MRI of pancreatic cancer for radiotherapy
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In radiotherapy, treatment plans are based on tumor delineations. As these treatment plans are used for all radiotherapy sessions, the delineations should be as accurate as possible. Currently, such delineations are often based on computed tomography (CT) images. In chapter 2 it was shown that there is a large interobserver variability in CT-based delineations of pancreatic cancer patients. In chapter 3 the interobserver variability decreased when MRI images were made available during tumor delineation on CT. The interobserver variability may further improve when CT and MRI images are registered, which was not done in chapter 3.

In order to register MRI to CT, it is desirable to have intratumoral fiducial markers that are visible on CT and MRI. The visibility of golden fiducial markers and their potential to cause artifacts was quantified in chapter 4, using a sequence-independent approach. It was shown that at least one of the commercially available marker types was visible in vivo, in a pancreatic cancer patient. However, markers that were visible also caused artifacts, especially on diffusion-weighted imaging (DWI). The artifacts caused by such markers were smaller than artifacts caused by typical biliary stents. As 70% of pancreatic cancer patients receive such biliary stents, the artifacts caused by several metal stents and a plastic stent were quantified in chapter 5.

In chapter 6 an alternative sequence for the T2-weighted turbo spin echo (T2W TSE) was optimized for abdominal use: the alternating repetition time balanced steady state free precession (ATR-SSFP) sequence. Contrary to T2W-TSE, this sequence allowed for isotropic high resolution (1.4 × 1.4 × 1.4 mm³) imaging within one breath-hold.

Despite encouraging results of radiotherapy treatment (neo-)adjuvant to surgery in pancreatic cancer patients, not all tumors respond to radiotherapy. As radiotherapy is a toxic treatment, it is desirable to only treat patients with tumors that are sensitive to radiotherapy. To avoid unnecessary irradiation in patients with non-responding tumors, treatment response monitoring or, ultimately, treatment response prediction is desirable. The intravoxel incoherent motion (IVIM) model for DWI potentially enables this. However, DWI acquisitions for IVIM data are often long and little is known about the optimal acquisition scheme and fitting. Therefore, in chapter 7 the acquisition scheme for DWI that renders the minimum acquisition time necessary for accurate and precise IVIM modeling was determined. In chapter 8 the best fit models and fitting algorithms for DWI data from pancreatic cancer patients were determined.

In chapter 9 (this chapter), the work is contextuallized to a larger perspective. First, the research in addition to the work in chapter 2 and chapter 3 that is required to determine appropriate treatment margins for pancreatic cancer patients is discussed. Then, the work from chapter 4 and chapter 5 is dealt with in the context of how it could be implemented to better understand artifacts. Following this, the
importance of having visible markers and the artifacts caused by metal markers is
discussed. Also, the future of DWI in tumor imaging is discussed in light of the results
from chapter 7 and chapter 8. Furthermore, several 4DMRI techniques that allow
monitoring of tumor positions throughout the respiratory cycle are considered. These
techniques could also be used to generate higher resolution MRI as they are not
limited to a single breath-hold. Finally, MRI-guided radiotherapy is discussed.

Treatment margins
In this thesis the interobserver variation, expressed as standard deviation (SD), of
pancreatic cancer target volume delineation on CT (chapter 2) and CT+MRI (chapter 3)
was assessed. These SDs are often used to determine treatment margins [1, 2]. However,
there are several reasons why the overall observer variation mentioned in chapter 2
and chapter 3 are not ideal for determining treatment margins. For instance, common
margin formulas are based on a normal distribution of errors. In pancreatic cancer,
there were many locations at which delineation errors were not normally distributed.
For example, some observers included a stent or a lymph node in the gross tumor
volume (GTV), and others did not. In these cases, the variation was not Gaussian (i.e.
either included or not included) and a treatment margin will not suffice to incorporate
such errors. These errors were the result of an incomplete delineation protocol and
poor observer compliance [3-5]. Therefore, clearer delineations guidelines should be
introduced to achieve a more precise delineation.

In chapter 3 it was shown that CT+MRI-based delineations often result in smaller
overall SDs than CT-only based delineations. Similar findings were reported for
several other organs too [6-9]. These findings suggest that more precise pancreatic
cancer delineations are achieved when MRI images are available during delineation.
As a result, smaller planning target volume (PTV) treatment margins may be used
when delineations are based on CT+MRI than when they are based on CT.

However, in chapter 3 as well as in other studies in pancreatic [10, 11] and other
tumors [6-8], delineations based (partially) on MRI were smaller than delineations
based on CT. Therefore, it is important to know how well the delineation represents
the tumor size. So far, a study with one observer showed that the tumor size was
underestimated by 4 mm on contrast-enhanced (CE) MRI when compared with
pathology [12]. Such underestimations are a result of microscopic extensions of
the tumor and are commonly incorporated in the clinical target volume (CTV) margin
[13]. To determine appropriate CTV-margins, more elaborate multi-observer studies
are required that compare delineations with pathology. Interestingly, the size of the
delineated tumor is different when delineated on images from different MRI sequences [10]. This suggests that the required CTV margins may be sequence dependent.

**Artifacts**

Metal implants can cause susceptibility artifacts in MRI images. Such artifacts can obscure the underlying pathology or deform the anatomy in the image. In many applications, including radiotherapy, such artifacts are undesired. Therefore, many studies have investigated artifacts caused by patient anatomy [14, 15], fiducial markers [16], stents [17-19] and other implants [20-22]. These studies described the artifacts for one specific sequence. Consequently, their results are often limited to the sequence presented. More generalizable results can be obtained if such artifacts are studied using a sequence independent approach. Such an approach was implemented in chapter 4 and chapter 5. In those chapters, the usefulness of the approach was already illustrated for markers and stents. In a separate study [23], we also verified the applicability of the sequence independent approach for a brachytherapy applicator for cervical cancer.

In this sequence independent approach, the parameters underlying the artifacts, \( \Delta B_0 \) and \( T_2^* \), are deduced from MRI measurements. Alternatively, these quantities can be simulated if the shape and materials of the implants are known [24-27]. Such an approach is very useful for developing new implants.

Once the \( \Delta B_0 \)- and \( T_2^* \)-maps around the implants are obtained either from simulations or measurements, they can be used to simulate artifacts [24-28]. Using this method, one can discriminate the extent to which specific anatomical features are contaminated by artifacts in the real image. Such simulated artifacts are particularly useful when based on \( \Delta B_0 \)- and \( T_2^* \)-maps acquired \textit{in vivo}, in the patient being studied [28]. The data required for such \( \Delta B_0 \)-maps and \( T_2^* \)-maps can be obtained within a 20-second breath-hold. This \textit{in vivo} approach was explored in the supplementary materials from chapter 5.

Finally, there are many ways to reduce artifacts. When a \( \Delta B_0 \)-map is acquired, the artifact can be reverted by applying a transformation which is the inverse of the expected deformation (from the \( \Delta B_0 \)-map) [29-31]. Also matching to a reference image can undo deformations [32]. However, these methods cannot solve signal summation (i.e. signal from multiple voxels shifting to the same voxel). Alternatively, by acquiring multiple images with different read-out directions it becomes possible to undo deformations and signal summation in some cases [33, 34]. Also, the sensitivity of the sequence to such artifacts can be reduced during acquisition [35]. All these
methods, however, have their limitations and often come at the cost of additional scan time. This is especially challenging when scanning the abdomen, where scan duration is restricted by breath-holding.

**Fiducial markers**

In radiotherapy, matching MRI, CT and CBCT is important to ensure accurate treatment. Matching images requires visualization of several landmarks in the patient. In some cases, these landmarks can be anatomical, such as bony anatomy for matches between CT and CBCT [36] or major vessels in matches between MRI and ultrasound [37]. However, the location of several organs (e.g. pancreas [38] and prostate [39, 40]) with respect to the bony anatomy, varies over time. Furthermore, due to the poor soft tissue contrast on CT, and in particular on CBCT, matching other anatomical features, such as major vessels, remains challenging.

Therefore, matching CT/CBCT to different MRI images of such organs requires intratumoral fiducial markers to ensure alignment of the tumor [38, 39, 41]. From chapter 4 it is clear that for golden fiducial markers the visibility is related to the marker’s potential to cause artifacts. Therefore, all gold markers that were visible on MRI in earlier studies [42-45] will probably also cause artifacts on artifact sensitive sequences such as sequences with EPI read-out [16]. Furthermore, it is likely that all markers in which visibility is based on local $T_2^*$ decay, will also cause signal shifting artifacts. As a result, when marker visibility is desired without artifacts, an alternative approach is required.

Alternative markers that are visible on MRI and CT have been proposed, such as hydrogel [46, 47] or a mixture of iodinate contrast agent and water [48]. The hydrogel was tested in vivo in other organs [46, 47]. The iodinate mixture was tested in vitro. Both fit through a 22 gauge needle and hence might be implantable in pancreatic cancer patients [49]. However, many factors still need to be investigated, such as the stability of those gels in vivo.

**Diffusion-weighted imaging**

DWI and other functional imaging, such as dynamic contrast-enhanced (DCE) and $T_2^*$ acquisitions, may help in predicting treatment outcome or enabling treatment monitoring [50, 51]. Correlating MRI parameters, including DWI model parameters, to treatment outcome of neoadjuvant chemoradiotherapy and resection of pancreatic
cancer is being investigated in the MIPA study at the AMC (NCT01989000). Potentially, DWI can be used to determine which patients benefit from neoadjuvant chemoradiotherapy in the future.

Furthermore, DWI and other functional imaging may be used to detect, characterize and map different tumor regions. More aggressive or radiation resistant parts of the tumor could then be selected to receive a higher radiation dose. This approach is called dose painting [52-54]. Dose painting in the pancreas, however, would require sophisticated motion management techniques to prevent the high dose from blurring. Furthermore, a better observer agreement on the tumor location (chapter 2 and chapter 3) should be achieved before dividing the tumor into smaller subsections.

DWI is often obtained at 1.5 T and 3 T [55]. All DWI data presented in this thesis were obtained at 3 T. DWI has low SNR and therefore higher field strengths may improve DWI. However, the echo planar imaging (EPI) read-out associated with DWI is very sensitive to susceptibility artifacts, which are accentuated at higher field strength. Alternatively, read-outs that are less sensitive to artifacts can be used, such as diffusion prepared TSE or bSSFP [56-58]. When used at higher field strengths, such sequences benefit from added SNR without the drawback of artifacts. We illustrated the feasibility of a diffusion prepared stimulated TSE sequence in the prostate [59]. Alternatively, a diffusion-weighted steady state sequence could be used [60, 61]. The challenge that comes with the application of the sequences mentioned above for abdominal use is their strong sensitivity to motion combined with acquisitions much longer than a breath-hold (typically > 5 minutes).

Competing models

Before performing treatment monitoring or dose painting, one needs to select a DWI model. Depending on the purpose, several factors should be considered when selecting a model. E.g., when depicting tumors is the goal, the model with largest tumor contrast is desired, whereas when treatment response monitoring is the goal, a model with good test-retest stability is desired. Currently, the monoexponential decay model and IVIM model are most popular for abdominal DWI [55, 62-65]. There are many competing DWI models and therefore, in chapter 8 their performances were compared.

Classically, DWI data is modelled as a monoexponential decay as a function of diffusion weighting, in which the exponent is the apparent diffusion coefficient. The IVIM model describes the signal decay as a biexponential decay as a function of diffusion weighting. One exponent is assumed to relate to diffusion in tissue and
The non-monoexponential behavior of DWI data was illustrated in multiple studies and related to perfusion [67, 68]. In the triexponential model, blood from large vessels is also modeled. Another alternative model is the stretched exponent model [69]. This model is a data-driven model with no thorough physical model behind it, and hence the parameters have no straight forward physical meaning.

In chapter 8 it was shown that for DWI of pancreatic cancer, the IVIM, stretched exponent and triexponential models performed best of the seven models tested. In other research [70, 71] we illustrated the necessity of a triexponential model to accurately relate model parameters to kidney function. Also, it was shown for multiple organs that the stretched exponent model was more precise [72, 73], more sensitive to treatment response [74] or better at tumor classification [75] than the monoexponential and IVIM models. The fact that different models describe the data better in different organs and for different applications illustrates that the underlying mechanism of diffusion is not yet fully understood.

We believe that part of the discrepancy between the IVIM model and the data is due to incoherent bulk motion (e.g. blood in large vessels flowing at different speeds). Such bulk motion would cause additional signal decay, which in the exponential model approach necessitates a third exponent. Signal decay from incoherent bulk motion can be eliminated by using motion compensated diffusion gradients [76]. This way, the data decay should follow a more biexponential shape. However, whether this approach would be clinically beneficial is doubtful. The approach would eliminate part of the signal related to the ultra-fast signal decay in the triexponential model. We found that the parameter related to this ultra-fast signal decay showed the largest contrast between pancreatic cancer and healthy pancreatic tissue (chapter 8) in one study and correlated with kidney perfusion in another study [71].

Faster acquisitions

Acquiring data for IVIM modelling costs time, as data from several diffusion-weighted are required. Therefore, in chapter 7, we investigated the shortest acquisition scheme available to obtain data that allowed for accurate and precise IVIM model fitting. In this chapter, data from healthy volunteers was used. To see if this also holds true in patient data, we simulated the optimal accelerated acquisition scheme from chapter 7 in our patient data from chapter 8 by removing the redundant data. This accelerated acquisition had a within subject coefficient of variation that was less than 20% higher than the full acquisition for all parameters from the IVIM model. As an increase of the within subject coefficient of variation of less than 20% was the criteria
for the accelerated acquisition in chapter 7 we can conclude that the scheme holds in patients.

4DMRI and high resolution

In radiotherapy, it is desirable to know the location of the tumor throughout the respiratory cycle. Therefore, for abdominal tumors, a 4DCT is often obtained on which the tumor motion can be tracked and included in the GTV. For example, in chapter 2 and chapter 3 radiation oncologists delineated the tumor on 4DCTs. A 4DCT consists of several sets (typically 10) of CT images, each representing a part of the respiratory cycle. Tumor visibility is often poor on such CTs. As MRI has stronger tumor contrast, a similar MRI (4DMRI) could help improve tracking tumor motion over the respiratory cycle. There are several approaches to generate such a 4DMRI.

A straightforward implementation is by obtaining fast 2D slice images, for example by a single shot TSE or EPI acquisition, during free breathing. If each slice acquisition is interleaved with a navigator acquisition tracking the liver dome, the respiratory cycle can be monitored. The 2D slice images can be sorted retrospectively according to respiratory phase. We showed the feasibility of this approach for pancreatic imaging [77]. This approach was relatively simple and robust; however, several limitations were associated with it. The acquisition was limited to 2D acquisitions, which resulted in a small number of thick slices. This is undesirable when delineating tumors in radiotherapy. Furthermore, the acquisitions were long (approximately 7 minutes). Also, the reconstruction often missed data for certain slice-respiratory phase combinations. In a variation to this approach, acquisitions are triggered at certain

![Figure 9.1](image-url). A frame of a 4DMRI from a pancreatic cancer patient obtained with ATR-bSSFP (a). MRI was obtained using the tiny golden-angle radial stack of stars ATR-bSSFP acquisition. A 3D CE T1-weighted gradient echo image is added as reference (b). Solid arrow indicates solid tumor region whereas the dotted arrow indicates cysts/necrotic region.
respiratory phases to ensure data completeness [78, 79]. However, the prospective nature of that approach requires determining the amplitude of the respiratory cycle at an early stage during acquisition. This makes the prospective method more sensitive to irregular breathing. Furthermore, these acquisitions were reported to last up to 18 minutes.

Alternatively, a 4DMRI acquisition can be achieved with a tiny golden angle [80, 81] radial stack of stars gradient echo acquisition, obtained during free breathing. The respiratory signal can then be obtained from the center of k-space for each stack of k-lines at a given angle. The respiratory signal can be used to sort the k-space data in different respiratory phases. This allows reconstructing high-resolution 3D images (instead of multiple 2D slices) for every respiratory phase [82]. Furthermore, by using a compressed sensing reconstruction [83] the acquisition can be accelerated to obtain 4DMRI to within a minute [84]. This approach can be applied to most gradient echo sequences and therefore allows for a variety of contrasts. As an extension of the work discussed in chapter 6, we applied this 4DMRI technique to the ATR-SSFP sequence to obtain high-resolution 4D ATR-SSFP images (Fig. 9.1) [85]. Furthermore, we are working on a similar approach to generate 4D T2*-maps to quantify T2* values in abdominal lymph nodes. In such an application, acquiring images during breath-holding does not allow for sufficient resolution to discern the lymph nodes. These k-space sorting techniques can be extended further to generate MRI from all respiratory and cardiac phases [86].

Future technologies

MRI-guided radiotherapy
The recent development of several radiotherapy treatment systems with integrated MRI [87-90] enabled MRI-guided radiotherapy (MR-IGRT). Currently, the only commercially available and clinically released MR-IGRT system is the MRIdian system (ViewRay, Oakwood Village, USA) [87]. This system uses a 0.35 T MRI combined with three Cobalt–60 irradiation units perpendicular to the main magnetic field. A major point of criticism on this system was the use of Cobalt sources instead of a linear accelerator. However, a linear accelerator (linac) module upgrade of this system recently received CE mark approval.

There are three alternative systems that all use a 6 MV linac but are not yet clinically released: the MR-Linac (1.5 T) [88], MRI-Linac (1.0 T) [89] and Linac-MR (0.5 T) [90]. The MR-IGRT systems with higher field strengths should enable more flexible
imaging. However, when a magnetic field is present, the secondary electrons that are created during irradiation will have different paths due to the Lorentz forces than when no magnetic field is present. This effect is magnetic field strength dependent and therefore is stronger for the MR-Linac (1.5 T) than the Viewray (0.35 T) [91].

MR-IGRT allows patient alignment based on MRI images, in which soft tissue is clearly visible. Furthermore, MR-IGRT systems can obtain fast 2D images for 2D tracking/gating of the tumor during irradiation [92]. Additionally, MR-IGRT systems can acquire 4DMRI before treatment [77, 82, 85]. When continuously interleaving the acquisition of two perpendicular oriented 2D images continuously during treatment, the 4DMRI can be used as a model to enable 3D tumor tracking [93].

With the introduction of MR-IGRT, the added value of intratumoral fiducial markers will become debatable. MRI images allow for soft tissue matches, making markers potentially redundant. However, we believe that if markers are visible on MRI, they could still serve for several purposes in such systems. During radiotherapy treatment, it is unlikely that daily (typically 30 days) intravenous CE MRI will be obtained due to patient discomfort (due to intravenous infusion) and associated costs. Some tumors may be poorly visible on other sequences. Therefore, soft tissue matches may be based on several landmarks close to the tumor. It was shown that landmarks such as biliary stents or bony anatomy do not necessary correlate to tumor position due to deformations between both acquisitions [38, 41]. Therefore, intratumoral markers may help to align patients or to verify soft tissue registrations.

Then again, one might argue that with markers visible on MRI, CT and CBCT, there is limited added value in introducing an expensive MR-IGRT system compared to a conventional linac. To align patients, intratumoral markers can be used for conventional linacs. Furthermore, the markers can be utilized for 2D tracking of the tumor [94]. Moreover, 3D tracking of fiducial markers can be achieved by linacs with two integrated X-ray tubes at an angle to each other, such as in the Vero [95, 96]. The 3D position of the marker is then found by triangulation. For conventional linacs 3D tracking can be achieved using a combination of triangulation and/or digital tomosynthesis. We already illustrated the feasibility of tracking bony anatomy in 3D during treatment for this approach [97, 98].

Despite the possibilities of conventional linacs and markers, there are some clear advantages of MR-IGRT systems over conventional linacs. MR-IGRT may not require implanting of fiducial markers in the future. This would reduce the related work load and increase patient comfort. Also, contrary to the MR-IGRT, the conventional linac will require several CBCTs during treatment. These CBCTs cause additional radiation exposure for a large region of the patient. Finally, one of the major advantages of MR-IGRT, compared to a conventional IGRT, is that for several tumors, MR-IGRT provides
sufficient soft tissue contrast and tumor visibility to see organs at risk (OARs) and tumor prior to and during treatment. This enables daily replanning [99-101] or real-time replanning during irradiation of such tumors, which can increase the irradiation dose for the tumor and decrease dose for OARs and other healthy tissue. This is particularly interesting for tumors in a deformable anatomy and for tumors that change shape during treatment.
CHAPTER 9

References


