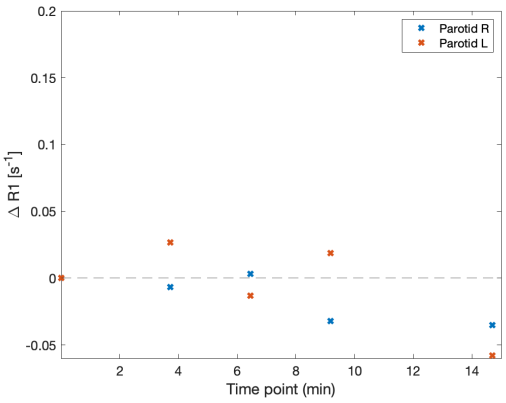
When the patient was breathing oxygen the mean T1-value decreased for tongue and tumor, see table 4.7.

Table 4.7: Mean T1-values with standard deviation in parotid, muscle, tongue and tumor obtained with the MP2RAGE sequence during OE-MRI of a patient that was 2.5 weeks into radiotherapy.

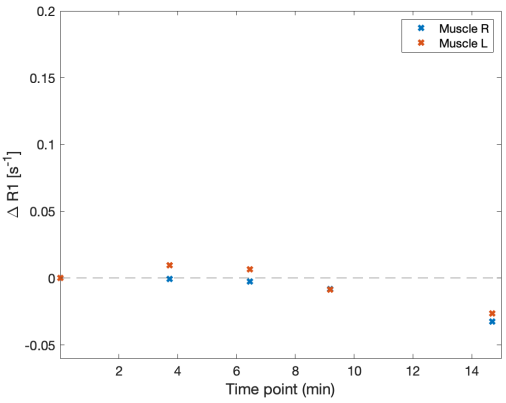
T1 [ms]	**Parotid L**	**Parotid R**	**Muscle L**	**Muscle R**	**Tongue**	**Tumor**
Preoxy	769.1±154	904.3±74.4	919±69.1	950.5±47.7	1012.8±41.7	1333.3±152.3
Oxy 1	753.5±154.6	909.7±65.7	910.9±65.9	951.2±42.6	1007.7±41.2	1217.8±76.9
Oxy 2	777±160.6	901.7±69.2	913.5±74.1	952.8±46.7	1001.9±43.7	1181.7±84.8
Oxy 3	758.2±119	931.4±73.8	926.3±67	958±46.2	1000.9±42	1086.8±69.7
Postoxy	805±140.5	933.9±63.1	942±83.3	980.8±60.7	1008±46.9	1168.5±83.8

The corresponding ΔR1-values are shown as graphs in figure 4.6. For tongue and tumor the ΔR_1 is constantly positive while it fluctuates around zero for parotid and

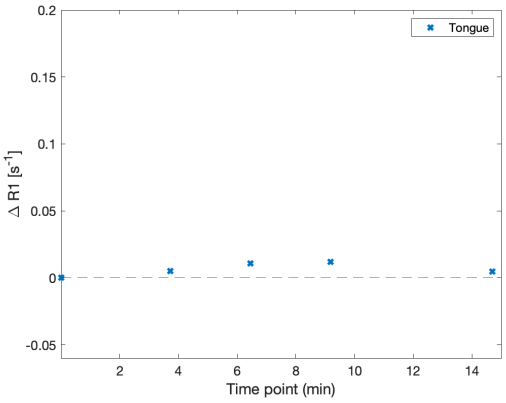
muscle.



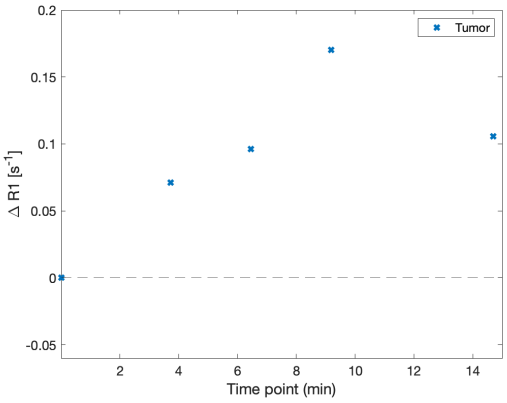
(a) Parotid



(b) Muscle



(c) Tongue



(d) Tumor

Figure 4.6: ΔR_1-values relative to the R_1-value pre-oxygen for parotid, muscle, tongue and tumor during OE-MRI.

5 | Discussion & Conclusions

The MP2RAGE sequence provides a T1-weighted image that is independent of the T_2^*-value and $B1^-$-inhomogenities, giving it a high potential to be used for T1-mapping and OE-MRI. The aim of this study was to optimize the parameters of the MP2RAGE sequence to obtain minimized deviations and fluctuations in the estimated T1-maps used for T1-mapping and OE-MRI in H&N cancer. This was done by simulating MP2RAGE parameters to obtain a large signal range between two T1-values in the Signal-to-T1 calibration curve, while also limiting the the slope of the curve.

The parameters obtained from the simulation was used during phantom measurements. From the measurements it could be shown that the fluctuation and deviation in the conversion from signal to T1-value was small, which makes the parameters suitable for T1 mapping.

5.1 Estimating T1 relaxation times in the head and neck area

As seen from the estimation of T1-values with IR, the T1-values are highly individual. When computing the mean T1-values in the H&N area by inversion recovery it was found that parotid, that is an organ at risk for H&N radiation therapy, had a T1-value of approximately 600 ms and pre-treatment tumor had a T1-value of approximately 1200 ms. Since the T1-value in individual voxels could be higher, or lower, the optimization for the MP2RAGE sequence was done for a greater T1-interval.

5.2 Optimization of MP2RAGE parameters

The flip angles were limited to 5 degrees to reduce the impact of $B1^+$-inhomogeneities [11]. Even when larger flipangles (up to 15 degrees) were allowed the result of the optimization were the same, indicating that the difference in signal cannot get any greater if the curve is to be as linear as possible.

For the patient's sake, the acquisition time should be kept short to avoid inconveniences. For patients undergoing MRI in radiation therapy, a short acquisition time

is important since the patient is immobilized by a mask. The acquisition time is dependent on TR, which is why TR was limited to a maximum of 3500 ms. But since the TI-values is dependent of TR, the number of possible combinations of parameters was limited.

When optimizing the calibration curve to range over the relatively large T1-interval for H&N tissue, there is a trade-off between the slope of the calibration curve and the steepness of the end tail. With as flat slope and large signal difference as possible ([-0.5 0.5]), the calibration curve becomes robust for signal fluctuations meaning that a small signal fluctuation would not give rise to a large deviation in T1-value. But if a large interval of the curve has a slope near 0, the end tails have to be very steep if the entire H&N T1-interval is to be covered. The requirement on the calibration curve was therefore a slope steeper than $0.8 \cdot K$ over the entire T1-interval incorporated as a weighting factor. The requirement may have influenced the curve to not be as ideal as if no requirement was set for the purpose of translating the signal to T1 values, but was a much needed weighting factor to moderate signal fluctuation influence.

The requirement on the calibration curve to have a slope steeper than $0.8 \cdot K$ over the entire T1-interval resulted in signal differences that never were higher than 0.93. If allowing the Signal-to-T1 calibration curve to be flatter, the difference in signal can become higher. Instead of having the same requirements for the slope over the entire T1-interval, the slope could have different restrictions in different sub-intervals of the curve. By doing so, the slope of the curve could be determined at a detailed level, and areas of the curve which are of low significant could be allowed to be steeper while other areas could be flatter.

All optimization parameters were not allowed to change independently of each other which may have caused a loss of combinations of MP2RAGE parameters that would have resulted in more eligible Signal-to-T1 calibration curves when used for translating signal to T1-values.

5.3 Simulation parameters and phantom validation

Phantom measurements A, B and C showed that a narrower T1-interval gave a lower AMD. This may be due to the fact that with a flatter curve, the signal needs to change more for there to be a change in T1-value (see figure 4.1). A smaller interval however, limits the window of T1-values to be used for T1-mapping. By expanding the T1-interval the deviation from the specified T1 increased, as seen in table 4.4, but the T1-values were still of the correct order of magnitude. This is an indication that the optimization can be done over any interval, as long as it covers the T1-values of interest.

Measurement B was acquired with optimal MP2RAGE parameters with an acqusition time of 2 min 55 s. To investigate if shorter acqusition time, i.e a shorter TR, produced accurate signal to T1 conversions measurement 1, 2 and 3 was acquired with suboptimal MP2RAGE parameters and a shorter TR (TR = 3100 ms, TR = 2800 ms, TR = 2700 ms, respectively). The result showed that the measured T1-values for all measurements had about the same difference in percentage for the compartments with T1-values $\leq$ 1012 ms (table 4.3). The difference in percentage for measured T1 values in the compartments with T1 $\geq$ 1489 ms was highest and lowest for simulation B and 3, respectively. This might be the reason for why measurement 3 have the lowest absolute mean difference for all compartments within a set of MP2RAGE parameters.

In the signal-to-T1 calibration curves it was shown that simulation B and 1 have a steeper end tail for T1-values around 2033 ms compared to simulation 2 and 3, see figure 4.2. This makes these measurements more sensitive for signal fluctuation which may be the cause of the higher standard deviation in measured T1-value for compartment T1 = 2033 ms (table 4.3).

Measurement 4, which was optimized for TRflash = 3 ms and shorter TR-interval (2000-3000 ms), had a higher SNR for almost all compartments compared to measurement 1, 2 and 3 which is expected due to the narrowed bandwidth. The measured T1-values had about the same difference in percentage as measurement 2 and 3 for all T1 compartments. Measurement 4 also resulted in a smaller absolute mean difference for all compartments within a set of MP2RAGE parameters compared to measurment B, 1, 2 and 3. This indicated that the measurement 4, with the shortest TR and ergo the shortest acquisition time, generates the most accurate T1-values and could be used for T1-mapping and OE-MRI.

Measurement B was acquired with the MP2RAGE parameters that gave the greatest difference in signal (0.92) in the Signal-to-T1 calibration curve. The measurements acquired with suboptimal MP2RAGE parameters as well as parameters optimized for shorter TR-interval and larger TRflash had a difference in signal equal or smaller than measurement B. Since measurement 1-4 resulted in smaller absolute mean difference for all compartments within a set of MP2RAGE parameters compared to measurement B, it was indicated that the difference in signal might not be the ideal to use for establishing the optimal MP2RAGE parameters to be used for T1-mapping and OE-MRI.

The phantom validation showed that during measurement 1_{mod}, the measured T1-values were higher than the specified T1-value for all compartments except for one. For the compartments with T1-value 514 ms and 368 ms the measured T1-values differed the most than for measurement 1. Since the parameters in measurement 1_{mod} was modified from measurement 1 without an optimization it was expected that the accuracy in T1-value would decrease, which it also did. A higher NZ reduces the slice thickness which will decrease the SNR. By applying a narrower bandwidth this effect was averted and the SNR in measurement 1_{mod} was higher or similar as in

measurement 1. Since the bandwidth has no effect on the Signal-to-T1 calibration curve, it is difficult to predict how to balance bandwidth to NZ so that SNR is not reduced to much. Just changing NZ, without redoing the optimization, is not recommended if the accuracy in T1 and a high SNR is of importance.

In measurement 2_{mod} the same MP2RAGE parameters were used as in measurement 2, except the bandwidth that was decreased to 1010 Hz/px and as a result TRflash was increase to 3 ms (see table 4.3). TRflash determines which values TI_1 and TI_2 obtains in the optimization, but only changing TRflash without redoing the optimization will not affect the Signal-to-T1 calibration curve much, which is why there was no visual difference between simulation 2 and simulation 2_{mod} in figure 4.3. The bandwidth does not affect the simulation but the effect during the measurements was clear. The SNR in measurement 2_{mod} increased for all compartments, and the increase was large for the compartments with T1-values in the middle of the optimized interval, see table 4.5. In addition the absolute mean difference for all compartments was slightly lower compared to measurement 2. This indicates that a small change in bandwidth and TRflash can be made, without redoing the optimization, if it is necessary.

Simulation 4 and 4_{mod} were optimized for TRflash = 3 ms and TR was limited to 3000 ms. Overall measurement 4 and 4_{mod} gave the desirable result with a low standard deviation, high SNR and accurate T1-values. In addition the acquisition time was the shortest which is better for the patient. The difference in bandwidth between measurement 4 and 4_{mod} was too small for there to be a clear difference between results in from the measurements. A more narrow bandwidth will reduce the geometric accuracy, when MRI is used for radiotherapy a high geometric accuracy is desirable to ensure that the right area is treated. If the parameters are to be used for OE-MRI, where hypoxic areas in a tumor are to be investigated, the geometric accuracy is key. Therefore, the settings for measurement 4 may be preferable.

The compartment with T1 = 1489 ms had the highest difference in percent from the specified T1-value for all measurements conducted in this paper. This is an indication that the specified T1-value in this compartment may be incorrect.

To obtain completely accurate T1-values using the MP2RAGE sequence is not per se of interest. It is rather the change in T1, or ΔR_1, between breathing air and oxygen that is of interest. As long as the deviation in T1-value are constant over time, the comparison between ΔR_1 over time would still be valid.

5.4 OE-MRI on patient with MP2RAGE

Since the simulation was not completely finalized before the OE-MRI patient measurement, the parameters were not optimal. During the OE-MRI the highest T1-value was found to be 1300 ms, which is distant from the region in the calibration curve that was almost vertical (at 2000 ms, see figure 4.4). Muscles had the lowest T1-value of ≈850 ms and according to figure 4.4 T1-values as low as 350 ms should

be measurable. From the phantom measurements it was found that the estimated T1-values were relatively correct from at least 500 ms, meaning that the measured T1-values in the patient should be in the correct order of magnitude . However, for the phantom compartment with T1 = 1489 ms the deviation was 8%, since the T1-values from this compartment always have deviated the most, it may not be due to the Signal-to-T1 calibration curves accuracy.

When calculating the ΔR_1-values the tumor had a positive ΔR_1 indicating that it was not hypoxic. Since the patient was 2.5 weeks into treatment and the tumor had shrunk, this was expected. Tongue also showed a positive ΔR_1, while the ΔR_1 for muscle and parotid fluctuated around zero, which indicated that either the muscle and parotid is hypoxic or that it is not a tissue where OE-MRI can measure oxygen differences. For all tissues, the ΔR_1 did not returned to its value preoxygen which may be due to that the time between image 4 and 5 were to short, in previous studies the "cooling down period" has been almost twice as long [12] than during this study. Additionally, only one image acquisition was performed pre- and post-oxygen which do not provide a robust baseline but the time had to be shortened for the sake of the patient.

5.5 Conclusion

This thesis shows that optimization of the MP2RAGE sequence is possible. Via Bloch simulations in MATLAB, several combinations of parameters were conducted that later were validated with phantom measurements. The phantom validation showed that different set of optimized MP2RAGE parameters could obtain accurate T1-values, proving that the MP2RAGE sequence can be used for T1-mapping. The proof of concept of OE-MRI was successful for a patient with H&N cancer, even though the sequence parameters were not optimal. This is a promising indication that the MP2RAGE sequence can be useful for OE-MRI.

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A | Appendix 1

The signal from image 1, GRE_{TI1}, can be calculated with equation A.1.

$$\begin{aligned}\mathrm{GRE}_{TI1} =& B_1^- e^{-TE/T_2^*} M_0 \sin(\alpha_1) \cdot \left[\left(\frac{\mathrm{eff} \cdot m_{z,ss}}{M0} EA + (1 - EA) \right) \right. \\ & \left. \cdot (\cos(\alpha_1) E1)^{n/2-1} + (1 - E1) \frac{1 - (\cos(\alpha_1) E1)^{n/2-1}}{1 - (\cos(\alpha_1) E1)} \right]\end{aligned} \tag{A.1}$$

The signal from image 2, GRE_{TI2}, can be calculated with equation A.2.

$$\begin{aligned}\mathrm{GRE}_{TI2} =& B_1^- e^{-TE/T_2^*} M_0 \sin(\alpha_2) \\ & \cdot \left[\frac{\frac{m_{z,ss}}{M0} - (1 - EC)}{EC(\cos(\alpha_2) E1)^{n/2}} - (1 - E1) \frac{(\cos(\alpha_2) E1)^{-n/2} - 1}{1 - \cos(\alpha_2) E1} \right]\end{aligned} \tag{A.2}$$

For both equation A.1 and A.2, $\mathrm{E1} = \mathrm{e}^{-TR/T1}$, $\mathrm{EA} = \mathrm{e}^{-TA/T1}$, $\mathrm{EB} = \mathrm{e}^{-TB/T1}$ and $\mathrm{EC} = \mathrm{e}^{-TC/T1}$. TE is the echo time, TA, TB and TC are delay times in the MP2RAGE sequence, pictured in 2.2. α_1 and α_2 is the flipangles, M_0 is the magetization at time 0, B_1^- is the inhomogenites from the reciver field, T_2^* is the effective T2 relaxation time, *eff* is the efficiency of the inversion pulse and $\mathrm{m}_{z,ss}$ is the steady state condition, described in equation A.3. The steady state condition is needed because the the longitudinal magnetization between the two inversions needs to be the same for the signal after each TE not to change over time.

$$\begin{aligned}m_{z,ss} = M0 & \left[\left(\left((1 - EA)(\cos(\alpha_1) E1)^n + (1 - E1) \tfrac{1 - (\cos(\alpha_1) E1)^n}{1 - \cos(\alpha_1) E1)} \right) EB \right. \right. \\ & \left. \left. + (1 - EB) \right) (\cos \alpha_2 E1)^n + (1 - E1) \tfrac{1 - (\cos(\alpha_2) E1)^n}{1 - \cos(\alpha_2) E1} \right] EC + (1 - EC) \\ & \frac{}{1 + \mathrm{eff}(\cos(\alpha_1) \cos(\alpha_2))^n e^{-MP2RAGETR/T_1}}\end{aligned} \tag{A.3}$$

When equation A.1 and A.2 is inserted in 2.2 the dependence on B_1^-, M_0 and T_2^* will disapear.