

Optimized MRI techniques for image-guided ^{166}Ho SIRT

Meike Wilhelmina Maria van Wijk



Twinkle, twinkle, T_2^ , how I wonder what you are!
XY signal soon decays, why do the spins go out of phase?
Twinkle, twinkle, T_2^* , something pulls those spins apart.
Spin-spin crosstalk sets T_2 , but by then T_2^* is through.
A brief duration here is sealed, by an inhomogeneous field.*

- Greg Crowther

Optimized MRI techniques for image-guided ^{166}Ho SIRT

Report graduation internship Technical Medicine

M.W.M. van Wijk BSc.

Committee members:

Prof.dr. J.J. Fütterer

Dr.ir. F.F.J. Simonis

Dr. M. Groenier

Dr. E. Groot Jebbink

Drs. J. Roosen

Final Version

Nijmegen, 07-09-2021

Acknowledgements

While working hard and being enthusiastic were a big part of my graduation, there are some people that made really big contributions to this year, whether it was on the content of the thesis, the methods on the way, or personally, and I would like to thank some of these people in particular.

First of all, Joey, maybe you do not remember, but at the beginning of my internship you said that you looked forward to learning a lot from me, and I thought you were crazy for saying that because you were the supervisor and I was the student. But in the end I think we learned a lot from each other, and I really look forward to keep on doing that in the future! Then Lovisa, I really liked the technical discussions, and I liked it a little less if you found mistakes in my MATLAB code (over and over), but I did really learn to keep on being critical! You both have grown to be much more than a supervisor, and I hope that next to working together we can also make some music, have some fika, and mostly have a lot of fun! Frank Nijssen, thank you for always being enthusiastic about my work, your words helped me put my insecurities aside a lot of times. I am really glad that in the upcoming years I can keep on working on your ultimate goal of MRI-guided SIRT, in the great group of people you have surrounded yourself with!

I would also like to thank my supervisors from the UT, my technical and process supervisor. Frank Simonis, while the biggest common challenge did not work out the way it was planned, we still had plenty to discuss on our common interest, MRI. And I would not be surprised if there would be some kind of collaboration in the future! Marleen, I think a big theme of the past two years were my insecurities, which kept me from being what I wanted to be, someone that would say and do everything without hesitation. You always pointed out that I should also see the charm of being more of an introvert, which always made me take every persons opinions and feelings into account. And while I was definitely not the biggest star in reflecting on it, I really found the balance between showing myself and keeping an eye for others!

There are a lot more persons that helped me make the most of this graduation internship. Jurgen, and all the supervisors I had during my clinical weeks, I am sorry for all the weird technical questions related to the imaging techniques you are using, while not knowing half of the differential diagnoses that belong to certain radiological findings. The people from Quirem, especially Gerrit and Robin, thank you for always making time, and for working with me on the implementation of the voxelwise method. The vaccination team of the Radboud, thank you for letting me practise on all of you and thank you for all the bandages I needed to remove after letting other people practise.

And last but certainly not least, my mom and Wim, my dad and Nellie, thank you for the unlimited support, and for being proud of me during the highs and during the lows, who were equally present during the past years! Thank you to my sisters and brothers, I am sorry for bothering you with stories about MRI, livers and microspheres, but I'm afraid I will not stop soon, I will try to talk about it a little bit less. And thank you to my friends, who have been there in very different ways, but all contributed in one way or another!

Summary

Selective internal radiation therapy (SIRT) is a locoregional therapy for inoperable primary or metastatic diseases within the liver. During the treatment, an amount of microspheres that is determined beforehand, containing either the isotope yttrium-90 or holmium-166 is administered in the hepatic artery. These microspheres then irradiate the liver tissue using high-energetic β -radiation. Since tumours are mostly vascularized by the hepatic artery, while healthy liver tissue is mostly supplied by the portal vein, the majority of the microspheres lodge in the vascularity of the tumours, and most of the healthy tissue is spared.

A unique property of the holmium-166 microspheres is that next to their therapeutic properties, due to the γ -radiation and due to paramagnetic properties these microspheres can be imaged with both SPECT and MRI. These imaging possibilities are normally used for the evaluation of the treatment after the procedure. However, recently a study was performed on image-guided SIRT at the Radboudumc, during which MR imaging was performed during the procedure, in between the administration of the microsphere fractions. The ultimate goal of image-guided SIRT is to be able to adjust the administered dose and injection positions during the procedure, based on MR imaging, thereby precisely irradiating the tumours while minimizing healthy liver dose.

To perform the MRI-based quantification during the procedure, and to perform decision-making based on the MR dosimetry, a good workflow and accurate dosimetry is needed. Image-guided SIRT consists of many steps, of which a couple are referred to in this thesis. Research has been done on both the workflow (use of a gadolinium-based contrast agent) and the techniques of the MR quantification (alternative subtraction method and techniques for a single acquisition), to find alternative or optimized methods for image-guided SIRT.

With the results of this thesis several steps have been made in optimizing image-guided SIRT in both increasing knowledge on and implementation of new techniques. With these new insights a new clinical study will be started in the near future, focusing on the feasibility of performing MRI quantification and decision-making during the procedure. The future goal is to study whether decision-making during treatment using MRI dosimetry would lead to a better patient outcome.

Samenvatting

Selectieve interne radio therapie (SIRT) is een locoregionale behandeling voor inoperabele primaire of gemetastaseerde maligniteiten in de lever. Tijdens de therapie wordt een van tevoren bepaalde hoeveelheid microsferen met het isotoop yttrium-90 of holmium-166 toegediend in de arteria hepatica. Hier bestralen de microsferen het leverweefsel door de hoogenergetische β -straling. Doordat tumoren in de lever vooral door de arteria hepatica gevasculariseerd worden, terwijl gezond leverweefsel voornamelijk door de vena porta wordt voorzien van bloed loopt het grootste deel van de microsferen vast in de tumoren, en wordt het meeste gezonde weefsel gespaard.

Uniek aan de holmium-166 microsferen is het feit dat deze naast een therapeutisch effect door de γ -straling en door de paramagnetische eigenschappen van de microsferen met zowel met SPECT als met MRI gevisualiseerd kunnen worden. Normaal worden deze beeldvormingsmogelijkheden voornamelijk gebruikt voor de evaluatie van de behandeling naderhand. Echter is er recent een studie naar beeldgestuurde SIRT uitgevoerd in het Radboudumc, waarbij er ook beeldvorming met MRI tijdens de behandeling wordt gemaakt, tussen de toediening van fracties microsferen door. Het uiteindelijke doel van beeldgestuurde SIRT is om op basis van MRI beeldvorming de toegediende dosis en injectie posities aan te passen, en de tumoren zo gericht mogelijk te behandelen met behoud van het gezonde lever weefsel.

Om de quantificatie van de MR beelden tijdens de behandeling uit te kunnen voeren en om beslissingen op basis van deze beeldvorming te kunnen maken is een goede workflow en accurate dosimetrie nodig. Beeldgestuurde SIRT bestaat uit vele stappen, waarvan er een aantal in deze thesis besproken worden. Zowel met betrekking op de workflow (het gebruik van een contrastvloeistof met gadolinium) als met betrekking tot de technieken binnen de quantificatie (alternatieve subtractie methode en technieken voor een enkele acquisitie) is onderzoek gedaan naar alternatieve of verbeterde methodes voor beeldgestuurde SIRT.

Vanuit de resultaten van deze thesis zijn er weer een aantal stappen gezet in het verbeteren van beeldgestuurde SIRT, in zowel kennis over als implementatie van nieuwe technieken. Met deze nieuwe inzichten zal in de nabije toekomst gestart worden met een nieuwe klinische studie, waarin de haalbaarheid van quantificatie en besluitvorming tijdens de therapie onderzocht zal worden. Het uiteindelijke doel is om te onderzoeken of besluitvorming tijdens de behandeling op basis van MRI dosimetrie kan leiden tot een betere behandeling voor de individuele patiënt.

Contents

Acknowledgements	i
Summary	ii
Samenvatting	iii
Contents	iv
1 General introduction	1
1.1 Clinical background	1
1.2 MRI quantification of holmium-166 SIRT	3
1.3 Aims	4
2 The influence of a gadolinium-based contrast agent (DOTAREM®) on holmium-166 quantification	7
2.1 Introduction	7
2.2 Methods	8
2.2.1 Study participants	8
2.2.2 Imaging	8
2.2.3 Post-processing	8
2.3 Results	9
2.4 Discussion	11
2.5 Conclusion	13
3 Improving MRI-based dosimetry after holmium-166 selective internal radiation treatment using a voxelwise subtraction method to calculate ΔR_2^*	14
3.1 Introduction	14
3.2 Methods	15
3.2.1 Patient population	15
3.2.2 Treatment	15
3.2.3 MRI	15
3.2.4 Holmium quantification – mean subtraction method	16
3.2.5 Holmium quantification – voxelwise subtraction method	16
3.2.6 Image registration accuracy	18
3.2.7 ^{166}Ho -SPECT/CT imaging	18
3.2.8 Dosimetry	18
3.3 Results	19
3.4 Discussion	22
3.5 Conclusion	24
4 Feasibility of a single sequence acquisition for holmium-166 MRI-quantification: techniques of the SOFIDSE sequence	25
4.1 Introduction	25

4.2	Methods	26
4.2.1	Acquired imaging	26
4.2.2	Pre-processing	27
4.2.3	S_0 and SE for fitting R_2	28
4.2.4	R_2' as a quantitative value for ^{166}Ho dosimetry	28
4.2.5	Case study	28
4.3	Results	29
4.3.1	S_0 and SE for fitting R_2	29
4.3.2	R_2' as a quantitative value for ^{166}Ho dosimetry	29
4.3.3	Case study	30
4.4	Discussion	31
4.5	Conclusion	33
5	Future perspectives for image-guided holmium-166 SIRT	34
	References	36
A	Additional results for Voxelwise post-processing	41
B	Voxelwise subtraction: from implementation to clinical use	44
B.1	Introduction	44
B.2	Implementation	44
B.3	Future improvements	46

General introduction

1.1 Clinical background

Primary liver cancer is the sixth most common malignancy in the world, with 841,000 new cases and 782,000 deaths in 2018 [1]. It accounts for 5.7% of the total incidence of cancer worldwide, with a big geographic variability [2]. Hepatocellular carcinoma (HCC) comprises 75% of all primary liver cancer cases, and is one of the two primary liver cancer types together with intrahepatic cholangiocarcinoma (ICC) [1]. The clearest characteristic associated with the development of HCC is liver cirrhosis, which can be the result of infections with hepatitis B (HBV) or hepatitis C (HCV) and the overuse of alcohol. For ICC some risk factors are hepatolithiasis and primary sclerosing cholangitis [3]. Primary liver cancer has a five year survival of 18%, making it the second most lethal cancer after pancreatic cancer [4]. Besides primary liver cancer, metastases from breast, lung and colorectal cancer are common causes of secondary liver cancer [2].

The clinical presentation of patients with primary liver cancer depends mostly on the stage of the disease. Many patients with early stage primary liver cancer suffer from underlying liver diseases rather than from the tumour. In case of a more advanced disease, symptoms such as abdominal pain or weight loss may be observed [5]. Diagnosis is most often done using contrast-enhanced CT or MRI, in which the Liver Imaging Reporting and Data System (LI-RADS) classification is used to specify the lesions [6]. In some cases (if lesions get a LR-5 LI-RADS score), imaging alone is enough to diagnose a lesion as a malignancy, while in other cases follow-up imaging or a biopsy is needed to confirm the diagnosis [6].

The treatment choice of liver cancer is dependent on the type and the stage of the disease. All treatment options can be divided into surgical, systemic, and local or locoregional therapies. Surgical therapies include partial hepatectomy and liver transplantation, which can only be applied in case of early-stage disease, and is the only curative option [7, 8]. In case of a more advanced stage disease for which surgical treatment is no option, systemic therapies such as chemotherapy and immunotherapy are used [7]. Lastly, a lot of local and locoregional therapy options are available as primary treatment for patients with inoperable liver disease, as a treatment to bridge towards liver transplantation or as palliative care [7]. Among these are radiofrequency ablation, cryoablation or transarterial embolization (TAE).

One of the types of TAE is Selective Internal Radiation Therapy (SIRT), which is also called radioembolization. This treatment technique uses radioactive microspheres which are injected into different branches of the hepatic artery with a (micro)catheter [9]. Once injected, the microspheres lodge in the hepatic arterioles, where the spheres irradiate the liver tissue. Because of the unique double vascularity of the liver, and the division of the oxygenation of the healthy and tumour tissue, microspheres injected in the hepatic artery mostly lodge in and irradiate the tumorous tissue while healthy tissue is mostly spared, as can be seen in Figure 1. [10, 11]

Three different kinds of radioactive microspheres, with two different radionuclides, are used for SIRT of liver malignancies. The first two are TheraSpheres and SIR-Spheres, which are produced

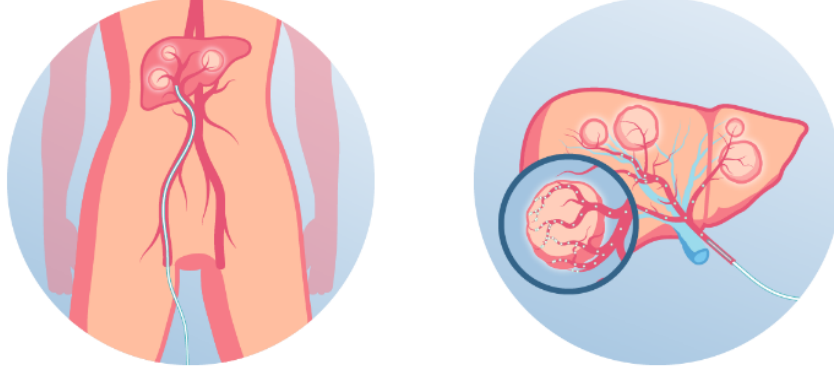


Figure 1: *Simplified image of the catheterization and administration during SIRT. In the left image, the catheterization of the external iliac artery can be seen, after which the catheter is navigated towards the common hepatic artery. On the right the portal vein (blue) and the hepatic artery (red) can be seen. Since the hepatic artery mostly vascularizes the tumours, while the portal vein supplies the healthy tissue, the administered microspheres mostly lodge in the vascularity of the tumours. (Image acquired from [12])*

by BTG international and Sirtex Medical and both contain the isotope yttrium-90 (^{90}Y) [13]. ^{90}Y has a half-life of 2.66 days, and emits high energy β -particles ($E_{\beta\text{-max}}=2.28\text{ MeV}$) to irradiate the tumours [14]. The third kind are QuiremSpheres, which are produced by Quirem Medical and contain holmium-166 (^{166}Ho). ^{166}Ho has a half-life of 1.12 days, and is a high energy β -emitting radioisotope ($E_{\beta\text{-max}}=1.86\text{ MeV}$ and 1.77 MeV) as well [9]. Furthermore, ^{166}Ho is also a γ emitter (81 KeV), and the microspheres are paramagnetic, allowing for SPECT and MR imaging [9, 15]. All three products are CE marked for treatment of tumours in the liver. In the Netherlands, ^{166}Ho microspheres are reimbursed for treatment of colorectal cancer metastases and ^{90}Y microspheres are reimbursed for both hepatocellular carcinoma and colorectal cancer metastases [16].

In the current workflow of SIRT, patients undergo two sessions. During the first session, called the scout procedure, the supplying arteries are mapped under X-ray guidance using visceral angiography. This enables planning of the injection positions of the treatment. Furthermore, a small amount of technetium-99m-labeled albumin macroaggregates ($^{99\text{m}}\text{Tc-MAA}$) is injected to verify the uptake of the activity by the malignancy or malignancies [17]. Another goal of this scout procedure is to identify possible shunting to the lungs, stomach and duodenum, and if possible to coil shunting vessels. After the procedure, SPECT imaging is performed to quantify the shunting and tumour uptake. If the shunting fraction is too high, or if the tumour is not targeted, a patient may be turned down for the treatment [13]. If the patient is eligible for the treatment, the administered activity of the final treatment is determined based on the desired liver absorbed radiation dose (LD) and the liver mass (LM) as determined on imaging using Equation 1 [18], and the microspheres are administered at the planned injection positions.

$$A_{\text{total}}(\text{MBq}) = \text{LD}(\text{Gy}) \times 63(\text{MBq/J}) \times \text{LM}(\text{kg}) \quad (1)$$

1.2 MRI quantification of holmium-166 SIRT

The MR imaging possibilities of ^{166}Ho microspheres give them an advantage over ^{90}Y microspheres, which only has limited imaging possibilities with PET-CT and SPECT. The MR imaging of ^{166}Ho microspheres is possible because of the paramagnetic properties of the used holmium, which shortens the T_2^* relaxation time (ms), or increases the R_2^* relaxation rate (s^{-1}) of the tissue when in proximity to the microspheres [19]. This shortened relaxation time can be used as a quantitative value to determine the administered activity using Equation 2, since R_2^* increases linearly with increasing holmium concentrations. The increased R_2^* (ΔR_2^* [s^{-1}]) can be converted to an activity map using the voxel volume (V_{voxel} [mL]), specific activity of the microspheres (SA_{MS} [MBq/mg]), field strength (B_0 [T]), the measured holmium relaxivity ($r_2^* = 286.8 [\text{s}^{-1} \cdot \text{mg}^{-1} \cdot \text{mL} \cdot \text{T}^{-1}]$), and the holmium content of the microspheres (HoMS content),

$$A_{\text{voxel}} = \frac{\Delta R_2^* \times V_{\text{voxel}} \times SA_{MS}}{B_0 \times r_2^* \times \text{HoMScontent}} \quad (2)$$

A multi gradient echo (MGRE) sequence is used before and after the microsphere administration to map the R_2^* values per voxel. The MGRE, which can be seen in Figure 2, consists of a single excitation pulse, after which 10-15 echos on short echo times are acquired. From the signal intensities that are found over time, the R_2^* can be determined using a monoexponential fit with Equation 3.

$$S(t) = S(0) \times e^{R_2^* \times t} \quad (3)$$

The calculation of R_2^* from the MGRE sets is implemented in the software package named Q-suite®, which was developed by Quirem Medical, to be used with the QuiremSpheres. The workflow of this software can be found in Figure 3. In the software, the two MGRE image sets can be imported, and the livers can be segmented manually. Next to the livers, a noise contour is drawn manually as well, on a homogeneous part of the erector spinae muscle, to quantify the noise in the images. Next, the monoexponential fit is applied to each voxel to find R_2^* , while excluding the signal intensities below the noise threshold, as determined by the noise contour. The result is a pre- and post-treatment R_2^* map, and by subtracting the mean pre-treatment R_2^* value from the post-treatment R_2^* values, a ΔR_2^* map is made, which represents the influence of the ^{166}Ho microspheres. This map is then converted to an activity map by applying Equation 2 to each voxel. Lastly, this activity map is converted to a dose map using a convolution with a dose point kernel.

The use of the ^{166}Ho microspheres and the MRI evaluation of ^{166}Ho SIRT has grown in the last decades from the use in veterinary patients to clinical use in centres within and outside of the Netherlands [20]. However, since the quantitative imaging possibilities could provide even more insight in the treatment and because of a global interest in personalized medicine, more possibilities of improving ^{166}Ho SIRT are studied. At the Medical Innovation and Technology expert Center (MITeC) of the Radboudumc, a more personal and image-guided approach of ^{166}Ho SIRT has been developed and studied. MITeC is a special operation suite in which two operating rooms (a conventional and a hybrid operating room) are connected to an operating room with a 3T MRI system (Siemens). In this setting a study on performing imaging during ^{166}Ho SIRT has been conducted recently, of which the workflow can be found in Figure 3. During this study the

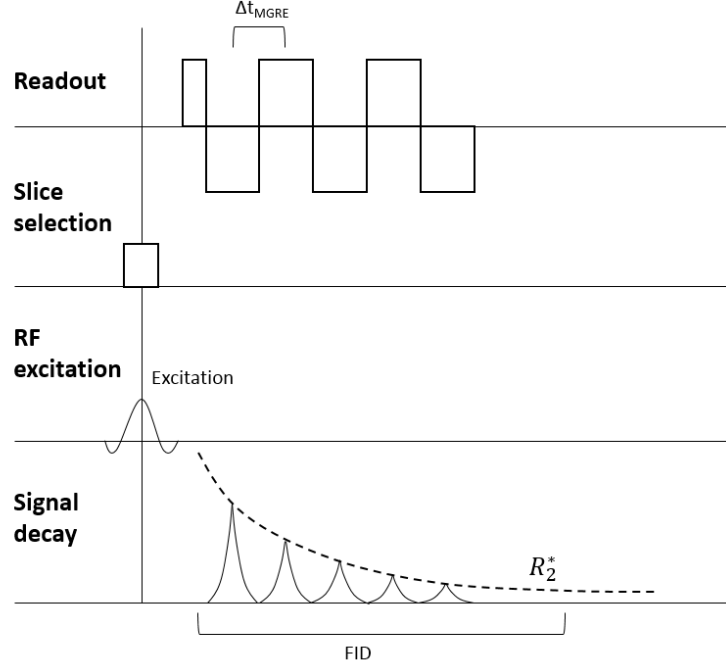


Figure 2: A simplified sequence diagram of the MGRE sequence that is used for the MRI quantification. After a single excitation pulse, several echoes are acquired (10 in the current clinically used sequence), of which five are shown in the image. The R_2^* can be found by applying a monoexponential fit using the signal intensities on the acquired echos.

catheter was positioned under X-ray guidance in the hybrid operating room, after which the patient was transported to the MRI scanner. In the MRI scanner, the planned dose was administered in fractions instead of at once, which is done in the conventional workflow. In between the given fractions, imaging was performed. This was done to study the feasibility of performing imaging during the procedure, with the goal of adjusting the injection positions and administered activity during the treatment, based on the acquired imaging. Currently, these injection positions and the administered dose are all planned before the treatment. The end goal is to study the possibility of performing the complete treatment under MRI guidance and adjusting dose and injection positions during the treatment, building towards a more personalized treatment.

1.3 Aims

The goal of image-guided ^{166}Ho SIRT resulting in a more personalized treatment demands several changes in the current workflow. The goal of performing the treatment under MRI guidance and adjusting the administered dose during the treatment asks for accurate dosimetry based on fast acquisition and post-processing of the imaging during the treatment. The current methods and workflow have been designed for evaluating the success of the treatment, and not for decision making during treatment. These methods do therefore not focus on finding all administered activity and executing the processing steps in a timeframe that would be feasible to execute during the treatment. Therefore, the goal of this graduation internship was to explore methods to improve

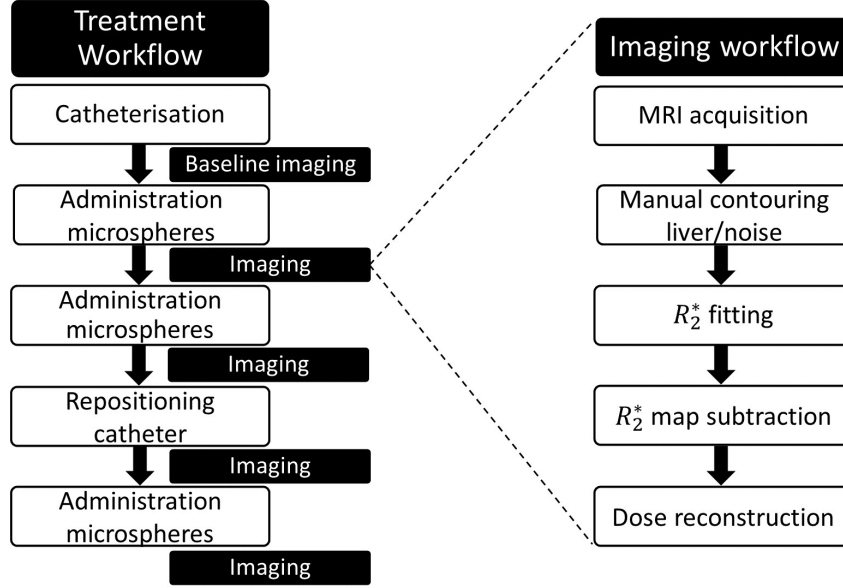


Figure 3: *The workflow of the image-guided ^{166}Ho treatment as was used during the performed study. After catheterization, the microspheres were administered in fractions (two fractions are shown). In some cases, the catheter was repositioned, after which more microsphere fractions were administered (one fraction shown). In between all administrations, imaging was performed, which was converted to dosemaps after the treatment in Q-suite[®]. The quantification steps that are needed to produce a dose map from the acquired imaging to a dose map can be seen in the imaging workflow on the right.*

the accuracy and duration of ^{166}Ho quantification with the goal of MRI guided ^{166}Ho SIRT. This was done on different aspects of the MRI quantification process.

First of all, in case the treatment would be performed completely under MRI guidance, a new challenge would be presented. In the normal workflow, the catheter is placed with the use of X-ray and a iodine-based contrast agent. In case the X-ray guidance would be replaced by MRI, a contrast agent compatible with MRI, most probably gadolinium-based, would be needed to guide the catheter through the branches of the hepatic artery. Gadolinium is paramagnetic and increases the R_2^* relaxation rate, just like the holmium microspheres do. Because of the identical working mechanism of gadolinium contrast and the ^{166}Ho microspheres, performing the procedure under MR guidance with gadolinium could influence the accuracy of the ^{166}Ho microsphere quantification. However, the magnitude of this influence, and whether this would influence the workflow of MR guided SIRT is unknown. To be able to perform highly accurate holmium quantification in combination with gadolinium-based contrast, the influence of gadolinium-based contrast on the R_2^* quantification will be studied (Chapter 2).

After the catheter is positioned, the acquisition of the MGRE images that are used for the quantification is done. With the currently used MGRE sequence, two scans (pre- and post-treatment) are needed to isolate the influence of the ^{166}Ho microspheres. Furthermore, the subtraction of

the pre-treatment liver values is currently based on a single (mean) R_2^* value for all liver voxels. However, since the liver tissue is not completely homogeneous, pre-existing regional R_2^* differences exist, and therefore using a mean R_2^* for the whole pre-treatment liver decreases the accuracy of the quantification. This induces a great uncertainty if decision-making would be done based on this quantification. This uncertainty can be reduced by altering the MRI techniques in several ways, of which two methods are explored in this thesis.

The first method is a post-processing based solution, in which the subtraction step with the mean pre-treatment R_2^* is altered to a voxelwise subtraction, to improve the accuracy of the ΔR_2^* map of the ^{166}Ho microspheres. This voxelwise subtraction can be realized by using a registration method, that needs to be both accurate and fast, in order to meet the needs of image-guided SIRT. The possibilities of using a registration method to perform a voxelwise subtraction have been studied and its results can be found in Chapter 3.

The other, acquisition based, method is to use a sequence presented in 2015 by van de Maat et al., which is capable of estimating R_2^* , R_2 and R_2' , with the use of a MGRE and a single spin echo (SE) within one sequence [21]. A single sequence would bypass the problem of the mismatch between pre- and post-treatment differences of the liver. This sequence showed some promising results, but it would also induce some new uncertainties concerning influences of other inhomogeneities on R_2^* . Therefore, the theory of using a single acquisition for ^{166}Ho SIRT quantification was studied (Chapter 4).

The influence of a gadolinium-based contrast agent (DOTAREM®) on holmium-166 quantification

2.1 Introduction

In the conventional workflow of ^{166}Ho SIRT, the complete treatment is conducted under X-ray guidance. The interventional radiologist uses an iodine-based contrast agent (Iomeron 300) to visualize the hepatic vascularization, and to position the catheter in the injection positions that were chosen during the scouting procedure [9]. The nuclear medicine physician will then administer the microspheres, together with the interventional radiologist. These two steps, the positioning of the catheter and administering the microspheres, are repeated for each injection position until microspheres have been administered in all injection positions.

As stated in the general introduction, a study on performing MRI during ^{166}Ho SIRT has been conducted at the MITeC at Radboudumc. In the workflow of this study, the catheter was positioned under X-ray guidance, just like during the conventional procedure. However, instead of administering the microspheres once the catheter was in position, the patient was transferred to the adjacent room in which the microspheres were administered and MR imaging was performed. This new image-guided workflow introduced some challenges concerning this added patient transfer. For each injection position, or in case the catheter was dislocated due to the transfer, the patient needed to be transferred back to the hybrid operating room [22]. Therefore, the number of injection positions that were used were limited, in order to limit the number of transfers.

One solution to these challenges could be to perform the complete image-guided ^{166}Ho treatment under MRI guidance, omitting the need for patient transportation between the two operating rooms. Furthermore, a complete MRI-guided approach would make the treatment more accessible to different centres, as the combination of a hybrid operating room and an adjacent MRI room is scarce. This means the catheterization has to be performed while the patient is positioned in the MRI bore, which demands several alterations of the current catheterization.

In order to be able to position the catheter under MRI-guidance, the most important properties of a X-ray guided catheterization would need to be reproduced using MRI. Firstly, in order to get feedback during the catheter positioning, a suitable real-time MRI sequence, with a high temporal resolution would be needed, given that the temporal resolution of X-ray guidance can be up to 1-10 ms [23]. Furthermore, this sequence also needs a high spatial resolution to be able to image all relevant structures, which mostly consists of the hepatic arterial system. Finally, MRI angiography makes use of a contrast agent, which is needed to ensure visibility of the vessels up to the first branches of the hepatic artery [24].

Contrast enhancement is broadly available to MRI scanning, almost half of the MRI studies are conducted with contrast enhancement [25], with different contrast types that are used for different applications. Most contrast agents available are paramagnetic or superparamagnetic, and are gadolinium, manganese, iron oxide, or iron platinum based. Of these contrast agents, gadolinium-

based contrast agents are most commonly used, because it possesses a high magnetic moment and is the most stable ion out of all clinically available agents. [25]

Contrast agents containing gadolinium shorten both the longitudinal (T_1) and transverse (T_2) relaxation times, which can be used to increase signal intensity on T_1 weighted images, and decrease signal intensity on T_2 weighted images [26]. The influence on T_1 is big for low gadolinium concentrations, while a visible influence on the T_2 relaxation requires higher concentrations [25]. As the toxicity of the contrast agent is dependent on its concentration, the contrast agent is mostly used for T_1 weighted image contrast.

While the use of gadolinium-based contrast agents seems straightforward, the use of a paramagnetic contrast agent in combination with holmium microspheres could introduce a new challenge for MRI-guided holmium SIRT. While literature states that the influence of the T_2 -effects of gadolinium-based contrast agents on medical imaging is negligible [26], the contrast agent could interfere with the SIRT quantification. Since both the gadolinium based contrast agents and the holmium microspheres induce a shortened T_2 time, quantification could be hampered, even if no visual differences can be observed. The relaxivity of the gadolinium contrast is however much lower ($8.9 \text{ s}^{-1} \cdot \text{mL} \cdot \text{mg}^{-1}$ at 3T in blood at 37°C) than the relaxivity of the holmium microspheres ($860.4 \text{ s}^{-1} \cdot \text{mL} \cdot \text{mg}^{-1}$ at 3T in agarose at 37°C), suggesting limited interference to the quantification [27]. However, given the variability of the concentrations administered, it was preferable to also verify this experimentally. Therefore, the goal of this study was to investigate the influence of gadolinium-based contrast on liver R_2^* values and estimate its influence on the holmium microsphere quantification.

2.2 Methods

2.2.1 Study participants

The local medical ethics committee provided a waiver for this study (Dutch: niet WMO-plichtig), and written informed consent was obtained from all study patients. The inclusion criterion was that patients had to be scheduled for liver MRI with gadolinium contrast on a 3T MRI scanner, regardless of the reason for their MRI. Informed consent was obtained from 20 patients with an appointment for an MRI of the liver with DOTAREM® gadolinium-based contrast.

2.2.2 Imaging

The included patients received two additional acquisitions of a MGRE with 10 echo times during their planned liver MRI appointment. The MGRE ($\text{TE}_1=1.06 \text{ ms}$, $\Delta\text{TE}=1.38 \text{ ms}$, $\text{TR}=149 \text{ ms}$, flip angle= 33° , in-plane resolution $2 \times 2 \text{ mm}^2$, slice thickness 4 mm , $\text{FOV } 384 \times 384 \text{ mm}^2$) sequence as used for ^{166}Ho SIRT quantification was scanned twice, once before the contrast-agent was administered, and at the end of the scanning protocol.

2.2.3 Post-processing

The MGRE's acquired before and after contrast administration were imported into the Q-suite® software. For each MGRE, liver and noise contours were drawn by a single observer. Next, R_2^* values were determined using the monoexponential fit implemented in Q-suite® (SNR threshold: 2σ ,

minimum echo's: 2, S0 fit neighbour range: 3, S0 fit minimum neighbours: 9) for both MGRE's. The resulting pre- and post-contrast R_2^* maps and the MGRE image sets were then exported to be processed in both MATLAB (version 2020b) and Python (version 3.7).

To get insight in the overall increased R_2^* due to the contrast agent, for each pre- and post-contrast R_2^* map, a mean R_2^* was calculated. A visual inspection was done to analyze the locations of increased R_2^* values, by performing a voxelwise subtraction of the post-contrast and pre-contrast R_2^* map. To be able to do this voxelwise subtraction step, a rigid and deformable registration using symmetric normalization and mutual information optimization was used on the first echoes of the MGRE sets (see Chapter 3.2 for a more elaborate explanation) [28]. The registration list that was found was then used on the R_2^* maps that were made before gadolinium administration, mapping the pre-contrast R_2^* maps to the post-contrast R_2^* maps, resulting in a registered pre-contrast R_2^* map. This registered pre-contrast R_2^* map was then subtracted from the post-treatment R_2^* map.

In order to test the similarity of the R_2^* values before and after contrast administration, a paired sample T-test was executed on the mean R_2^* values of the R_2^* maps before and after contrast administration of each patient.

2.3 Results

From the 20 included patients, 15 image data sets were used for analysis of the influence of gadolinium contrast on the R_2^* quantification. The five patients that were not included in the analysis had retracted their informed consent (n=1), were rescheduled (n=1), cancelled (n=1), or the quality of the imaging was insufficient because of movement during acquisition (n=2). Post-contrast scanning was performed 5 or 6 minutes after contrast administration.

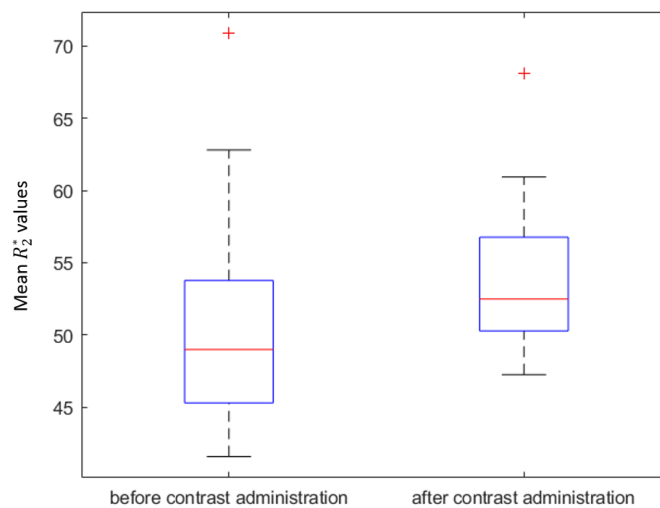


Figure 4: *Boxplot of the mean R_2^* values of the 15 data sets before and after contrast administration. The mean R_2^* values after contrast administration were significantly higher than the mean R_2^* values before contrast administration ($p=0.0023$)*

2 THE INFLUENCE OF A GADOLINIUM-BASED CONTRAST AGENT (DOTAREM®) ON HOLMIUM-166 QUANTIFICATION

Table 1: Patient characteristics divided in groups that showed a minor decreased/increased ($-0.8 - 3.2 \text{ s}^{-1}$) R_2^* or major increased ($3.8 - 8.8 \text{ s}^{-1}$) R_2^* value. Age, gender or disease did not show any cohesion with the influence of the contrast agent on R_2^*

		Total population (n=15)	Minor increase R_2^* (n=6)	Major increase R_2^* (n=9)
Median age (range)		48 (25 - 80)	53 (25-74)	62 (30-80)
Sex (M/F)		3/12	0/6	3/6
Disease extent	Generalized	9	3	6
	Focal	6	3	3
Disease subtype	Steatosis	2	1	1
	Cirrhosis	2	0	2
	Adenoma	3	1	2
	Focal Nodular Hyperplasia	2	1	1
	Cysts	1	1	0
	Metastasis	1	0	1
	Extrahepatic metastasis	1	0	1
	Regenerative nodule	1	1	0
	Sarcoidosis	1	1	0
	Hemangioma	1	0	1

The overall mean R_2^* value before contrast administration was $50.6 \text{ s}^{-1} (\pm 7.9 \text{ s}^{-1})$, which was significantly lower than after contrast administration, when R_2^* was $53.9 \text{ s}^{-1} (\pm 5.5 \text{ s}^{-1})$ ($p=0.0023$). The distribution of the mean R_2^* values before and after contrast administration can be seen in Figure 4. The mean increase of 3.3 s^{-1} would be quantified as an additional activity of 436 MBq on the whole liver, if it would be quantified using the current ^{166}Ho quantification method, given a hypothetical liver volume of 1800 mL, a holmium content of 19% and a specific activity of 12 MBq/mg. Given the same hypothetical measures, the most extreme R_2^* increase of 8.8 s^{-1} would be quantified as an additional 1163 MBq, while the administered activity for a liver volume of 1800 mL would be 7214 MBq.

While an overall increase of R_2^* values was observed, some patients ($n=6$) showed a small decrease or a constant mean R_2^* after contrast administration. Patient characteristics for the groups that showed a minor decrease or increase lower than the mean R_2^* difference (mean R_2^* difference $-0.8 - 3.2 \text{ s}^{-1}$) and an increase higher than the mean R_2^* difference (mean R_2^* difference $3.8 - 8.8 \text{ s}^{-1}$) are shown in Table 1. Based on age, gender and clinical features, no association between features and increase in R_2^* was found.

A visual analysis sometimes revealed apparent vascular structures in the liver ($n=2$), but most often identified a homogeneous, overall increase of R_2^* in the liver parenchyma (Figure 5), while other cases showed no increase at all (Figure 6).

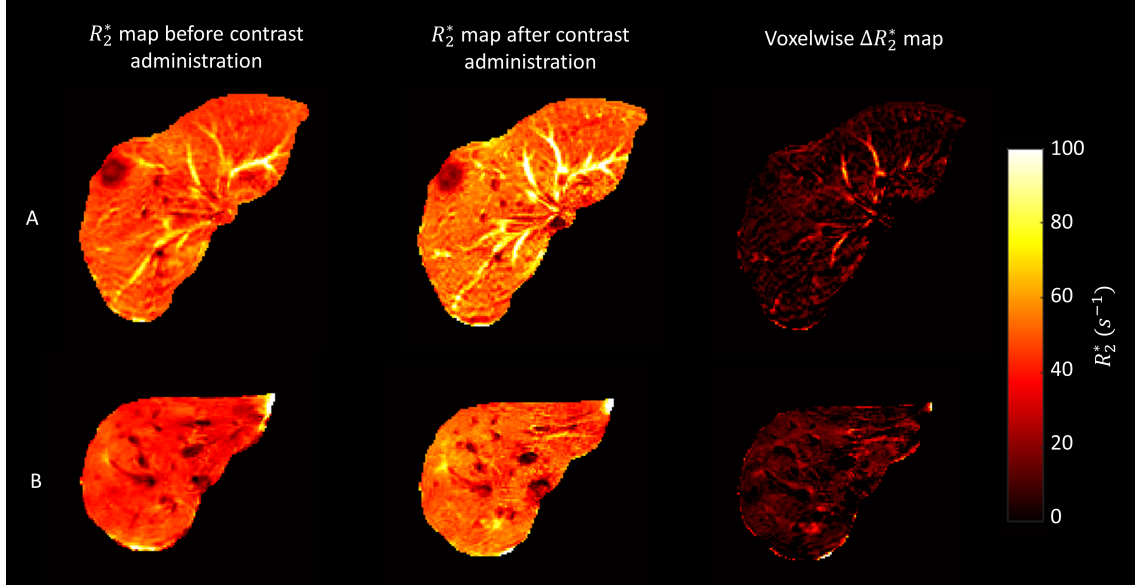


Figure 5: Two cases in which an increase of R_2^* was seen in different ways. For case A, the overall increase of R_2^* was 3.8 s⁻¹, and the increase was very visible in the vascular structures of the liver. In case B, the vascular structures are not visible, but an overall increase of R_2^* (6.1 s⁻¹) was found.

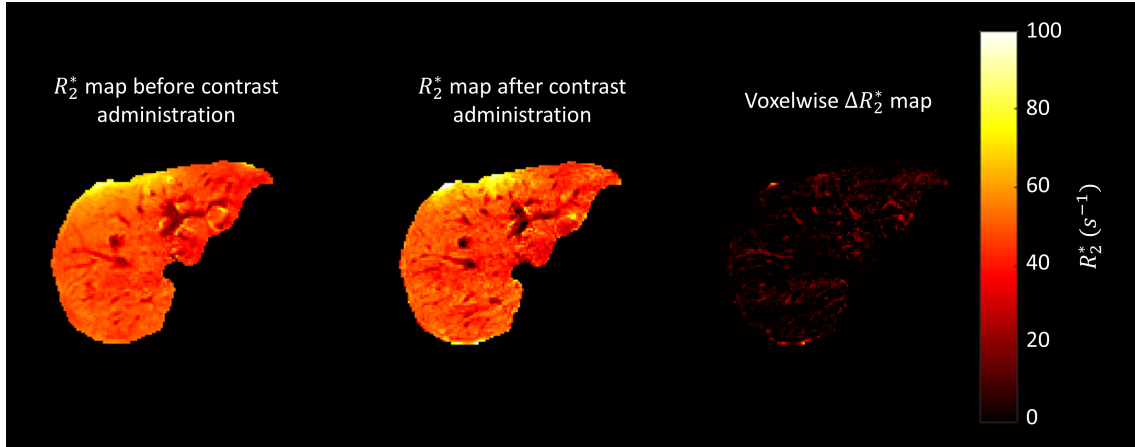


Figure 6: One of the cases that did not show an increase in R_2^* (-0.2 s⁻¹) 5 minutes after contrast administration.

2.4 Discussion

With the goal of performing ¹⁶⁶Ho SIRT completely under MRI guidance in mind, the influence of an MRI compatible contrast agent on the MRI quantification of holmium microspheres has been studied. Paramagnetic contrast agents increase relaxation rates, identical to the holmium microspheres, and could therefore hamper the MR-based dosimetry. The low relaxivity of contrast agents compared to the relaxivity of holmium microspheres would suggest limited interference of the contrast. However, dependent on the concentration of contrast that would need to be ad-

ministered compared to the concentration of administered microspheres, quantification could still be compromised. In order to be able to confirm usability of gadolinium-based contrast during image-guided SIRT, the influence was studied in an experimental setting. This was done with a clinical study of 20 subjects, of which 15 sets of MGRE images were used to study the influence of the contrast of R_2^* values.

Literature states that gadolinium based contrast agents induce T_1 shortening at lower gadolinium concentrations than at T_2 shortening, which is used for ^{166}Ho quantification [25]. Despite this, the results showed a significant difference between pre- and post-contrast R_2^* values. The mean increase of 50.6 to 53.9 s^{-1} would induce a dose increase of around 436 MBq on the whole liver, while in case of an average liver volume of 1800 mL, 7214 MBq of microspheres are administered. This would mean around 6% of the total quantified dose would be due to the contrast agent, which could influence the decision-making during image-guided treatment, mostly in terms of quitting the treatment due to a high healthy liver dose.

The observed R_2^* changes could not be correlated to any of the patient characteristics, such as age, gender or liver disease, possibly due to the heterogeneity of the studied population. Since all post-contrast MGRE acquisitions were performed 5-6 minutes after contrast administration, the relation between the relaxation rate and time after administration could not be studied either. A relation between the contrast influence on R_2^* and the time after administration would be expected. The mean whole-body elimination half-life of DOTAREM® is 1.47 hours, and renal clearance is the main excretion mechanism [29]. If the exact relation between time post injection and extent of increase in R_2^* in the liver would be studied, a tolerated ΔR_2^* due to the contrast agent could be determined, and a neutralization time could be incorporated in the treatment protocol, to limit the influence of the contrast-agent on decision-making. However, it would be unfavourable to the workflow of the treatment if a long waiting period would have to be introduced between contrast administration and MGRE acquisition, which has to be taken into account when setting this neutralization time.

Apart from the influence of the contrast agent on the ^{166}Ho quantification, there are some other challenges concerning the replacement of X-ray guidance with MRI-guidance during catheterization. While complete MRI-guidance would be advantageous to the workflow of image-guided SIRT, it is questionable whether catheterization could be performed under MRI-guidance, even with the use of a contrast agent. Real-time imaging techniques for MRI have been improving over the years, especially concerning their temporal resolution [30]. However, the need for 3D visualization would either increase acquisition time, or demand constant alterations of slice position and orientation. The applications used in clinical practise today are therefore not comparable to the temporal resolution and ease of X-ray guidance. Furthermore, the vascularity needs to be visible until at least the first branches of the left and right hepatic artery, which is feasible for X-ray guidance, but is questionable for MRI-guidance, since not all MR sequences are compatible with real-time imaging [30]. Lastly, during catheterization the interventional radiologist should be able to manoeuvre the catheter which asks for a position close to the patient. Considering the position of the patient in the bore of the MRI scanner compared to the open structure of the X-ray guidance, this induces another challenge.

Before image-guided SIRT with a MRI-guided catheterization would be usable, the feasibility of MRI-guided liver catheterization would have to be studied on its own. The needs for MRI-guided catheterization should be discussed thoroughly with involved interventional radiologists, and should be studied before a clinical application of this step for image-guided ^{166}Ho SIRT would be applicable.

2.5 Conclusion

The studied gadolinium-based contrast agent did show an increase of R_2^* values, and would therefore influence ^{166}Ho SIRT quantification. Setting a tolerated contrast influence on the quantification and adding a waiting time until this tolerated influence is reached could solve this problem. However, the increased R_2^* values combined with other challenges concerning an MRI-guided catheterization do hamper a complete MRI-guided treatment in the near future.

**Improving MRI-based dosimetry after holmium-166
selective internal radiation treatment using a voxelwise
subtraction method to calculate ΔR_2^***

To be submitted to the Journal of Magnetic Resonance in Medicine

Contribution: Conceptualization, implementation and development method in MATLAB/Python,

Original draft preparation and editing, shared first author.

3.1 Introduction

Selective internal radiation therapy (SIRT) is a locoregional treatment for liver tumours during which radioactive microspheres are injected into the hepatic artery. These microspheres, containing either of the beta emitters yttrium-90 (^{90}Y) or holmium-166 (^{166}Ho), are transported throughout the targeted liver volume via the blood flow, until they lodge in the arterioles because of the microspheres' size (approximately 30 μm). Over the past years, it has become increasingly clear that the key to a successful treatment lies in achieving a sufficiently high tumour dose, but also a homogenous dose coverage, which is a direct result of the microsphere distribution [31, 32, 33, 34]. An imaging advantage of ^{166}Ho microspheres over ^{90}Y microspheres is that they are paramagnetic and can therefore be visualized and quantified in with MRI, based on the local increase of transverse relaxation rate (R_2^*), resulting in dose maps with a very high spatial resolution [35]. Additionally, ^{166}Ho microspheres can be visualized with SPECT imaging, which is commonly performed after ^{166}Ho SIRT [35].

The unique MRI-based quantification of ^{166}Ho microspheres was first investigated in 2004, in a phantom and rabbit study [20]. In the research that followed, multiple MRI protocols were utilized to quantify the increase of R_2^* as a result of the presence of holmium microspheres [36]. Subsequently, multigradient echo (MGRE) sampling of the free induction decay (FID) was found to be superior to sampling of the spin echo envelope, as the latter is rather sensitive to diffusion and therefore resulted in underestimation of the concentration of ^{166}Ho microspheres [37]. MGRE sampling of the FID was therefore used in the phase 1 trial studying SIRT using ^{166}Ho microspheres for advanced liver tumours [38, 39] and has been incorporated in current clinical practice in the dedicated ^{166}Ho dosimetry software package Q-Suite[®] (Quirem Medical B.V., Deventer, The Netherlands).

In order to calculate the increase in R_2^* induced by the microspheres, MGRE images are acquired both before and after ^{166}Ho SIRT, after which the R_2^* maps are subtracted to find ΔR_2^* . However, the deformability of the liver during (inconsistent) breathing motion and differences in patient positioning between the two imaging time points hamper an accurate voxel-to-voxel subtraction. In the current workflow ΔR_2^* is therefore calculated by subtracting the mean R_2^* value of the whole liver before treatment from the R_2^* map after treatment. The main drawback of this method is that it does not take regional differences in baseline R_2^* values (such as between tumours and healthy tissue) into account, which intrinsically results in a systematic error in the estimated dose distribution [18].

A possible solution to the problem with a pre and post voxel-to-voxel subtraction could be to utilize a registration algorithm to transform the liver shape of the pre-treatment images to the shape of the post-treatment images. Registration methods for medical imaging are broadly used, but it often takes minutes to hours to perform deformable image registration, depending on image characteristics and the registration approach [40]. In the presented work we demonstrate the feasibility of voxel-based subtraction of the R_2^* maps in MRI-based dosimetry after ^{166}Ho SIRT and its added value for accurate MRI-based dosimetry, using a fast deformable registration algorithm based on symmetrical normalization and mutual information optimization.

3.2 Methods

3.2.1 Patient population

The patient data used in this study was acquired as part of a clinical trial (ClinicalTrials.gov Identifier: NCT04269499), for which ethical committee approval was obtained. All 6 patients provided written informed consent prior to treatment. The most important inclusion criteria were age ≥ 18 years, diagnosis of primary liver cancer (hepatocellular carcinoma or intrahepatic cholangiocarcinoma) or liver metastases (primary tumours: colorectal cancer, breast cancer, melanoma or neuro-endocrine tumour) not amenable for other standard therapies than SIRT, a life expectancy of 12 weeks or longer, and a WHO performance score of 0-1. Clinical results of this trial will be published elsewhere.

3.2.2 Treatment

Pre-treatment work-up was no different from standard clinical practice, including a diagnostic CT or MRI, angiography, and treatment simulation with technetium-99m labeled albumin macroaggregates. Treatment took place in our hybrid operating rooms, in which one room equipped with a cone-beam CT (CBCT) is positioned directly adjacent to another room equipped with a 3T MRI system (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany). The patient was transferred between these two rooms multiple times during treatment. First, the pre-treatment MRI was acquired. The patient was transferred to the adjacent CBCT-room, and the injection catheter was placed in the hepatic artery under X-ray guidance, at the first injection position determined during pre-treatment work-up. The patient was then moved back to the MRI bore for injection of ^{166}Ho microspheres (QuiremSpheres®; Quirem Medical B.V., Deventer, The Netherlands). Imaging was performed before and after administration of microspheres. If necessary, the patient was transferred back to the CBCT-room for placing the catheter in a second injection position.

3.2.3 MRI

All clinical MR imaging was performed on the aforementioned 3T clinical MRI scanner, using a spine 32 matrix and body 18 phased array receiver coil. For R_2^* sampling pre and post treatment, an MGRE sequence with 10 subsequent echoes was used (TE1: 1.06 ms, ΔTE : 1.38 ms, TR: 149 ms, flip angle: 33° , in-plane resolution: $2 \times 2 \text{ mm}^2$, slice thickness: 4 mm, FOV: $384 \times 384 \text{ mm}^2$). For anatomical information and segmentation purposes two sequences were used: a non-contrast enhanced T_1 -weighted volumetric interpolated breath-hold examination (VIBE) sequence

(TE: 1.91 ms, TR: 4.81 ms, flip angle: 6°, in-plane resolution $1.19 \times 1.19 \text{ mm}^2$, slice thickness: 4 mm, FOV: $308 \times 380 \text{ mm}^2$), and a T_2 -weighted half-Fourier single-shot turbo spin echo (HASTE) sequence (TE: 102 ms, TR: 3000 ms, flip angle: 180°, in-plane resolution $1.19 \times 1.19 \text{ mm}^2$, slice thickness: 5 mm, FOV: $308 \times 380 \text{ mm}^2$).

In order to determine the relaxivity of the holmium microspheres (relaxation rate per mg/ml holmium), needed for the in vivo quantification of the microsphere distribution, a calibration phantom setup containing 1% agarose gel (Merck - Millipore, Burlington, USA), 25 mg/L manganese(II) chloride tetrahydrate (Sigma-Aldrich, Saint Louis, USA) and known concentrations of non-neutron activated holmium-165 microspheres (0.5, 1.1, 1.5, 2.6, and 3.9 mg/ml; Quirem Medical B.V., Deventer, the Netherlands) was imaged at 37 °C using the abovementioned MGRE sequence, with a head coil instead of the body coil, similar to earlier work [18, 41].

3.2.4 Holmium quantification – mean subtraction method

The pre and post MGRE image sets of each subject were imported into a research version of Q-suite® (Quirem Medical B.V., Deventer, the Netherlands) to quantify the administered ^{166}Ho microspheres. The workflow of the Q-suite® software can be found in Figure 7. A manual segmentation was performed to obtain liver and noise (in the erector spinae muscle) volumes of interest (VOIs) by a single observer (JR) on the first echoes of the pre and post MGRE images. R_2^* values of the segmented liver volumes were determined for each voxel using a mono-exponential fitting method implemented in Q-suite® (SNR threshold: 2σ , minimum echo's: 2, S0 fit neighbor range: 3, S0 fit minimum neighbors: 9).

The mean R_2^* was calculated from the pre-treatment R_2^* map ($R_{2,pre}^*$ map), which was subtracted from each voxel included in the post-treatment R_2^* map ($R_{2,post}^*$ map) to obtain the holmium induced ΔR_2^* map. The acquired ΔR_2^* map was converted into an activity map using the voxel volume (V_{voxel} [mL]), specific activity of the microspheres (SaMS), field strength (B_0 [T]), the measured holmium relaxivity ($r_2^* = 286.8 [\text{s}^{-1} \cdot \text{mg}^{-1} \cdot \text{mL} \cdot \text{T}^{-1}]$), and the holmium content of the microspheres (HoMS content), according to Equation 4. Last, a dose map was calculated through convolution with a dose-point kernel.

$$A_{voxel} = \frac{\Delta R_2^* \times V_{voxel} \times SaMS}{B_0 \times r_2^* \times HoMScontent} \quad (4)$$

3.2.5 Holmium quantification – voxelwise subtraction method

For the voxelwise subtraction method (VW method), an additional workflow to the conventional Q-suite® software was developed, as can be seen in Figure 7. All post-processing steps were performed on a PC with an i7 core CPU at 2.60 GHz processor and 16.0 GB RAM with a NVIDIA® Quadro® P2000 video card. The MR images, liver VOIs, and R_2^* maps pre and post treatment were exported from Q-suite® and imported in MATLAB R2020b (Mathworks, Natick, United States). In MATLAB, the MR images were segmented using the previously generated liver VOIs, in order to only use the liver volumes as input for the registration algorithm. Furthermore, the first echo of the MGREs and the R_2^* maps were processed to be compatible with the registration method in Python version 3.7 (Python Software Foundation, Delaware, United States). The images corresponding to the first echo of the MGRE pre- and post-treatment were used to obtain

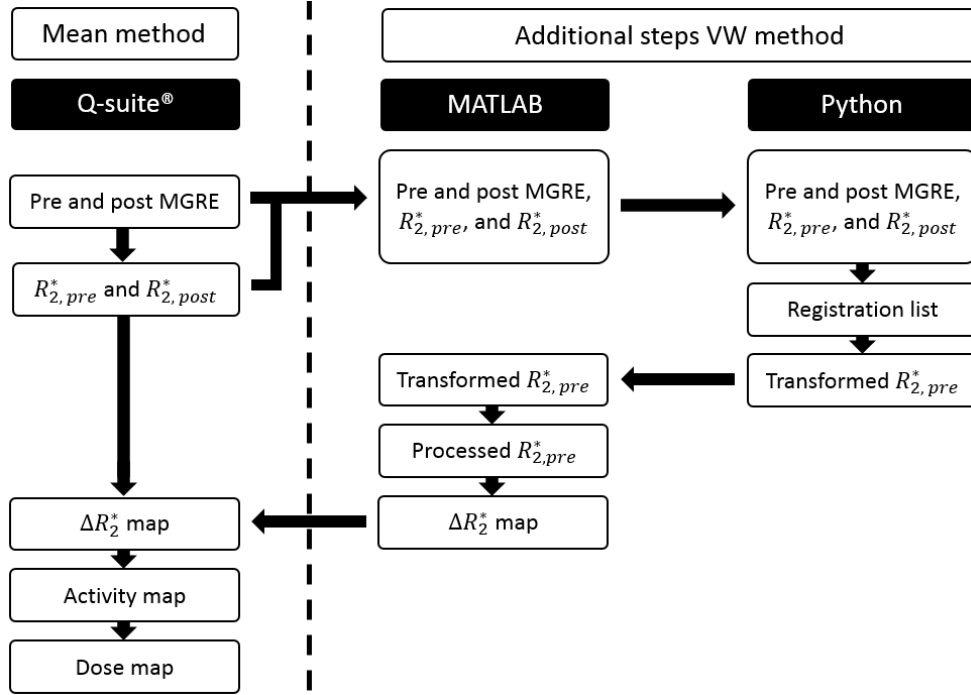


Figure 7: Workflow of the post-processing as implemented in Q-suite and the additional post-processing for the voxelwise (VW) subtraction method. MGRE = multigradient echo sequence.

the registration list, as these are least influenced by the presence of ^{166}Ho microspheres, which subsequently was used to transform the $R_{2,pre}^*$ maps. The pre-treatment images were registered to the post-treatment images using an affine and a deformable registration using symmetric normalization as the transformation model and mutual information as its similarity metric, as implemented in the SyN algorithm of the Advanced Normalization Tools (ANTs) Python package [28, 42]. The list of transformations that was created by the SyN method was then applied to the $R_{2,pre}^*$ map, in order to transform it to the image space of the $R_{2,post}^*$ map. Two examples of the transformation process are visualized in Figure 8. The transformed $R_{2,pre}^*$ map was then imported into MATLAB again for post-processing.

Voxelwise subtraction requires that for every voxel in the $R_{2,post}^*$ map, there is a corresponding voxel in the $R_{2,pre}^*$ map. However, after registration, not every voxel of the $R_{2,post}^*$ map was properly matched with a voxel in the $R_{2,pre}^*$ map yet. At the edge of the registered $R_{2,pre}^*$ map voxels could have either a value of 0 due to imperfect registration, or a very low R_2^* value as a result of blurring by the registration algorithm. These missing or incorrect R_2^* values (defined as a value $< 15 \text{ s}^{-1}$) of the $R_{2,pre}^*$ map were filled using a nearest neighbor approach, using the mean R_2^* of a minimal of nine neighbouring voxels, in a volume of $3 \times 3 \times 3$ voxels around the voxel to be filled. In case multiple adjacent voxels were incorrect or missing, only original voxels were used to find a voxel value. The processed $R_{2,pre}^*$ map was then voxelwise subtracted from the $R_{2,post}^*$ map, resulting in a ΔR_2^* map. This ΔR_2^* map was exported back to Q-suite®, after which the resulting processing to the dose map was performed identically to the mean method.

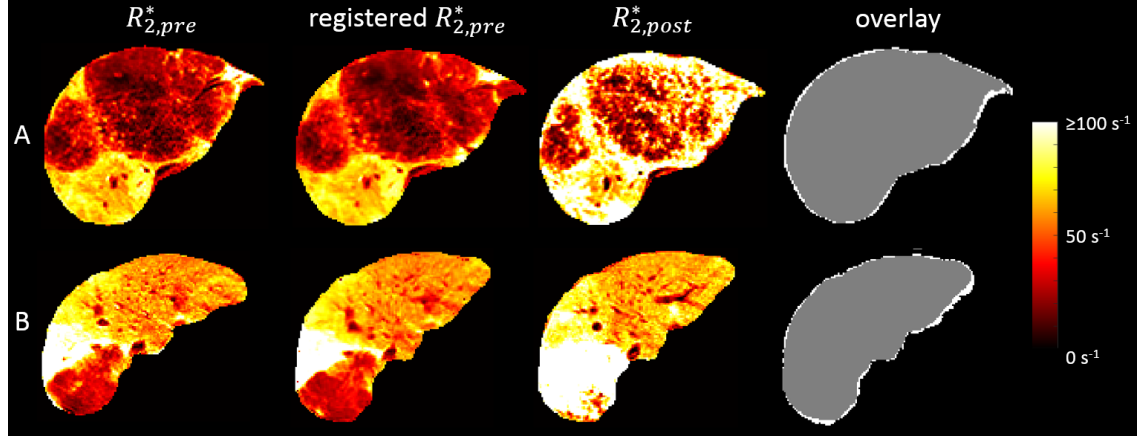


Figure 8: Registration process of the $R_{2,pre}^*$ map to the $R_{2,post}^*$ map as a result of the SyN algorithm in two different patients (A and B). Under overlay, the overlaying voxels after registration are visualized in white and the mismatching voxels (of either $R_{2,pre}^*$ or $R_{2,post}^*$) are visualized in grey.

3.2.6 Image registration accuracy

Registration accuracy was validated by calculating the Dice Similarity Coefficient (DSC; equation 5), the relative overlap (equation 6), and the surface Dice (fraction of surface distances below a set threshold) of the registered $R_{2,pre}^*$ and $R_{2,post}^*$ maps. The surface Dice threshold was set to 4 mm and was calculated using the surface_distance Python library [43].

$$DSC = 2 * \frac{|V_{pre} \cap V_{post}|}{|V_{pre}| + |V_{post}|} \quad (5)$$

$$Relative\ overlap = \frac{|V_{pre} \cap V_{post}|}{|V_{pre} \cup V_{post}|} \quad (6)$$

3.2.7 ^{166}Ho -SPECT/CT imaging

Two days after treatment, ^{166}Ho -SPECT/CT and planar imaging was performed on a Symbia Intevo scanner (Siemens Healthineers, Erlangen, Germany) using a medium energy collimator. SPECT was acquired with a photopeak window of 81 keV (15% width) over a 360 degree orbit with 2 detector heads each with 64 views (20 sec/view; non-circular, step-and-shoot; matrix size 128×128 , slice thickness 4.8 mm) of the liver region (1-2 bed positions). Planar imaging of the lungs and liver was performed with a matrix size of 256×256 for 5 minutes. A low-dose CT scan was acquired on the same scanner for attenuation correction and fusion (110 kV peak, 30 mAs, slice thickness: 3.0 mm). An attenuation-corrected SPECT was reconstructed using an ordered subset expectation maximization 3D algorithm (6 iterations, 16 subsets, Gaussian filter of 8.4 mm).

3.2.8 Dosimetry

All dosimetry was performed in the aforementioned research version of Q-suite[®], all segmentation was performed by a single author (JR) supervised by an experienced interventional radiologist

Table 2: *Relevant clinical characteristics of the patient population treated with ^{166}Ho SIRT.*

patient no.	age (years)	primary tumour	tumour load	treatment volume	number of tumours
1	32	breast cancer	62.4%	whole liver	confluent*
2	74	cholangiocarcinoma	32.4%	whole liver	confluent*
3	43	breast cancer	68.8%	whole liver	confluent*
4	79	hepatocellular carcinoma	16.4%	right hemiliver	2
5	60	colorectal cancer	36.2%	whole liver	5
6	81	hepatocellular carcinoma	4.3%	right hemiliver	3

Tumour load is defined as percentage of the whole liver volume that consisted of tumour tissue

* indicates it was not deemed possible to clearly define multiple separate tumours

(MJA) and an experienced nuclear medicine physician (MJRJ). Generated dose maps were fused manually with the T_1 -weighted VIBE images (MRI-based dosimetry) and automatically with low-dose CT images (^{166}Ho -SPECT-based dosimetry), and liver VOIs were drawn based on these image series. Segmentation of tumour VOIs was performed manually based on the multiple MRI series, and sometimes adjusted slightly after fusion with the dose map in case fusion on a tumour level was deemed suboptimal. The same MRI-based tumour contours were also used for ^{166}Ho -SPECT-based dosimetry. However, as the ^{166}Ho -SPECT/CT was acquired 2 days after treatment, a rigid registration of the tumour contours to the ^{166}Ho -SPECT/CT images was not possible in a single case (patient 1), as some tumours were large and spreading across multiple liver segments. Therefore, manual adjustment of the tumour contours was performed this patient, in order to fit the MRI-based tumour contours to the CT-based liver contour.

3.3 Results

A total of 6 patients were treated with ^{166}Ho SIRT, with a median age of 67 years old. Additional relevant patient characteristics are listed in Table 2. For the clinical examples that follow, patient 1 is referred to as patient A, and patient 4 is referred to as patient B.

The mean computation time for the additional steps of the VW subtraction method was 15.0 s (range: 12.3 – 19.7 s), of which the majority consisted of image registration steps (mean 12.0 s, range: 8.8 – 15.8 s). We found a mean DSC of 0.95 (range: 0.92 – 0.97), mean relative overlap of 0.90 (range: 0.86 – 0.94) and mean Surface Dice ($\leq 4\text{mm}$) of 0.97 (range: 0.96 – 0.98).

In order to visualize the impact of registration on the $R_{2,pre}^*$ values within the total liver volume, $R_{2,pre}^*$ distributions before and after registration are shown in Figure 9. Typically, registration resulted in only a slight increase in the most frequent R_2^* values, and a slight decrease in the less frequent R_2^* values. Similar plots of the other included patients are available in Appendix A.

Differences in $R_{2,pre}^*$ distributions between tumours and healthy liver tissue are visualized in Figure 10. Mean $R_{2,pre}^*$ values were lower in tumours (38.6 s^{-1} , range: $24.4 - 54.7 \text{ s}^{-1}$) than in healthy liver tissue (55.7 s^{-1} , range: $41.4 - 73.8 \text{ s}^{-1}$). The mean $R_{2,pre}^*$ of a total liver volume (48.4 s^{-1} , range: $34.5 - 68.3 \text{ s}^{-1}$) was therefore found to be an overestimation of the mean $R_{2,pre}^*$

3 IMPROVING MRI-BASED DOSIMETRY AFTER HOLMIUM-166 SELECTIVE INTERNAL RADIATION TREATMENT USING A VoxelWISE SUBTRACTION METHOD TO CALCULATE ΔR_2^*

value in tumours, and an underestimation in healthy liver tissue.

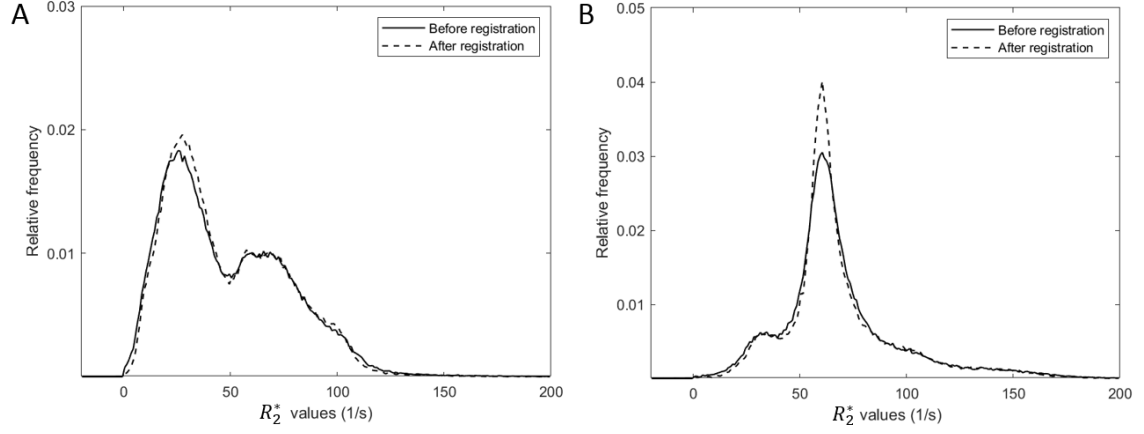


Figure 9: R_2^* distributions in the entire liver volume of patient 1 (A), and patient 4 (B) before and after registration. The registration algorithm resulted in a slight increase in occurrence of the most frequent R_2^* values, and a slight decrease in other values.

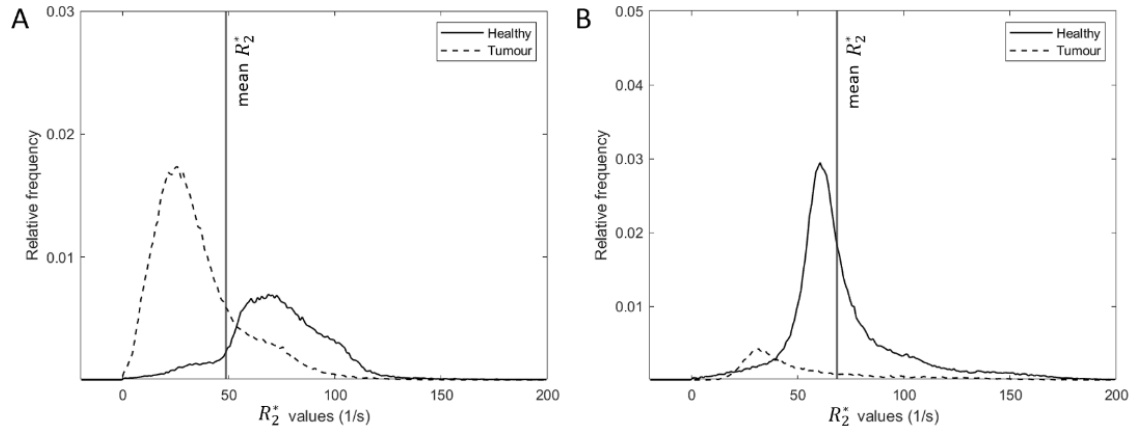


Figure 10: R_2^* distributions of patient 1 (A) and patient 4 (B) classified as either originating from tumours or healthy liver tissue. Additionally, the mean R_2^* value of the entire liver volume is visualized. In general, the mean R_2^* of the entire liver volume is an overestimation of the tumour R_2^* values.

The mean doses per VOI of all 6 patients are summarized for both the mean method and the VW method in Table 3. The mean total liver dose was comparable for all three methods, with a mean difference between the MRI-based methods of 1.7%. The VW method however yielded a decrease in healthy liver dose (mean of 16.9%) and an increase in tumour dose (mean of 9.7%) compared to the mean method. Inpatient variation was high, with in an extreme case a decrease in healthy liver dose of 55.9% (34.0 Gy to 15.0 Gy, patient 1) and in another case an increase in tumour dose of 15.9% (90.0 Gy to 104.3 Gy, patient 4). In 3/6 cases, the difference between the VW method and mean method on either the tumour dose or healthy liver dose was $\geq 10\%$. ^{166}Ho -SPECT dosimetry resulted in a lower mean tumour dose than either MRI-based method in all patients,

3 IMPROVING MRI-BASED DOSIMETRY AFTER HOLMIUM-166 SELECTIVE INTERNAL RADIATION TREATMENT USING A VOXELWISE SUBTRACTION METHOD TO CALCULATE ΔR_2^*

Table 3: Mean dose per volume of interest as calculated through the mean method and the VW method. Data is presented as mean with range between brackets.

	Mean method method	VW method method	SPECT
Mean liver dose (Gy)	45.2 (30.0 – 54.0)	44.5 (26.0 – 55.0)	44.0 (26.0 – 60.0)
Mean healthy liver dose (Gy)	35.4 (28.0 – 47.5)	29.8 (15.0 – 44.5)	33.3 (20.0 – 51.0)
Mean tumour dose (Gy)	71.3 (21.3 – 110.3)	78.1 (25.8 – 125.0)	63.3 (22.0 – 89.3)

and a mean healthy liver dose higher than the VW method but lower than the mean method.

In Figure 11 and Figure 12, the resulting MRI-based dose distributions in patients 1 and 4 were compared with the dose distribution after ^{166}Ho -SPECT/CT imaging. In these visual comparisons, it can be appreciated that the VW method also results in a different dose distribution on a voxel level, that corresponds more to SPECT than the mean method.

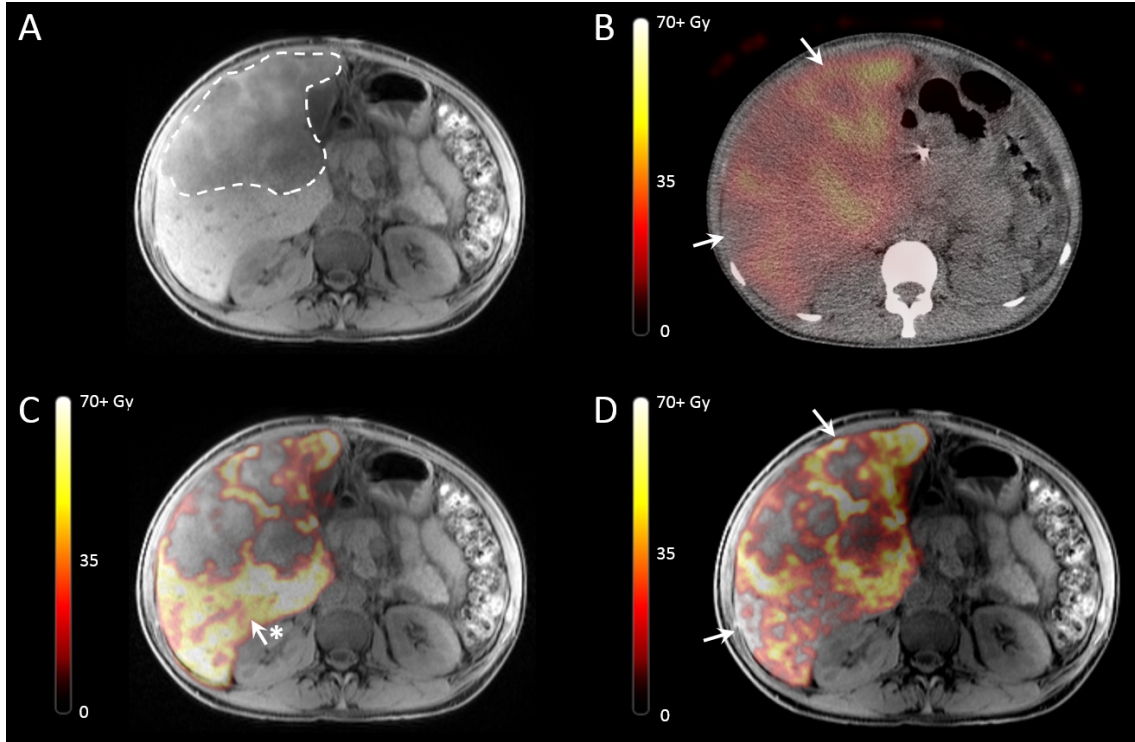


Figure 11: A patient with liver metastases originating from breast cancer (patient 1). A: a T_1 -weighted MRI in which the tumours are delineated with a dashed line. B: ^{166}Ho -SPECT fused with a low-dose CT. C and D are MRI-based dose maps, C was generated through the mean method, D through the voxelwise method. The arrow with asterisk (C) indicates the overestimation of the dose in the healthy liver tissue resulting from the mean method as compared to the SPECT images. Other arrowheads indicate similarities between the dose map resulting from the voxelwise method and the SPECT images.

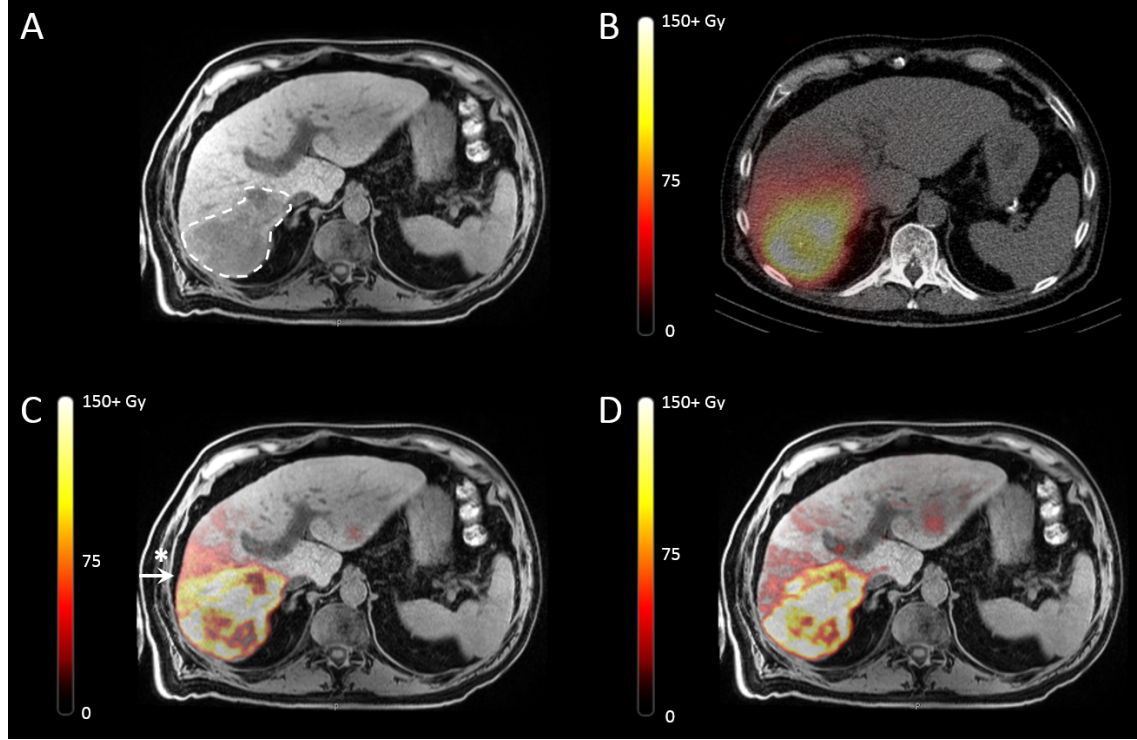


Figure 12: A patient with hepatocellular carcinoma (patient 4). A: a T_1 -weighted MRI in which the tumours are delineated with a dashed line. B: ^{166}Ho -SPECT fused with a low-dose CT. C and D are MRI-based dose maps, C was generated through the mean method, D through the VW method. The mean method resulted in an overestimation of the healthy liver dose directly adjacent to the tumour (arrowhead in Figure C) compared to SPECT imaging. This overestimation, resulting from locally increased R_2^* values prior to treatment, was attenuated by the VW method.

3.4 Discussion

The ability to perform MRI-based dosimetry after SIRT is one of the unique characteristics of the ^{166}Ho microspheres compared to the ^{90}Y based microspheres. In this work, we have presented a fast and robust alternative for the current method of calculating the ΔR_2^* map, based on voxelwise subtraction, with the aim of improving the accuracy of MRI-based dosimetry. Most noteworthy is that both the current and new method result in a similar mean dose of the entire liver volume, however, there is a shift in dose distribution between healthy liver tissue and tumour tissue.

The original publication on MRI-based ^{166}Ho dosimetry in patients [18] suggested that a voxel-based approach to calculate the ΔR_2^* map would improve the accuracy of the calculated dose distribution, as the VW method is less sensitive to differences in R_2^* prior to treatment due to tissue characteristics. In the presented work we quantified these differences, and measured a substantially lower mean R_2^* in tumours compared to healthy liver tissue. We therefore argue that the VW method is intrinsically superior to the mean method, provided that the image registration prior to subtraction is performed adequately.

After transformation of the $R_{2,pre}^*$ map to the $R_{2,post}^*$ map, we found a mean DSC and relative

overlap of respectively 0.95 (range: 0.92 – 0.97) and 0.90 (range: 0.86 – 0.94). The mean surface Dice was 0.97 for a cut-off of 4 mm. The upper limit of these metrics for registration of liver volumes is limited by several factors, such as consistency in delineation of the liver volumes (e.g. at the liver hilus), consistency of the breath holds of the patient and resulting image quality, and potential increase of the liver volume as a result of treatment. Ideally, the accuracy of registration within the liver volume itself would also be quantified, but as the soft tissue contrast in the MGRE images was too poor for delineation of for instance tumours or large vessels, this evaluation was limited to a visual inspection and the comparison of the R_2^* distributions. After registration, a shift towards the more frequent R_2^* values was apparent, which is probably due to the minor blurring that is induced by the registration. Other than this shift, the $R_{2,pre}^*$ distributions before and after registration are similar. A direct result of the imperfect (<1.0) DSC and relative overlap is the fact that not every voxel in the $R_{2,pre}^*$ map is paired with a voxel in the $R_{2,post}^*$ map, which is a requirement for a voxel-based subtraction method. This was resolved through a nearest neighbour-based filling approach, in which voxels with no value or values not representable for the liver are filled with an average of neighboring voxels. This method assumes voxels within a certain distance will have similar R_2^* values, the assumption being based on the regional homogeneity of the liver.

A caveat of the VW method is that the contouring strategy used for the pre- and post-MGRE images needs to be comparable (e.g. including or excluding the gall bladder, or parts of the portal vein), to avoid registration errors. This was not a problem using the current mean method, as the contour of the pre-scan is not used for the subtraction. However, since contouring within a single patient case is mostly done by the same observer, and intra-observer variability is assumed to be limited because of the well-defined contour of the liver, the influence on the quantification is expected to be negligible.

Ideally, the validity of our method would be confirmed through a comparison with a golden standard for ^{166}Ho dosimetry. The only other modality used for clinical dosimetry is ^{166}Ho -SPECT imaging. A comparison between MRI-based dosimetry (mean method) and SPECT-based dosimetry has been made in the past [35], resulting in a good correlation between mean doses and comparable tumour to normal tissue ratio's (T/N ratio's). In the presented work, tumour doses were always lower using SPECT than using either MRI-based dosimetry method. There is however more to SPECT quantification than meets the eye, hampering a proper comparison to MRI-based dosimetry. In a recent publication it was described that especially in high-activity regions such as tumours, reliable dosimetry is significantly hampered by dead time, and underestimations of up to 20-40% can occur [44]. Other aspects of ^{166}Ho -SPECT such as lack of respiratory gating during image acquisition, the partial volume effect, and decreased imaging resolution all complicate a proper dosimetric comparison between the two modalities. All these aspects could explain the low tumour doses found using SPECT dosimetry.

Another group has attempted to compensate for these uncertainties by adding a tumour contour dilatation step when transferring ^{18}F -FDG-PET based contours to ^{166}Ho -SPECT/CT [33, 45]. For calculating the mean dose, the original tumour volume was used. We have opted not to use a similar approach, as the 1 cm dilatation potentially introduces other uncertainties, such as whether the activity added to the tumour VOI's originates from only tumour tissue or also healthy liver

tissue. This would be especially be tricky if tumour VOI's are rather small.

An alternative to the investigated VW method that omits an image registration step could be a region based mean subtraction method, in which multiple means are calculated for different regions in the liver (such as healthy vs. tumour tissue). A downside is that the MGRE images have poor soft tissue contrast, making delineation an inaccurate and time-consuming process that would probably take longer than applying the presented registration algorithm. Another alternative could be to use a single acquisition to find the increase in R_2^* as a result of the holmium microspheres, such as the SOFIDSE sequence [21]. In this sequence, both R_2 , R_2^* , and R_2' are estimated in a single acquisition, which would not only omit the registration step, but also the need for pre-treatment imaging altogether. Existing single acquisition methods are however not developed far enough yet for implementation in the workflow of ^{166}Ho SIRT at our center.

Ultimately, the purpose of dosimetry is either to elucidate the dose-response relationship in order to establish a dose threshold that should be achieved (in a research context), or to predict whether a specific patient will respond to treatment (in a clinical context). Such a predictive value for ^{166}Ho -SPECT based dosimetry has been established in the past [33, 45]. MRI-based dosimetry mitigates some challenges found in SPECT dosimetry (lack of respiratory gating, dead time, relatively low imaging resolution), and we believe that our novel approach to MRI-based dosimetry after ^{166}Ho SIRT characterizes the dose distribution better than the currently implemented method. This suggests a bright future for MRI-based dosimetry in predicting dose-response, although its true value leaves to be investigated.

3.5 Conclusion

The currently implemented method for MRI-based quantification of ^{166}Ho microspheres after SIRT does not take regional differences in R_2^* values, such as between tumours and healthy tissue, into account. In this work, we have demonstrated the extent of these regional differences, and have developed a fast and robust improved method based on registration and subsequent voxelwise subtraction. The novel method appears to have better correspondence with the dose distribution as found through SPECT imaging, even though a direct, quantitative comparison is complicated. The potential added value in predicting dose-response after treatment compared to SPECT has to be investigated further.

Feasibility of a single sequence acquisition for holmium-166 MRI-quantification: techniques of the SOFIDSE sequence

4.1 Introduction

The paramagnetic properties of the ^{166}Ho microspheres enable their MR imaging possibilities, and give the microspheres an advantage over other microspheres used for SIRT. After SIRT, the concentration of ^{166}Ho microspheres can be quantified by computing the increased transverse relaxation (R_2^*) that the microspheres induce, which can be done by using several steps [20]. Currently this quantification is done by acquiring a MGRE before and after treatment and fitting R_2^* from the acquired datapoints, as explained in the general introduction. One of the drawbacks of this technique is that two acquisitions, one before and one after the microsphere administration, are needed to quantify the holmium influence on the MR images. This induces errors and inaccuracies because of movement and acquisition differences between sessions. Furthermore, it demands the need for additional post-processing to perform the subtraction to find ΔR_2^* by computing a mean pre-treatment R_2^* or by performing a registration (Chapter 3).

One of the methods to reduce these errors and inaccuracies induced by pre- and post-treatment scanning is to quantify the holmium microspheres within a single acquisition, which was presented before by van de Maat et al. in 2015 [21]. This sequence is based on a S_0 estimation of the free induction decay (FID) and a single spin echo (SE) (SOFIDSE), which enables simultaneous acquisition of R_2^* and R_2 . These relaxation rates are then subtracted to obtain R_2' , which is defined as the influence of all inhomogeneities on the imaged volume. The sequence, which can be seen in Figure 13, consists of a 90° RF pulse after which 10-15 gradient echo images are acquired during the FID. This is the same principle as the MGRE that is currently used for ^{166}Ho quantification. Afterwards, a 180° refocusing pulse redirects the spins and a single SE is acquired at $\text{TE}_{SE}=30$ ms in which B_0 heterogeneities, the tissue and the microspheres are minimized. The MGRE that is acquired during the FID is used to compute the R_2^* using a monoexponential fit, just like the current ^{166}Ho MR quantification method. Additionally, the R_2^* fit is used to obtain the signal intensity at timepoint 0 (S_0), which can be used with the SE measurement to estimate R_2 (dashed line in Figure 13). [21]

The R_2^* map and R_2 map that are made during post-processing of SOFIDSE can be subtracted to find R_2' , which represents the influence of all inhomogeneities on the physiologic R_2 values of the liver tissue. According to van de Maat et al, the magnitude of the holmium microsphere influence on R_2' is much larger than B_0 and tissue induced inhomogeneities, making the found R_2' map comparable to the conventional ΔR_2^* map. This method would eliminate the need for a pre- and post-treatment MGRE scan, and therefore reduce inaccuracies due to movement and acquisition errors between sessions.

Two separate techniques are of importance for the SOFIDSE sequence to work. Firstly, an accurate estimation of R_2 using the S_0 and SE, and secondly the subtraction of R_2^* and R_2 leaving only

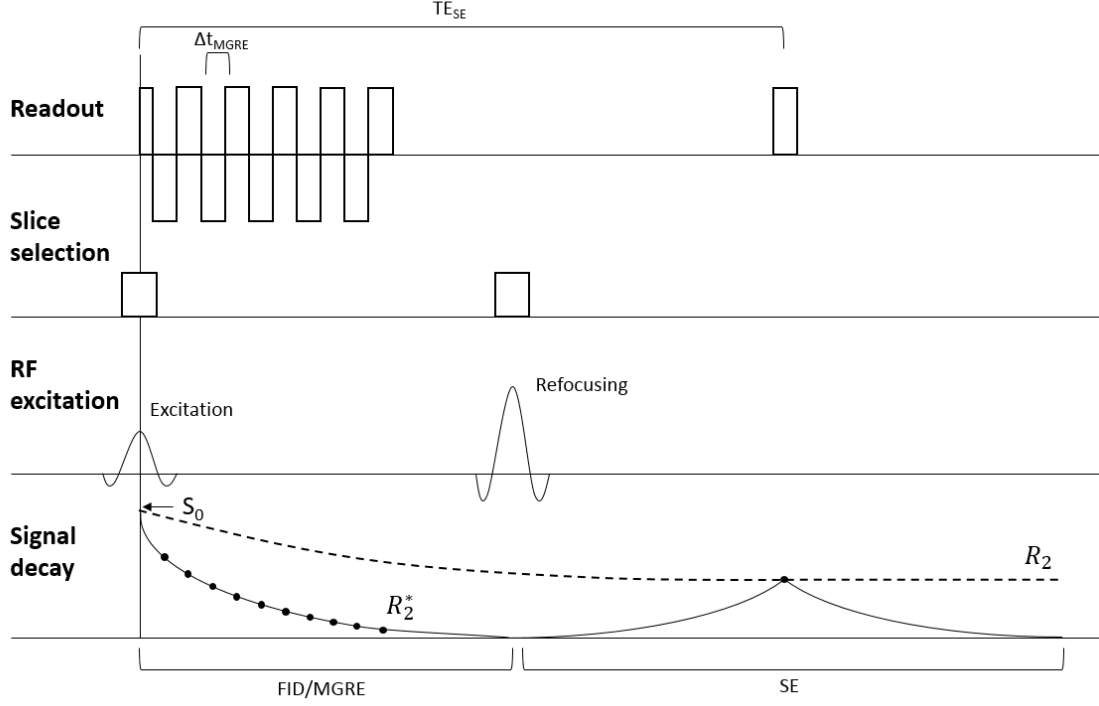


Figure 13: The acquisition scheme of the SOFIDSE sequence. The first part, which is referred to as the FID/MGRE in the image is the sampling of the FID after the initial excitation, which is the same as the currently used MGRE before and after treatment. From the data points sampled during the FID, R_2^* is computed. The second part, which is labelled SE, is the acquisition of the SE ($TE=30ms$) which is used together with the S_0 to find R_2 , which is represented by the dashed line.

the holmium induced R_2' . Before implementation of the sequence, the validity of finding R_2 from S_0 and SE, and of using R_2' to isolate the holmium influence needs to be studied. Therefore, an evaluation of these techniques that the SOFIDSE sequence relies on was performed using two experiments that were carried out using two existing MR sequences on healthy volunteers and one patient.

4.2 Methods

4.2.1 Acquired imaging

For this evaluation, three volunteers were scanned on a 3T clinical MRI scanner using a spine 32 matrix coil and an 18 phased array receiver body coil (Siemens Healthineers, Erlangen, Germany). The scanning protocol consisted of the clinically used MGRE sequence for R_2^* quantification, with 10 echos ($TE_1=1.06$ ms, $\Delta TE=1.38$ ms, $TR=149$ ms, flip angle= 33° , in-plane resolution 2×2 mm², slice thickness 4 mm, FOV 384×384 mm²). For the R_2 quantification a work in progress package (WIP) developed by Siemens was used, from which the sequence diagram can be found in Figure 14 [46]. This package provided a Turbo Spin Echo (TSE) with 24 echo times ($TE_1=8.05$

ms, $\Delta TE=8.05$ ms, flip angle= 166° , in-plane resolution 2×2 mm², slice thickness 4 mm, FOV 384×384 mm²), from which an R_2 map was computed by Siemens using a monoexponential fit on the 2nd to 20th echo [47]. Apart from the computed R_2 map, the images from all 24 echo times were exported for later use as well.

In order to mimic the clinical setting in which SOFIDSE would be implemented, movement between the acquisition of the MGRE and TSE sequences needed to be minimized. Therefore, for all three volunteers, first the MGRE was acquired, and then the TSE was acquired directly afterwards, minimizing movements. To be able to compare the SOFIDSE simulation with the normal workflow, the volunteers were instructed to move before a second MGRE was acquired.

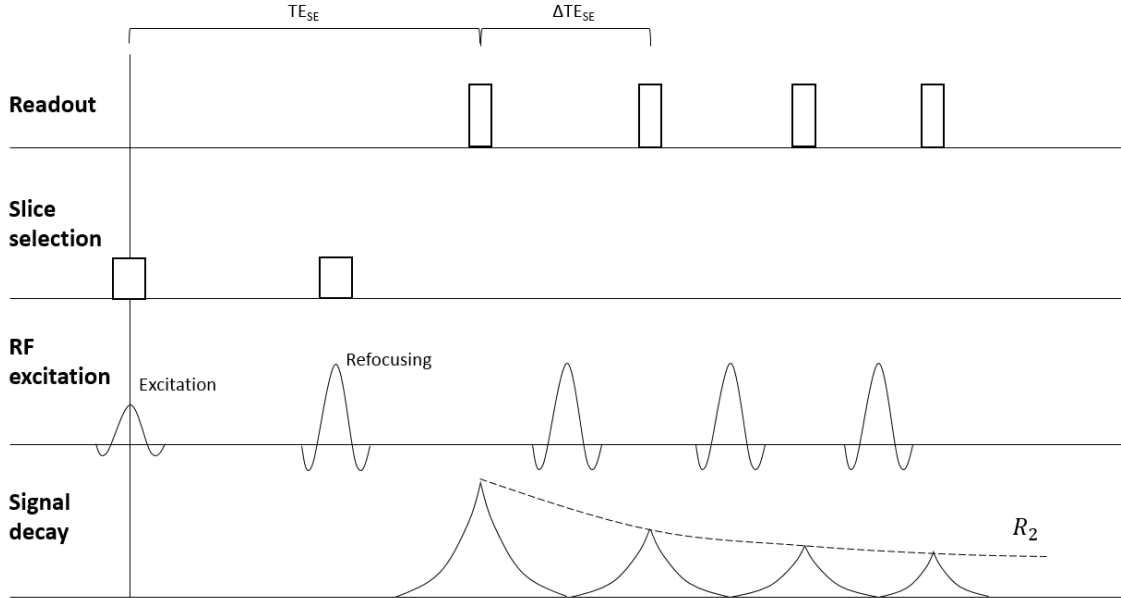


Figure 14: Simplified sequence diagram of the radial TSE as used for the image acquisition and R_2 quantification by the Siemens WIP. After each refocusing pulse, an echo is acquired ($TE1=8.05$ ms, $\Delta TE=8.05$ ms). From the resulting echo images, the R_2 relaxation was fitted, which is represented by the dashed line.

4.2.2 Pre-processing

In order to perform pre-processing the image data, consisting of two MGRE acquisitions and a single TSE acquisition, was loaded into Q-suite[®]. Liver contours were drawn on both MGRE image sets, and R_2^* maps were calculated within Q-suite[®] with the implemented monoexponential fit. The liver contours and R_2^* maps were exported for further analysis in MATLAB (version 2020b). In MATLAB the liver contour of the first MGRE was used to segment both the MGRE and the TSE images (both the separate echoes and the R_2 map) to perform analysis on only the liver part of the MR images.

4.2.3 S_0 and SE for fitting R_2

The first objective was to test the feasibility of computing R_2 with S_0 and a single SE. In order to mimic SOFIDSE, it would be needed to find the S_0 based on the FID signal, which was acquired during the MGRE sequence, and use the signal intensity from the 30 ms echo from the TSE. However, because of different flip angles, shimming and other acquisition parameters, the metrics from these two different sequences could not be used together to find R_2 . Therefore, S_0 was first estimated for each liver voxel based on the 2nd to the 20th echo from the TSE data using a monoexponential fit in MATLAB. This S_0 value was then combined with the signal intensity from TSE echo at 32.2 ms (S_t), which was the echo closest to the TE used in the SOFIDSE sequence (30 ms), in order to calculate R_2 according to Equation 7 [21].

$$R_{2_{SOFIDSE}} = \ln\left(\frac{S_0}{S_t}\right)/t \quad (7)$$

In addition to the R_2 map found with the S_0 and the SE, two more R_2 maps, both based on a monoexponential fit were used for comparison. The first as computed by Siemens, which was based on a monoexponential fit from the 2nd to the 20th echo from the TSE sequence [47]. The second was the fit performed within MATLAB, which was used for the determination of S_0 as well.

4.2.4 R_2' as a quantitative value for ^{166}Ho dosimetry

The next experiment was done to test the feasibility of using the R_2^* and R_2 instead of using ΔR_2^* for quantification of the microspheres. The R_2 map computed by the Siemens package was used rather than using the R_2 found in the previous experiment with the S_0 and the SE. To find the inhomogeneity induced R_2' , the R_2^* map from the first MGRE and the R_2 map from the TSE are subtracted voxelwise using equation 8.

$$R_2' = R_2^* - R_2 \quad (8)$$

The resulting R_2' maps were compared with the ΔR_2^* maps which were made with the two acquired MGRE sets using the new workflow with a registration as was proposed in Chapter 3.

4.2.5 Case study

In addition to the experiments performed on healthy volunteers, a case study was performed on a single patient, in order to study the influence of the ^{166}Ho administration on both ΔR_2^* and R_2' . This patient was part of a clinical trial (clinicaltrials.gov identifier: NCT04269499), during which ^{166}Ho SIRT was performed, and imaging was acquired on the same MRI system as stated before. As part of the clinical trial workflow, a MGRE was acquired before and after administration of the ^{166}Ho microspheres. Additionally, the TSE sequence using the same parameters as stated for the scanned volunteers was acquired before and after ^{166}Ho SIRT. Contrary to the scanned volunteers, for this patient only R_2 maps computed by Siemens were exported, without all echo time images. Post-processing to find R_2' was the same as for the scanned volunteers.

4.3 Results

4.3.1 S_0 and SE for fitting R_2

Mean R_2 values for each fitting method and for each volunteer can be found in Table 4. A single slice of the found R_2 maps for each method and each volunteer can be seen in Figure 15. Overall, the Siemens R_2 computing method gave the highest R_2 . The R_2 fit based on the S_0 and SE gave an average underestimation of 3.92% compared to the MATLAB monoexponential fit.

Table 4: Mean ($\pm SD$) R_2 as found by the two monoexponential fitting methods and the method based on S_0 and SE for all three volunteers.

R_2 (s^{-1})	Monoexp fit Siemens WIP	Monoexp fit MATLAB	S_0 and SE fit
Volunteer 1	21.07 (± 7.88)	15.81 (± 8.12)	15.26 (± 4.66)
Volunteer 2	21.16 (± 6.14)	14.64 (± 2.79)	13.39 (± 2.85)
Volunteer 3	23.66 (± 7.32)	16.41 (± 7.56)	15.82 (± 3.97)

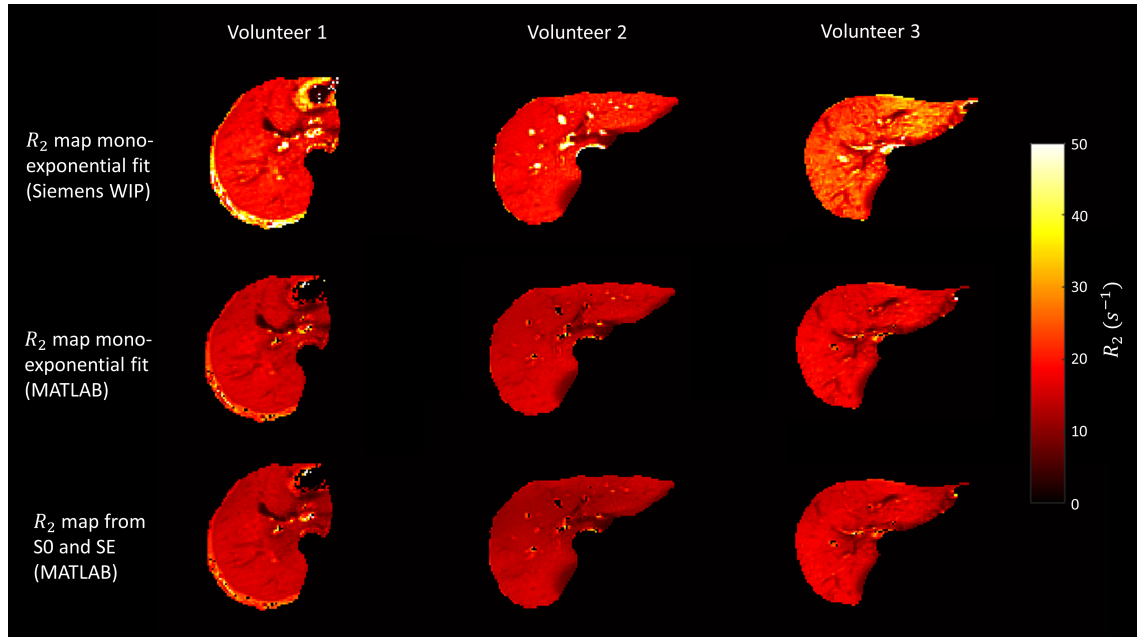


Figure 15: Map of the R_2 values found by using a monoexponential fit of the Siemens WIP, a monoexponential fit within MATLAB and the S_0 and SE fit for the three scanned volunteers. In all cases the monoexponential fit as applied by the Siemens WIP showed the highest R_2 . The MATLAB monoexponential fit and the S_0 and SE fit showed similar R_2 values.

4.3.2 R'_2 as a quantitative value for ^{166}Ho dosimetry

Mean ΔR_2^* and mean R'_2 for all volunteers can be found in table 5. In figure 16, an example of the difference between the currently used ΔR_2^* map made from the pre- and post-movement R_2^* maps and the R'_2 maps made using the pre R_2^* map and the R_2 map are shown. The R'_2 maps

of each volunteer showed a baseline R'_2 with an increase of around 20 s^{-1} compared to respective ΔR_2^* values.

Table 5: The resulting relaxation and SD after voxelwise R_2^* map subtraction and the SOFIDSE like subtraction for all three volunteers. Given that the volunteers did not undergo ^{166}Ho SIRT, values should ideally be zero.

	$\Delta R_2^* (\text{s}^{-1})$ MGRE	$R'_2 (\text{s}^{-1})$ MGRE and TSE
Volunteer 1	4.98 (± 25.48)	25.99 (± 30.74)
Volunteer 2	2.60 (± 19.89)	20.98 (± 23.96)
Volunteer 3	0.58 (± 20.79)	23.00 (± 25.18)

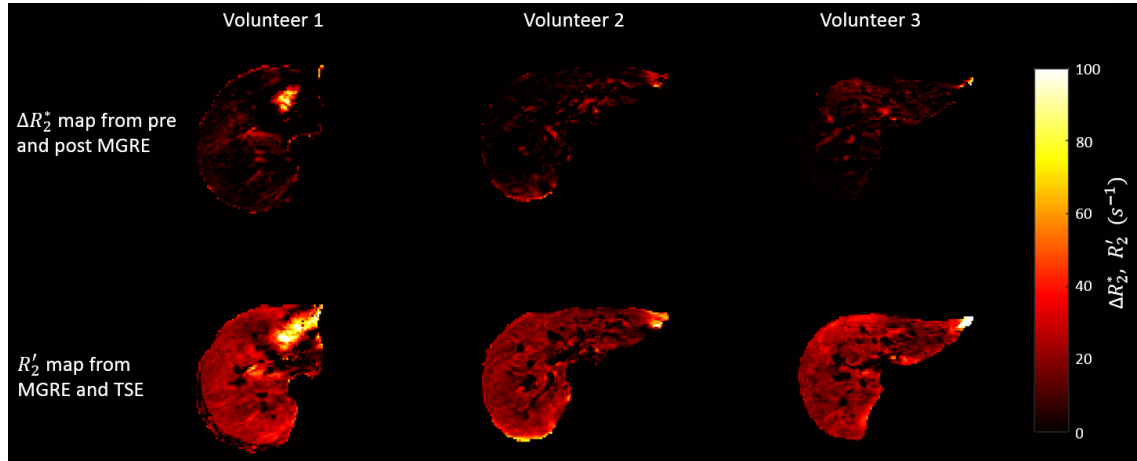


Figure 16: The quantitative maps showing ΔR_2^* (above) and R'_2 (below) for all three volunteers. Volunteers did not undergo ^{166}Ho SIRT, and therefore ΔR_2^* and R'_2 should ideally be 0. In all cases R'_2 showed a higher value than ΔR_2^* .

4.3.3 Case study

For the patient case, the influence of inhomogeneities other than the ^{166}Ho microspheres on the R'_2 map was lower than for the volunteers (Figure 17). The quantification based on the pre- and post-treatment MGRE showed a mean ΔR_2^* of 40.29 s^{-1} ($\text{SD} = \pm 43.52$), while the mean R'_2 after treatment was 46.36 s^{-1} ($\text{SD} = \pm 39.47$). Overall, the voxelwise difference between the ΔR_2^* map and the post treatment R'_2 map was 10.80 s^{-1} (± 18.86), and the difference was most apparent in the untreated liver part and in the regions in close proximity to air. The MGRE and TSE that were acquired before the microspheres were administered resulted in an average R'_2 of $21.38 (\pm 21.54)$.

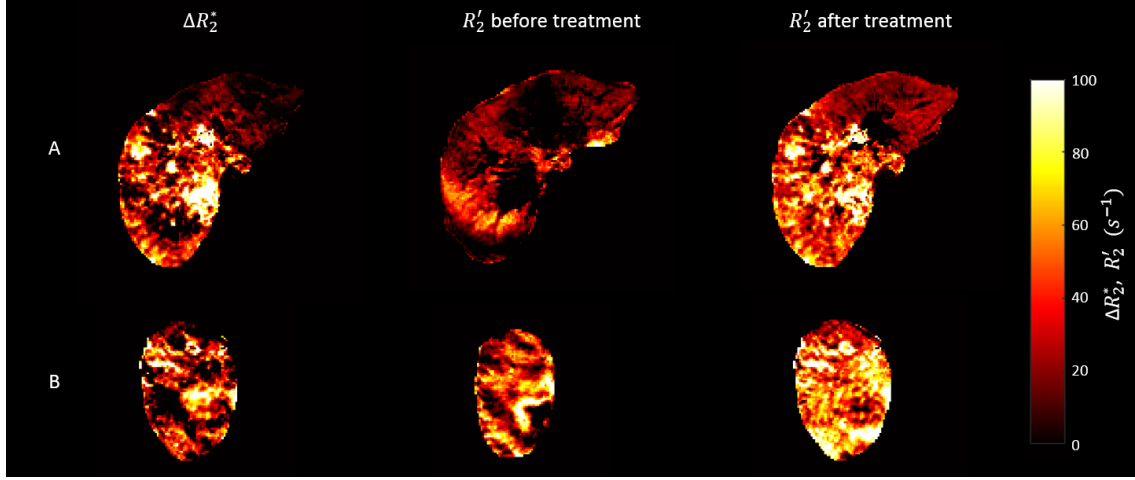


Figure 17: The MRI quantification results from a patient that underwent ^{166}Ho SIRT. From left to right the clinically used ΔR_2^* map, the R_2' quantification using the MGRE and TSE before the treatment and after treatment with ^{166}Ho microspheres is shown. Data is shown for two different slices, slice A on the level of the entrance of the left vena porta branch, and slice B on the upper part of segment VII/VIII, on which the liver tissue is surrounded by the lung.

4.4 Discussion

During this study two sequences were used to evaluate the techniques used by the SOFIDSE sequence for ^{166}Ho quantification. The SOFIDSE sequence utilizes S_0 and a single SE to calculate R_2 , and uses a subtraction of R_2 and R_2^* to find R_2' , which is then used for ^{166}Ho microsphere quantification. An implementation of this sequence would reduce pre- and post-treatment subtraction induced errors, since the single acquisition enables direct voxelwise subtraction of the R_2 and R_2^* map without post-processing. This would be favourable to image-guided ^{166}Ho SIRT, but given the new goal of performing decision-making based on MR dosimetry, the accuracy of the techniques used by the SOFIDSE sequence needed to be re-evaluated.

The first technique analyzed was performing R_2 estimation using S_0 and a single SE. In the three scanned volunteers, the R_2 found by using S_0 and SE was very comparable to the R_2 found by performing a monoexponential fit on 20 echoes within MATLAB. This does suggest that fitting using these two data points does result in a R_2 comparable to using a fit on several data points, which was also concluded by van de Maat et al. [21]. A remarkable outcome is that the found R_2 values for the MATLAB monoexponential and the S_0 and SE fit (range mean R_2 values: 13.39-16.41 s^{-1}) do not agree to liver R_2 values that can be found in literature, in which values around 30 s^{-1} are stated [48]. The R_2 values found by the Siemens monoexponential fit are more similar to the values stated in literature, which could be due to a different handling of the SNR or to other fitting differences, but the exact cause of the differences between the Siemens, MATLAB monoexponential fit and values stated in literature is unknown. The SOFIDSE paper did show R_2 values similar to literature [21].

It should be noted that while the methods that have been studied are the same for the SOFIDSE sequence as for the MGRE and TSE, the difference between a single acquisition or a double ac-

quisition, could influence the outcome of the experiments. This could explain the fact that the implementation of the sequence in the published paper did show values comparable to literature. The calculation of R_2 from S_0 and SE is likely to be influenced by the acquisition differences, for example the imperfect refocusing pulse of the TSE and the S_0 that was found by fitting the TSE instead of the FID from the MGRE. An imperfect refocusing pulse would ask for a correction in the fitting method, which has not been performed in this case [46, 47]. Therefore, hard conclusions on the performance of SOFIDSE in finding R_2 can not be made.

The second principle studied was the feasibility of using R_2' to define the presence of holmium microspheres, instead of the currently used ΔR_2^* . In the SOFIDSE paper it was stated that most B_0 and B_1 inhomogeneities are negligible compared to the influence of the microspheres [21]. An exception would be the inhomogeneities caused by air (for example in the lungs or bowel) or inhomogeneities due to iron overload of the liver. However, during this experiment a baseline R_2' value of approximately 20 s^{-1} was found in healthy volunteers and in the patient case before microsphere administration. Because in these cases no microspheres have been administered, R_2' should ideally be around zero, as is the case for the current workflow with the ΔR_2^* maps.

A baseline R_2' value could be acceptable, as long as the baseline can be neglected when holmium microspheres are administered. This was studied in the patient case, and this case indeed showed less influence of this baseline on R_2' when microspheres were injected. Instead of the initial baseline of 20 s^{-1} , that was observed for all volunteers and the patient case before microsphere administration, R_2' after microsphere administration showed an overall increase of approximately 10 s^{-1} compared to the ΔR_2^* map. However, since the mean ΔR_2^* was around 40 s^{-1} for this patient, the found baseline would have a major influence on the dose quantification. Especially when taking the image guided procedure in mind, the accuracy of the dose distribution needs to be as high as possible, because the mean dose of both the tumours and the healthy tissue is used to do decision making.

The influence of using two acquisitions instead of one is expected to be less prominent for the second experiment. The results could differ slightly due to movement between the acquisitions, leading to imperfect subtraction because a single liver contour was used for all images for a single subject. However, upon visual inspection, the errors induced by the movement were deemed to be negligible. Furthermore, literature confirms the found differences between R_2^* and R_2 due to inhomogeneities, which states values of around 50 s^{-1} for R_2^* and around 30 s^{-1} for R_2 [49, 48]. This corresponds to the baseline R_2' value of 20 s^{-1} that was found for all volunteers. Therefore, conclusions made on this second experiment are more likely to correspond to the outcomes of an implementation of the SOFIDSE sequence.

When the SOFIDSE sequence will be implemented for clinical use in the future, there are some challenges to overcome. One of these challenges is that for each vendor, a version of the SOFIDSE sequence would have to be made. This would be possible, taking the limited number of vendors used in clinical practise into account. However, the ease of improving the ^{166}Ho SIRT workflow would be limited, given that all changes need to be implemented for each vendor. With the current workflow this is not a problem, because the MGRE is available on standard MRI machines, and all post-processing is done within the Q-suite® software. This enables easy adaptation of

the quantification by the development team. The importance of this challenge should be weighed against the benefits of using the sequence.

The most important challenge is regarding the high accuracy needed for image guided SIRT. Correcting for the baseline difference between R_2^* and R_2 could possibly be done with the use of B_0 and B_1 mapping before treatment [50]. This inhomogeneity map could then be used to correct the initial inhomogeneities that are present in the R_2' map. This does mean that another acquisition has to be done, and more post-processing would be needed, while the single acquisition and the easy processing are the big advantages of the SOFIDSE sequence.

4.5 Conclusion

Using a single acquisition would be preferable for quick and robust quantification during image-guided ^{166}Ho SIRT. However, the decision making during the treatment does ask for highly accurate dose-maps, and from the performed experiments it can be concluded that the accuracy of the current workflow is still higher. Therefore, the benefits of the single acquisition and the drawbacks of the inhomogeneity induced errors should be weighted, and possible improvements should be considered before a new implementation of SOFIDSE for image guided SIRT is made.

Future perspectives for image-guided holmium-166 SIRT

The key of enabling image-guided ^{166}Ho SIRT is a highly accurate and rapid MRI quantification to generate dose maps fit for decision-making. In the near future a new clinical study will be executed to further study the feasibility of image-guided SIRT. During this study imaging will be performed in between injection fractions, and based on the imaging, decision making will be done on the injection of more or less microspheres than planned. Therefore, the MRI quantification needed to be validated, and new possible techniques needed to be developed. In this thesis, several topics concerning image-guided ^{166}Ho SIRT have been discussed. In the following paragraphs the most important conclusions are repeated, and some general future perspectives are stated.

Firstly, with the goal of performing the complete treatment under MRI-guidance, the influence of gadolinium contrast was studied (Chapter 2). The contrast agent did influence on overall R_2^* values, and therefore, questions were raised on the feasibility of performing a liver catheterization under MRI-guidance. While there are possibilities to minimize this influence, the visibility of the smaller vascular structures and further development of real-time sequences are two constraints that need to be improved before an MRI-guided liver catheterization can be implemented in the ^{166}Ho SIRT workflow.

In order to improve the accuracy of the pre- and post-treatment R_2^* map subtraction, a voxelwise alternative for this post-processing was studied (Chapter 3). This new method takes pre-treatment heterogeneity of the livers' R_2^* values into account, because heterogeneity between healthy and tumour tissue, or heterogeneity of cirrhotic liver tissue is very common. The new method consists of a deformable registration and additional post-processing, which enables a voxelwise subtraction of pre- and post-treatment R_2^* values. The method showed a better visual similarity to SPECT imaging and to patient outcome. The VW method has been implemented in Q-suite® as part of this thesis as well (Appendix B), and will be used during the next clinical study and is recommended for other users of the software as well.

The last technique studied, which enables MRI-based ^{166}Ho quantification in a single acquisition, was the SOFIDSE sequence (Chapter 4). Despite the lack of an implementation of the sequence, the techniques that the sequence uses were evaluated using two separate sequences for R_2^* and R_2 calculations. Both the outcomes from the used sequences and literature raised challenges concerning the accuracy and usability of the SOFIDSE sequence. Despite these challenges, a single acquisition would still be of great value to image-guided ^{166}Ho SIRT, and therefore an implementation of the sequence, with possible improvements, remains a goal for the near future.

While the topics discussed provided more insight on the optimizations required for image-guided SIRT, there are still other parts of the workflow (Figure 3) that could be optimized, to either increase the accuracy or the speed of the ^{166}Ho quantification. The manual contouring takes approximately 10-15 minutes for every liver that needs to be segmented, which has to be done for each new quantification. The other processing steps, such as the fitting and registration take a maximum of 5 additional minutes, implying that the contouring is the biggest bottleneck for

having a feasible real-time workflow. While some improvements have already been done on reusing contours to save time during the treatment, a delay caused by this step is still expected. Existing AI systems could reduce this time and, if well trained, these systems can produce accurate segmentations. This is therefore definitely a step that needs to be developed in the future.

Another part of the workflow that could be improved is the R_2^* monoexponential fit, which is a time-consuming process, and sometimes shows questionable results, while a faster method would be beneficial for image-guided SIRT. A computational method as an alternative to using a monoexponential fit has been studied before, which would increase processing speed, but which needs to be validated to be used for fitting R_2^* [51].

In the future clinical study, the main goal will be to study the feasibility of performing MRI dosimetry during SIRT, and making decisions based on the acquired imaging. Parallel to this study, additional developments concerning MRI-based dosimetry and the image-guided workflow will be studied in order to optimize image-guided SIRT even further. The ultimate goal is to study possible beneficial patient outcomes as a result of using imaging during SIRT for a more personalized dose administration.

References

- [1] P. Dasgupta, C. Henshaw, D. R. Youlden, P. J. Clark, J. F. Aitken, and P. D. Baade, "Global Trends in Incidence Rates of Primary Adult Liver Cancers: A Systematic Review and Meta-Analysis," *Frontiers in Oncology*, vol. 10, no. February, pp. 1–17, 2020. 1
- [2] A. Ananthakrishnan, V. Gogineni, and K. Saeian, "Epidemiology of primary and secondary liver cancers," *Seminars in Interventional Radiology*, vol. 23, no. 1, pp. 47–63, 2006. 1
- [3] O. Clements, J. Eliahoo, J. U. Kim, S. D. Taylor-Robinson, and S. A. Khan, "Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis," *Journal of Hepatology*, vol. 72, no. 1, pp. 95–103, 2019. 1
- [4] R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer statistics, 2018," *CA: A Cancer Journal for Clinicians*, vol. 68, pp. 7–30, 1 2018. 1
- [5] E. S. Bialecki and A. M. Di Bisceglie, "Diagnosis of hepatocellular carcinoma," *HPB*, vol. 7, no. 1, pp. 26–34, 2005. 1
- [6] American College of Radiology Committee on LI-RADS® (Liver), "Liver Reporting & Data System (LI-RADS)," 2018. 1
- [7] C. Y. Liu, K. F. Chen, and P. J. Chen, "Treatment of liver cancer," *Cold Spring Harbor Perspectives in Medicine*, vol. 5, no. 9, pp. 1–16, 2015. 1
- [8] M. Feng, Y. Pan, R. Kong, and S. Shu, "Therapy of Primary Liver Cancer," *The Innovation*, vol. 1, pp. 1–19, 8 2020. 1
- [9] J. F. Prince, M. A. Van Den Bosch, J. F. Nijsen, M. L. Smits, A. F. Van Den Hoven, S. Nikolakopoulos, F. J. Wessels, R. C. Bruijnen, M. N. Braat, B. A. Zonnenberg, and M. G. Lam, "Efficacy of radioembolization with ^{166}Ho -Microspheres in salvage patients with liver metastases: A phase 2 study," *Journal of Nuclear Medicine*, vol. 59, no. 4, pp. 582–588, 2018. 1, 2, 7
- [10] C. Breedis and G. Young, "The blood supply of neoplasms in the liver.," *The American journal of pathology*, vol. 30, no. 5, pp. 969–977, 1954. 1
- [11] N. Ackermann, W. lien, E. Kondi, and N. Silverman, "The blood supply of experimental liver metastases. I. The distribution of hepatic artery and portal vein blood to "small" and "large" tumours," *Surgery*, no. 66, pp. 1072–1076, 1969. 1
- [12] Quirem Medical, "Workflow of holmium-166 SIRT." 2
- [13] M. Lam, J. Huijbregts, R. Bennink, W. Noordzij, M. Wondergem, J. de Jong, and B. de Keizer, "Radioembolization Treatment for Hepatic Malignancies," tech. rep., 2007. 2
- [14] M. A. Vente, M. Wondergem, I. van der Tweel, M. A. van den Bosch, B. A. Zonnenberg, M. G. Lam, A. D. van het Schip, and J. F. Nijsen, "Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: A structured meta-analysis," *European Radiology*, vol. 19, no. 4, pp. 951–959, 2009. 2

-
- [15] C. G. Radosa, J. C. Radosa, S. Grosche-Schlee, K. Zöphel, V. Plodeck, J. P. Kühn, J. Kotzerke, and R. T. Hoffmann, “Holmium-166 Radioembolization in Hepatocellular Carcinoma: Feasibility and Safety of a New Treatment Option in Clinical Practice,” *Cardio Vascular and Interventional Radiology*, vol. 42, no. 3, pp. 405–412, 2019. 2
 - [16] ‘Zorginstituut Nederland’, “Standpunt holmium-166 radioembolisatie bij inoperabele lever-tumoren,” Tech. Rep. 2013, 2018. 2
 - [17] A. Kennedy, D. Coldwell, B. Sangro, H. Wasan, and R. Salem, “Radioembolization for the treatment of liver tumors: General principles,” *American Journal of Clinical Oncology: Cancer Clinical Trials*, vol. 35, no. 1, pp. 91–99, 2012. 2
 - [18] G. H. Van De Maat, P. R. Seevinck, M. Elschot, M. L. Smits, H. De Leeuw, A. D. Van Het Schip, M. A. Vente, B. A. Zonnenberg, H. W. De Jong, M. G. Lam, M. A. Viergever, M. A. Van Den Bosch, J. F. Nijsen, and C. J. Bakker, “MRI-based biodistribution assessment of holmium-166 poly(L-lactic acid) microspheres after radioembolisation,” *European Radiology*, vol. 23, no. 3, pp. 827–835, 2013. 2, 14, 16, 22
 - [19] J. F. Nijsen, B. A. Zonnenberg, J. R. Woittiez, D. W. Rook, I. A. Swildens-Van Woudenberg, P. P. Van Rijk, and A. D. Van het Schip, “Holmium-166 poly lactic acid microspheres applicable for intra-arterial radionuclide therapy of hepatic malignancies: Effects of preparation and neutron activation techniques,” *European Journal of Nuclear Medicine*, vol. 26, no. 7, pp. 699–704, 1999. 3
 - [20] J. F. Nijsen, J. H. Seppenwoolde, T. Havenith, C. Bos, C. J. Bakker, and A. D. Van Het Schip, “Liver Tumors: MR Imaging of Radioactive Holmium Microspheres - Phantom and Rabbit Study,” *Radiology*, vol. 231, no. 2, pp. 491–499, 2004. 3, 14, 25
 - [21] G. H. Van De Maat, H. De Leeuw, P. R. Seevinck, M. A. Van Den Bosch, J. F. Nijsen, and C. J. Bakker, “Simultaneous R2, R2, and R2* quantification by combining S0 estimation of the free induction decay with a single spin echo: A single acquisition method for R2 insensitive quantification of holmium-166-loaded microspheres,” *Magnetic Resonance in Medicine*, vol. 73, no. 1, pp. 273–283, 2015. 6, 24, 25, 28, 31, 32
 - [22] J. Roosen, “clinicaltrials.gov identifier NCT04269499, Unpublished work,” 2021. 7
 - [23] E. Lin and A. Alessio, “What are the basic concepts of temporal, contrast, and spatial resolution in cardiac CT?,” *Journal of Cardiovascular Computed Tomography*, vol. 3, pp. 403–408, 11 2009. 7
 - [24] J. B. Ayache and J. D. Collins, “MR angiography of the abdomen and pelvis,” *Radiologic Clinics of North America*, vol. 52, no. 4, pp. 839–859, 2014. 7
 - [25] Y. D. Xiao, R. Paudel, J. Liu, C. Ma, Z. S. Zhang, and S. K. Zhou, “MRI contrast agents: Classification and application (Review),” *International Journal of Molecular Medicine*, vol. 38, pp. 1319–1326, 11 2016. 7, 8, 12
 - [26] M. Ibrahim, Hazhirkarzar B, and Dublin AB, *Gadolinium Magnetic Resonance Imaging*. 2021. 8

REFERENCES

- [27] M. Rohrer, H. Bauer, J. Mintorovitch, M. Requardt, and H.-J. Weinmann, "Comparison of Magnetic Properties of MRI Contrast Media Solutions at Different Magnetic Field Strengths," *Investigative Radiology*, vol. 40, no. 11, pp. 715–724, 2005. 8
- [28] B. B. Avants, N. J. Tustison, G. Song, P. A. Cook, A. Klein, and J. C. Gee, "A reproducible evaluation of ANTs similarity metric performance in brain image registration," *NeuroImage*, vol. 54, no. 3, pp. 2033–2044, 2011. 9, 17
- [29] FDA, "DOTAREM (gadoterate meglumine) Injection for intravenous use," pp. 1–13, 2013. 12
- [30] K. S. Nayak, Y. Lim, A. E. Campbell-Washburn, and J. Steeden, "Real-Time Magnetic Resonance Imaging," *Journal of Magnetic Resonance Imaging*, 2020. 12
- [31] E. Garin, L. Tselikas, B. Guiu, J. Chalaye, J. Edeline, T. De Baere, E. Assenat, V. Tacher, C. Robert, M. Terroir-Cassou-Mounat, D. Mariano-Goulart, G. Amaddeo, X. Palard, A. Hollebecque, M. Kafrouni, H. Regnault, K. Boudjema, S. Grimaldi, M. Fourcade, H. Kobeiter, E. Vibert, S. Le Sourd, L. Piron, D. Sommacale, S. Laffont, B. Campillo-Gimenez, Y. Rolland, C. R. Robert, M. Pracht, V. Ardisson, L. Lenoir, F. Deschamps, M. Ducreux, M. Gelli, C. Cassinotto, C. Allimant, S. Bonnot-Lours, M. Marie, E. Itti, L. Lerman, M. Abulizi, A. Luciani, C. E. Costentin, and M. Milliner, "Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial," *The Lancet Gastroenterology and Hepatology*, vol. 6, no. 1, pp. 17–29, 2021. 14
- [32] A. L. Hermann, A. Dieudonné, M. Ronot, M. Sanchez, H. Pereira, G. Chatellier, E. Garin, L. Castera, R. Lebtahi, and V. Vilgrain, "Relationship of tumor radiation-absorbed dose to survival and response in hepatocellular carcinoma treated with transarterial radioembolization with ^{90}Y in the SARAH study," *Radiology*, vol. 296, no. 3, pp. 673–684, 2020. 14
- [33] R. Bastiaannet, C. van Roekel, M. L. Smits, S. G. Elias, W. A. van Amsterdam, D. Doan, J. F. Prince, R. C. Bruijnen, H. W. de Jong, and M. G. Lam, "First Evidence for a Dose-Response Relationship in Patients Treated with ^{166}Ho Radioembolization: A Prospective Study," *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*, vol. 61, no. 4, pp. 608–612, 2020. 14, 23, 24
- [34] J. Roosen, N. J. Klaassen, L. E. Westlund Gotby, C. G. Overduin, M. Verheij, M. W. Konijnenberg, and J. F. W. Nijsen, "To 1000 Gy and back again: a systematic review on dose-response evaluation in selective internal radiation therapy for primary and secondary liver cancer," *European Journal of Nuclear Medicine and Molecular Imaging*, 2021. 14
- [35] M. L. Smits, M. Elschot, M. A. Van Den Bosch, G. H. Van De Maat, A. D. Van Het Schip, B. A. Zonnenberg, P. R. Seevinck, H. M. Verkooijen, C. J. Bakker, H. W. De Jong, M. G. Lam, and J. F. Nijsen, "In vivo dosimetry based on SPECT and MR imaging of ^{166}Ho - microspheres for treatment of liver malignancies," *Journal of Nuclear Medicine*, vol. 54, no. 12, pp. 2093–2100, 2013. 14, 23
- [36] J. H. Seppenwoolde, J. F. Nijsen, L. W. Bartels, S. W. Zielhuis, A. D. Van Het Schip, and C. J. Bakker, "Internal radiation therapy of liver tumors: Qualitative and quantitative magnetic

- resonance imaging of the biodistribution of holmium-loaded microspheres in animal models,” *Magnetic Resonance in Medicine*, vol. 53, no. 1, pp. 76–84, 2005. 14
- [37] P. R. Seevinck, J. H. Seppenwoolde, J. J. Zwanenburg, J. F. Nijsen, and C. J. Bakker, “FID sampling superior to spin-echo sampling for T2*-based quantification of holmium-loaded microspheres: Theory and experiment,” *Magnetic Resonance in Medicine*, vol. 60, no. 6, pp. 1466–1476, 2008. 14
- [38] M. L. Smits, J. F. Nijsen, M. A. Van Den Bosch, M. G. Lam, M. A. Vente, J. E. Huijbregts, A. D. Van Het Schip, M. Elschot, W. Bult, H. W. De Jong, P. C. Meulenhoff, and B. A. Zonnenberg, “Holmium-166 radioembolization for the treatment of patients with liver metastases: Design of the phase I HEPAR trial,” *Journal of Experimental and Clinical Cancer Research*, vol. 29, no. 1, pp. 1–11, 2010. 14
- [39] M. L. Smits, J. F. Nijsen, M. A. van den Bosch, M. G. Lam, M. A. Vente, W. P. Mali, A. D. van Het Schip, and B. A. Zonnenberg, “Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): A phase I, dose-escalation study,” *The Lancet Oncology*, vol. 13, no. 10, pp. 1025–1034, 2012. 14
- [40] Y. Ou, H. Akbari, M. Bilello, X. Da, and C. Davatzikos, “Comparative evaluation of registration algorithms in different brain databases with varying difficulty: Results and insights,” *IEEE Transactions on Medical Imaging*, vol. 33, no. 10, pp. 2039–2065, 2014. 15
- [41] G. H. Van De Maat, P. R. Seevinck, C. Bos, and C. J. Bakker, “Quantification of holmium-166 loaded microspheres: Estimating high local concentrations using a conventional multiple gradient echo sequence with S 0-fitting,” *Journal of Magnetic Resonance Imaging*, vol. 35, no. 6, pp. 1453–1461, 2012. 16
- [42] N. J. Tustison, P. A. Cook, A. J. Holbrook, H. J. Johnson, J. Muschelli, G. A. Devenyi, J. T. Duda, S. R. Das, N. C. Cullen, D. L. Gillen, M. A. Yassa, J. R. Stone, J. C. Gee, and B. B. Avants, “The ANTsX ecosystem for quantitative biological and medical imaging,” *Scientific reports*, vol. 11, no. 1, p. 9068, 2021. 17
- [43] “Python library surface_distance by Deepmind, as downloaded from GitHub through <https://github.com/deepmind/surface-distance>.” 18
- [44] M. Stella, A. J. Braat, M. G. Lam, H. W. de Jong, and R. van Rooij, “Gamma camera characterization at high holmium-166 activity in liver radioembolization,” *EJNMMI Physics*, vol. 8, no. 1, 2021. 23
- [45] C. van Roekel, R. Bastiaannet, M. L. Smits, R. C. Bruijnen, A. J. Braat, H. W. de Jong, S. G. Elias, and M. G. Lam, “Dose-Effect Relationships of holmium-166 Radioembolization in Colorectal Cancer,” *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*, vol. 62, no. 2, pp. 272–279, 2021. 23, 24
- [46] M. I. Altbach, E. K. Outwater, T. P. Trouard, E. A. Krupinski, R. J. Theilmann, A. T. Stopeck, M. Kono, and A. F. Gmitro, “Radial fast spin-echo method for T2-weighted imaging and T2 mapping of the liver,” *Journal of Magnetic Resonance Imaging*, vol. 16, no. 2, pp. 179–189, 2002. 26, 32

REFERENCES

- [47] F. Han and Y. Natsuaki, “Applications Guide Radial TSE with inline T2 Mapping,” 2019. 27, 28, 32
- [48] J. Z. Bojorquez, S. Bricq, C. Acquitte, F. Brunotte, P. M. Walker, and A. Lalande, “What are normal relaxation times of tissues at 3 T?,” *Magnetic Resonance Imaging*, vol. 35, pp. 69–80, 2017. 31, 32
- [49] V. C. Obmann, N. Mertineit, C. Marx, A. Berzigotti, L. Ebner, J. T. Heverhagen, A. Christe, and A. T. Huber, “Liver MR relaxometry at 3T – segmental normal T1 and T2* values in patients without focal or diffuse liver disease and in patients with increased liver fat and elevated liver stiffness,” *Scientific Reports*, vol. 9, no. 1, pp. 1–11, 2019. 32
- [50] M. Schär, E.-J. Vonken, and M. Stuber, “Simultaneous B0- and B1+-map Acquisition for Fast Localized Shim, Frequency and RF Power Determination in the Heart at 3T,” *Magnetic Resonance in Medicine*, vol. 63, no. 2, pp. 419–426, 2010. 33
- [51] R. Song, R. B. Loeffler, J. L. Holtrop, M. B. McCarville, J. S. Hankins, and C. M. Hillenbrand, “Fast quantitative parameter maps without fitting: Integration yields accurate mono-exponential signal decay rates,” *Magnetic Resonance in Medicine*, vol. 79, no. 6, pp. 2978–2985, 2018. 35

APPENDIX A

Additional results for Voxelwise post-processing

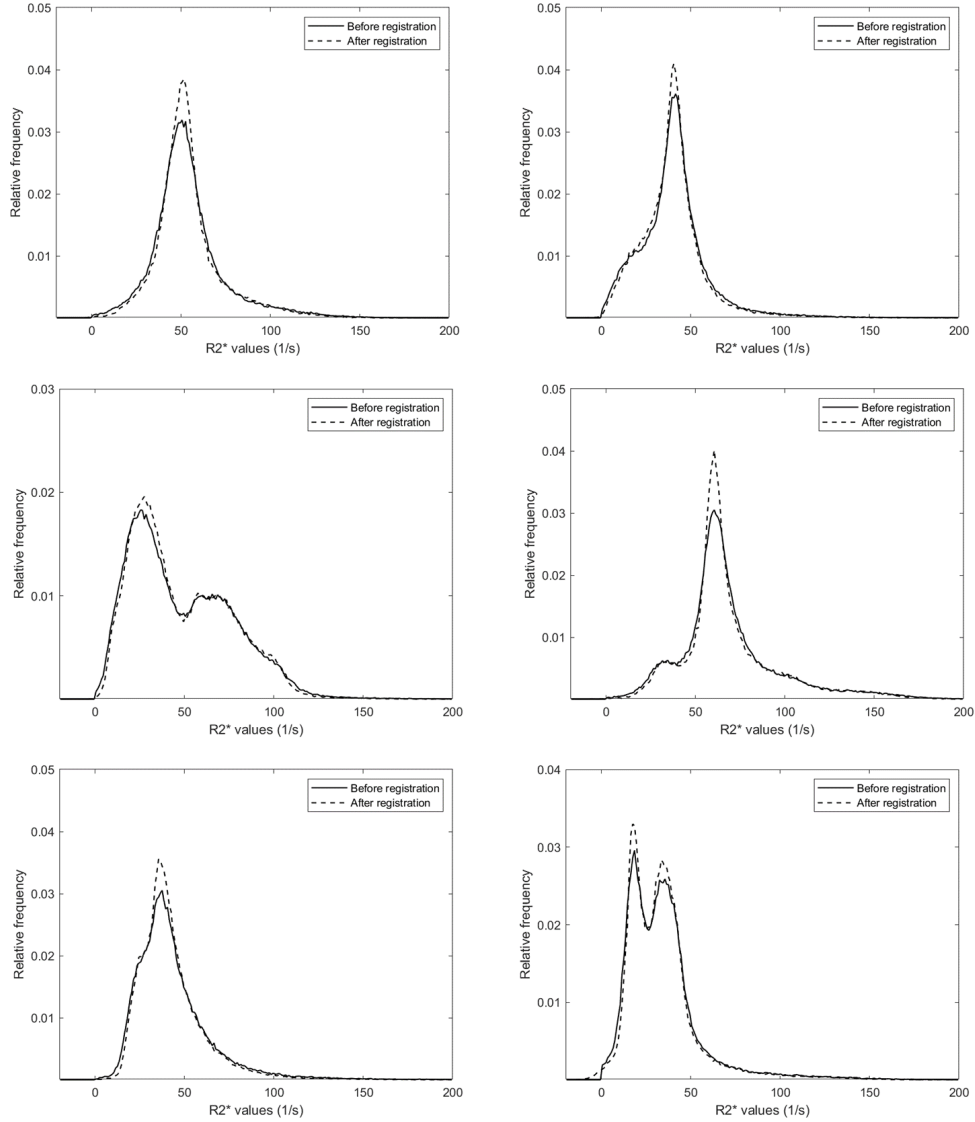


Figure 18: Relative occurrence of $R_{2,pre}^*$ values before and after registration for all patients. After registration there is an increased frequency of the more apparent values, possibly due to the minimal blurring of the registration algorithm.

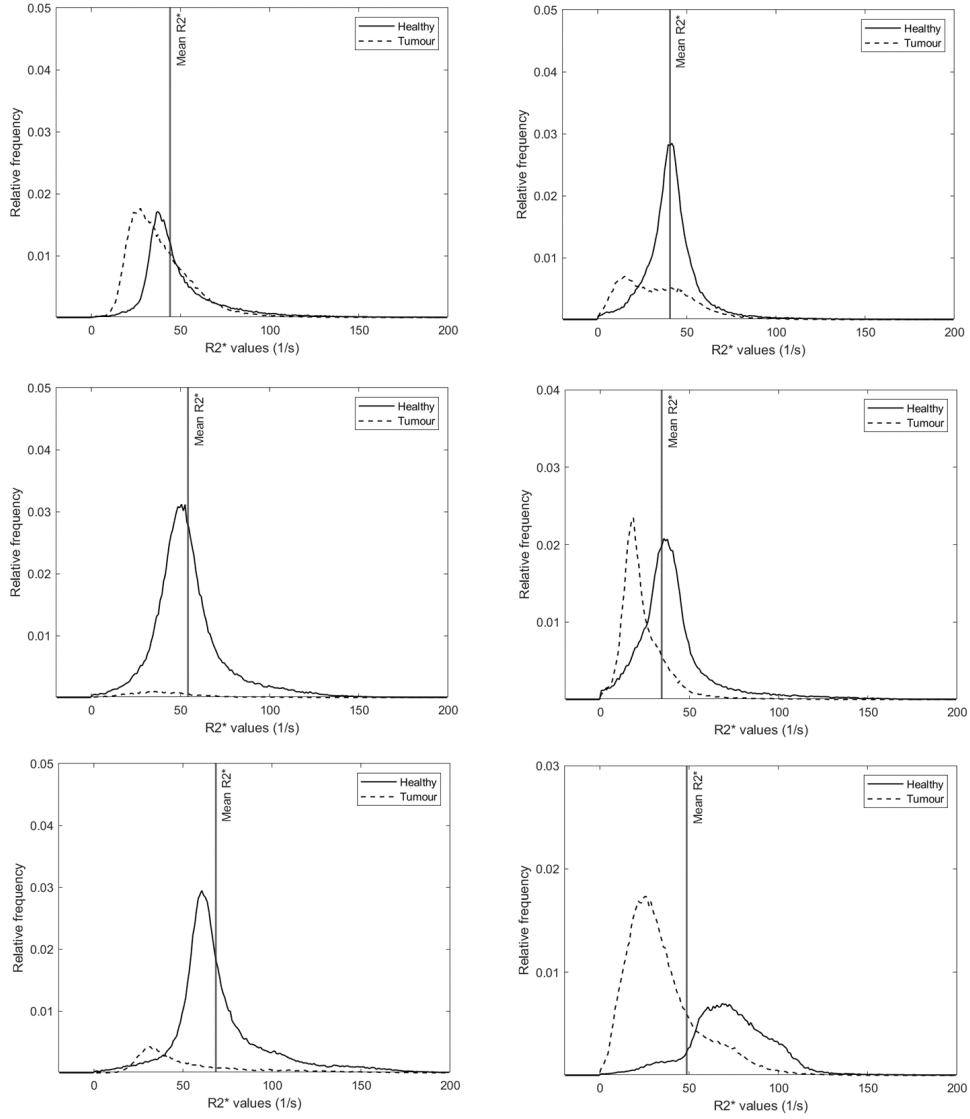


Figure 19: Relative occurrence of $R_{2,pre}^*$ values in tumour and healthy liver tissue for all patients. tumour tissue had a lower R_2^* value in all patient cases. The value used for the mean method was most often more representable for healthy liver tissue values.

Patient $R_{2,pre}^*$	total (s^{-1})	$R_{2,pre}^*$ tumour (s^{-1})	$R_{2,pre}^*$ healthy liver (s^{-1})
001	48.77	35.30	73.75
002	40.58	33.46	42.31
003	44.19	39.26	51.15
004	68.30	54.70	70.62
005	34.47	24.35	41.44
006	54.28	44.40	54.72
Mean	48.43	38.58	55.67

Table 6: Mean R_2^* values for each patient, in all cases healthy liver values were substantially higher than tumour values. The total mean R_2^* value, as used for the mean method was closets to the healthy liver values, except in case 001, due to a high tumour load.

Voxelwise subtraction: from implementation to clinical use

B.1 Introduction

For the goal discussed in the introduction of performing ^{166}Ho radioembolization in an image guided environment, several steps in the current MRI-workflow needed to be optimized. In this thesis, some possible improvements have been shown. One of these improvements has shown to increase the accuracy of the MRI dosimetry, and therefore it was preferable to use this method for the next clinical study. The voxelwise method, which was discussed in Chapter 3, improves the accuracy of the subtraction step of the R_2^* maps, and will be submitted to be published in the near future.

However, the voxelwise subtraction as discussed had only been studied, while in order to apply the method to the next clinical study, the method needed to be implemented in the currently used software for the dose reconstruction. Besides the development of the voxelwise method, the implementation of the method into the Q-suite[®] software was also performed during this graduation internship in cooperation with the Imaging and Software team of Quirem Medical. Because this implementation became a significant part of my graduation internship as well, I would like to discuss the methods of implementing the designed code as used for research to software that can be used during the next clinical study and possibly for other users of the software as well.

B.2 Implementation

The Q-suite[®] software works with MATLAB executables, which are standalone applications that are built within MATLAB, and can be called from any computer, with or without a MATLAB license. The only constraints are that MATLAB runtime in the version that the executive was built in needs to be installed, which is freely available for all institutes. The currently used mean method is such an executable, and the proposed voxelwise method needed to be this as well, to be able to work within the Q-suite[®] software.

The first step of the implementation was to incorporate the different programming languages in a single workflow. As explained in Chapter 3, the data was processed in three steps using two different programming languages. First the data exported by Q-suite[®] was pre-processed in MATLAB, then the required data was used in Python to perform the registration, and lastly the data was post-processed in MATLAB again. The finalized pre-treatment R_2^* map was then imported in Q-suite[®] again. Since Q-suite[®] works with MATLAB executables a base MATLAB code that would call the needed Python code was preferred.

A MATLAB executable was made, in which the code of the pre- and post-processing that was performed in MATLAB was combined. Files needed for the registration were saved in a location defined by the user. Between the pre- and post-processing, a system call was implemented in the executable, to execute the Python registration from the MATLAB executable without interfer-

ence from the user. In this system call, the location of the pre-processing files was passed to the Python code. The registered R_2^* map was stored in the same file location, to be picked up by the MATLAB executable once the registration was finished, in order to perform post-processing. Once all the steps that were presented in Chapter 3 could be executed in a single executable, the executable was altered to be called by the Q-suite® software. An schematic view of the steps that are executed by the built executable can be found in Figure 20.

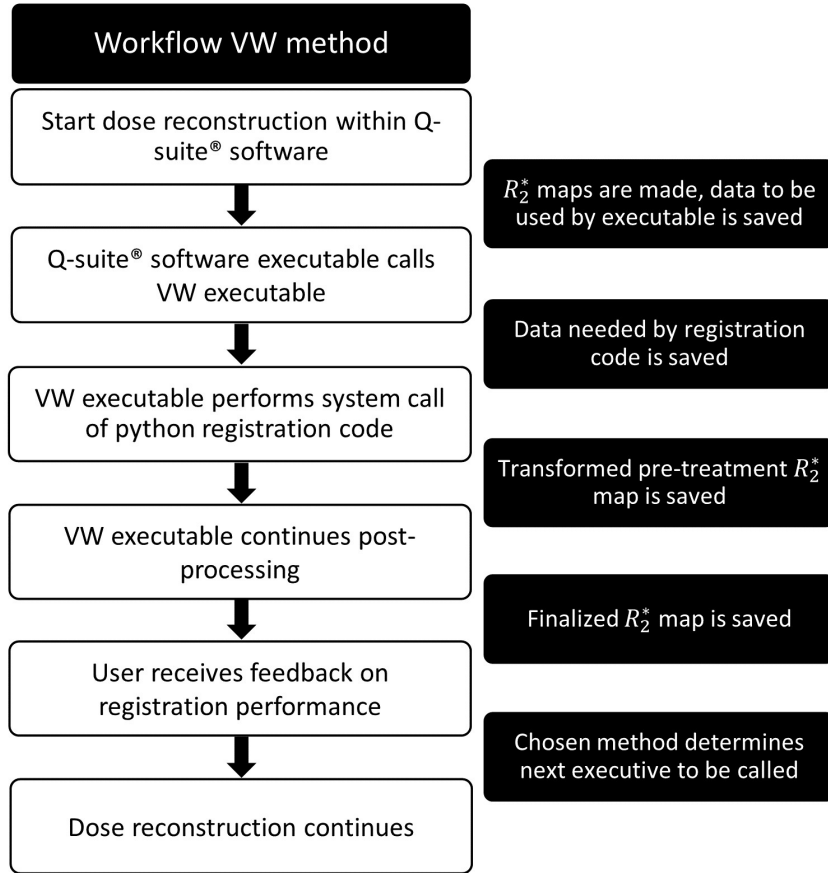


Figure 20: The new workflow of the VW method, as has been implemented in the Q-suite® software to be used during the next clinical study

During the development of the VW method, the registration performance was measured by the DSC, relative overlay and surface DSC, together with a visual inspection. While the patients studied during the development never showed failure of the registration algorithm, a quality check needed to be implemented in order to be sure about performance of the registration. This quality control ended up as a feedback system in which the user of the software gets a pop-up screen with the DSC and the relative overlay score was implemented. On this screen the user then gets to select whether the user wants to continue using the VW method, or if the mean method should be used (if the registration score is insufficient).

B.3 Future improvements

While the currently implemented VW method increases the accuracy of the MR dosimetry while being fast enough to work in an image-guided setting, there are still possible improvements that can be made in the future. For example, while the current registration can be performed in 10-15 seconds, registration algorithms keep on being developed that are able to perform registrations even faster. Furthermore, in the field of artificial intelligence registration algorithms that are learning are being developed as well. Concerning the feedback on the performance of the registration for the user, the DSC and relative overlap is shown to the user. To make the feedback more intuitive, some visual feedback would be favorable as well. This could consist of an image window in which the user could scroll through the pre-treatment unregistered, the registered and the post-treatment images in order to quickly assess the registration.