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4D magnetic resonance imaging applications towards MR-guided proton therapy of pancreatic cancer

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Erklärung

Ich erkläre hiermit, dass ich die vorgelegte Dissertation selbst verfasst und mich dabei keiner anderen als der von mir ausdrücklich bezeichneten Quellen und Hilfen bedient habe.

Heidelberg, den 13.05.2019

Kai Dolde

4D magnetic resonance imaging applications towards MR-guided proton therapy of pancreatic cancer

Abdominal organ motion compromises the targeting accuracy of proton therapy of pancreatic cancer. Time-resolved volumetric magnetic resonance imaging (4D-MRI) is a promising technology to visualize organ motion and deformation while providing a high soft-tissue contrast and avoiding additional imaging doses. The aim of this thesis is to quantify motion-induced impacts on dosimetry, based on 4D-MRI, and to determine suitable strategies to improve the treatments.

For this purpose, a method was developed that utilizes repeated 4D-MRI measurements to analyze motion-induced impacts on dosimetry along the treatment course in proton therapy. The clinical impact of organ motion was evaluated in a patient cohort by statistical analyses. Moreover, counter-strategies to mitigate the motion-induced dosimetric impacts were investigated using abdominal corsets or beam-gating.

Fractionation helps to reduce the motion-induced tumor underdosage substantially. However, especially for patients with large motion amplitudes, further motion mitigation may be required. Physical compression by abdominal corsets and beam-gating with certain pre-selected gating criteria showed high potential to improve the dose distributions.

The developed method allows an effective evaluation of the motion-induced dosimetric uncertainties and is applicable in both pre-treatment and prospective real-time MR-guided proton therapy scenarios with online MR imaging during irradiation.

This cumulative dissertation comprises six peer-reviewed publications.

Anwendungen von 4D-Magnetresonanztomographie auf dem Weg zur MR-geführten Protonentherapie von Bauchspeicheldrüsenkrebs

Abdominelle Organbewegung beeinträchtigt die Bestrahlungsgenauigkeit in der Protonentherapie von Patienten mit Bauchspeicheldrüsenkrebs. Zeitaufgelöste volumetrische Magnetresonanztomographie (4D-MRT) ist eine neuartige Bildgebungsmodalität, die es ermöglicht, Organbewegungen und Deformationen mit hohem Weichgewebekontrast darzustellen, ohne die Patienten zusätzlicher ionisierender Strahlung auszusetzen. Ziel dieser Dissertation ist es, mittels 4D-MRT den Einfluss von Organbewegung während der Bestrahlung auf die resultierende Dosisverteilung zu quantifizieren und geeignete Möglichkeiten zur Bewegungsreduktions zu ermitteln.
Dazu wurde eine Methode entwickelt, die es ermöglicht, basierend auf 4D-MRT Messungen, die dosimetrische Auswirkung von Organbewegung während der Protonentherapie zu quantifizieren. Anhand von Patientendaten wurden derartige Auswirkungen auf klinisch relevante Größen statistisch analysiert. Zudem wurden verschiedene Möglichkeiten zur effektiven Bewegungsreduktion mittels abdomineller Korsetts oder Gating-Strategien, in denen nur während bestimmter Atmungsphasen bestrahlt wird, untersucht.
Während für einige Patienten der resultierenden Unterdosierung im Tumor mittels Fraktionierung entgegengewirkt werden konnte, zeigte sich, dass vor allem für Patienten mit großen Organbewegungsamplituden weitere Bewegungskompensationsmaßnahmen notwendig sind. Abdominelle Korsetts zur physischen Bewegungsreduktion, aber auch Gating-Strategien stellten sich dabei als vielversprechende Ansätze heraus um die Dosisverteilungen zu optimieren.
Die entwickelte Methode ermöglicht eine effektive Analyse der bewegungsinduzierten dosimetrischen Unsicherheiten und kann auch in zukünftiger MR-geführter Protonentherapie mit Echtzeit MRT-Bildgebung angewendet werden.

Dieser kumulativen Dissertation liegen sechs Publikationen zu Grunde, die von Experten begutachtet und in Fachzeitschriften veröffentlicht wurden.

Contents

List of Publications

Peer-reviewed Publications

(I)
Dolde K, Dávid C, Echner G, Floca R, Hentschke C, Maier F, Niebuhr N, Ohmstedt K, Saito N, Alimusaj M, Fluegel B, Naumann P, Dreher C, Freitag M, Pfaffenberger A. *4DMRI-based analysis of inter- and intrafractional pancreas motion and deformation with different immobilization devices.* Biomedical Physics and Engineering Express (2019); 5, 025012. doi: 10.1088/2057-1976/aaf9ae.

(II)
Dolde K, Naumann P, Dávid C, Gnirs R, Kachelrieß M, Lomax AJ, Saito N, Weber DC, Pfaffenberger A, Zhang Y. *4D dose calculation for pencil beam scanning proton therapy of pancreatic cancer using repeated 4DMRI datasets.* Physics in Medicine and Biology (2018); 63,165005. doi: 10.1088/1361-6560/aad43f.
(selected for inclusion in the *PMB 2018 Highlights collection*)

(III)
Dolde K, Zhang Y, Chaudhri N, Dávid C, Kachelrieß M, Lomax AJ, Naumann P, Saito N, Weber DC, Pfaffenberger A. *4DMRI-based investigation on the interplay effect for pencil beam scanning proton therapy of pancreatic cancer patients.* Radiation Oncology (2019); 14:30. doi: 10.1186/s13014-019-1231-2.

(IV)
Dolde K, Naumann P, Dávid C, Kachelrieß M, Lomax AJ, Weber DC, Saito N, Burigo LN, Pfaffenberger A, Zhang Y. *Comparing the effectiveness and effciency of various gating approaches for PBS proton therapy of pancreatic cancer using 4DMRI datasets.* Physics in Medicine and Biology (2019); 64,085011. doi: 10.1088/1361-6560/ab1175.

(V)
Dolde K, Schneider S, Stefanowicz S, Alimusaj M, Flügel B, Saito N, Troost EGC, Pfaf-

fenberger A, Hoffmann AL. *Comparison of pancreatic respiratory motion management with three abdominal corsets for particle radiation therapy.* Journal of Applied Clinical Medical Physics (2019); xx:x,1-9 (in press). doi: 10.1002/acm2.12613.

(VI)
Schneider S, Dolde K, Engler J, Hoffmann A, Pfaffenberger A. *Commissioning of a 4D MRI phantom for use in MR-guided radiotherapy.* Medical Physics (2019); 46(1):25-33. doi: 10.1002/mp.13261.

Conference Contributions

2019

Dolde K, Naumann P, Dávid C, Kachelrieß M, Lomax AJ, Weber DC, Saito N, Burigo LN, Pfaffenberger A, Zhang Y. **Poster:** *4DMRI-based investigation of the effectiveness of different gating approaches for pencil-beam scanning proton therapy of pancreatic cancer.* 58th annual conference of the Particle Therapy Co-Operative Group (PTCOG), June, 2019, Manchester/United Kingdom.

Dolde K, Dávid C, Echner G, Floca R, Hentschke C, Niebuhr N, Ohmstedt K, Saito N, Alimusaj M, Flügel B, Pfaffenberger A. **Poster:** *4DMRI-based abdominal corset study for radiotherapy purposes.* 27th annual conference of the International Society for Magnetic Resonance in Medicine (ISMRM), May 2019, Montreal/Canada.

Dolde K, Zhang Y, Chaudhri N, Dávid C, Kachelrieß M, Lomax AJ, Naumann P, Saito N, Weber DC, Pfaffenberger A. **Talk:** *Dependency of the interplay effect on the fractionation for proton therapy of pancreatic cancer.* 38th annual conference of the European Society for Radiotherapy and Oncology (ESTRO), April 2019, Milano/Italy.

Schneider S, Dolde K, Alimusaj M, Fluegel B, Saito N, Hoffmann A, Pfaffenberger A. **Poster:** *Comparison of pancreatic respiratory motion using three abdominal corsets for particle therapy.* 38th annual conference of the European Society for Radiotherapy and Oncology (ESTRO), April 2019, Milano/Italy.

2018

Dolde K, Zhang Y, Naumann P, Weber CD, Lomax AJ, Saito N, Pfaffenberger A. **Poster:** *4DMRI-based 4D dose calculation for MR-guided proton therapy of pancreatic cancer.* 3rd

Heidelberg Symposium on Novel Techniques in Ion Beam Radiotherapy, October 2018, Heidelberg/Germany.

Schneider S, Dolde K, Engler J, Hoffmann A, Pfaffenberger A. **Poster:** *Charakterisierung der MR-Relaxations- und Bewegungseigenschaften eines 4D MRT Phantoms im Rahmen der Kommissionierung an einem 3T MR Scanner.* 49. Jahrestagung der Deutschen Gesellschaft für Medizinische Physik (DGMP), September 2018, Nürnberg/Germany.

Homolka N, Niebuhr N, Dolde K, Pfaffenberger A. **Talk:** *Vermessung von MRT Verzerrungen über das komplette FOV mit dem ACR Phantom für die MR geführte Strahlentherapie.* 49. Jahrestagung der Deutschen Gesellschaft für Medizinische Physik (DGMP), September 2018, Nürnberg/Germany.

Sepúlveda Munoz CA, Dolde K, Burigo L, Saito N, Pfaffenberger A, Sanchez-Nieto B. **Poster:** *Feasibility study: use of cine-MRI for MRgPT.* 49. Jahrestagung der Deutschen Gesellschaft für Medizinische Physik (DGMP), September 2018, Nürnberg/Germany.

Dolde K, Zhang Y, Naumann P, Weber CD, Lomax AJ, Saito N, Pfaffenberger A. **Poster:** *4DMRI-based 4D dose calculation for MR-guided proton therapy of pancreatic cancer.* 6th MR in RT Symposium (Magnetic Resonance in Radiation Therapy), July 2018, Utrecht/Netherlands.

Dolde K, Schneider S, Pfaffenberger A, Hoffmann A. **Poster:** *3D motion validation with clinically used cine-MRI and an MR-LINAC phantom.* 37th annual conference of the European Society for Radiotherapy and Oncology (ESTRO), April 2018, Barcelona/Spain.

Dolde K, Zhang Y, Naumann P, Weber CD, Lomax AJ, Saito N, Pfaffenberger A. **Talk:** *4D dose evaluation for PBS proton treatment of pancreatic cancer using repeated 4DMRI datasets.* 57th annual conference of the Particle Therapy Co-Operative Group (PTCOG), May 2018, Cincinnati/USA.

2017

Dolde K, Maier F, Naumann P, Gnirs R, Saito N, Pfaffenberger A. **Talk:** *Motion extraction from 4D-MRI for MR-guided particle therapy of pancreatic cancer.* Dreiländertagung der Medizinischen Physik, September 2017, Dresden/Germany.

Dolde K, Maier F, Freitag MT, Naumann P, Saito N, Pfaffenberger A. **Poster:** *Contrast optimization in 4D-MRI as an essential step towards MR-guided particle therapy of pancreatic cancer.* 56th annual conference of the Particle Therapy Co-Operative Group (PTCOG), May 2017, Yokohama/Japan.

2016

Dolde K, Batista V, Maier F, Freitag MT, Naumann P, Pfaffenberger A, Saito N. **Poster:** *Optimization of 4D-MRI parameters for motion extraction in pancreas 4D treatment planning.* 4D treatment planning workshop, December 2016, Groningen/Netherlands.

Awards

12/2018 *Roland-Ernst-Preis* for interdisciplinary research in the area of radiology and interdisciplinary work on infrastructural projects

10/2018 *Poster award*, 3rd Heidelberg Symposium on Novel Techniques in Ion Beam Radiotherapy 2018, Heidelberg/Germany

11/2017 *Best presentation award* by Helmholtz International Graduate School for Cancer Research

Travel Grants

2019/02 *Educational stipend* by International Society for Magnetic Resonance in Medicine (ISMRM) for ISMRM conference in Montréal/Canada

2018/05 *Travel Fellowship* by Particle Therapy Co-Operative Group (PTCOG) for PTCOG conference in Cincinnati/USA

2018/04 *Travel Grant* by "Verein zur Förderung der Tumortherapie mit schweren Ionen e.V." for research stay at Paul-Scherrer-Institute (PSI), Villigen/Switzerland

2018/04 *Travel Grant* by Helmholtz International Graduated School for Cancer Research for research stay at Paul-Scherrer-Institute (PSI), Villigen/Switzerland

2017/10 *Mobility Grant* by European Society for Radiotherapy and Oncology (ESTRO) for research stay at Paul-Scherrer-Institute (PSI), Villigen/Switzerland

List of Abbreviations

CT	Computed tomography
CTV	Clinicial target volume
DNA	Deoxyribonucleic acid
DVF	Deformation vector field
HIT	Heidelberg Ion-Beam Therapy Center
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
LINAC	Linear accelerator
MRgPT	MR-guided proton therapy
MRgRT	MR-guided radiation therapy
MRI	Magnetic resonance imaging
OAR	Organ at risk
PET	Positron emission tomography
SOBP	Spread-out Bragg peak
SPECT	Single photon emission computed tomography
US	Ultrasonography

1. Introduction

If you can't see it, you can't hit it.
And if you can't hit it, you can't cure it! [1]
Harold Johns (1915-1988), Canda
Medical Physicist

1.1 Radiation Therapy

Radiation therapy utilizes ionizing radiation to cause damage to cancerous cells. This is mainly achieved by means of induced double-strand breaks in the DNA along the tracks of ionizing radiation, which may finally lead to cell deaths or prevent further tumor growth [2].
The discovery of X-rays by Wilhelm Conrad Röntgen in 1895 [3] set the basis for the development of radiation therapy. Since then, huge scientific progress gradually improved the delivery and treatment techniques to allow more precise and effective patient treatments with improved survival rates [4]. Nowadays, in most of the cases, external photon irradiation is used to deliver a prescribed amount of dose (energy per mass) to the tumor while at the same time trying to spare healthy tissues in the beam path. In photon therapy, these combined goals are usually achieved by irradiation from multiple angles and shaped irradiation fields with modulated intensities of the photon beams, so-called intensity-modulated radiation therapy (IMRT) [5]. It allows a highly localized dose in the tumor while keeping the undesired dose to organs at risk (OAR) at a low toxicity level.
The depth-dose profile of X-rays shows its maximum a few centimeters after the X-rays enter the patient's body. By means of electromagnetic interactions, the X-rays get exponentially attenuated. Consequently, the delivered dose decreases with increasing depth. This can lead to considerable dose depositions in the OARs, located in front of and behind the tumor, see Figure 1.1, which may induce to undesired side effects to the patients.

Novel radiation therapy techniques like particle therapy with proton or ion beams, however, show huge potential to reduce these undesired dose depositions in healthy tissues. In particular, first promising results have been reported with respect to treatment outcomes after particle therapy of pancreatic cancer [6–9]. The depth-dose curve of such particles is determined by the stopping power, i.e., the energy loss $\mathrm{d}E$ per distance $\mathrm{d}x$, given by the famous Bethe formula [10]. The shape of the depth-dose curve of charged particles is characterized by a low entrance dose due to the high initial velocity of particles. While the particles slow down, they undergo more interactions which leads to an increasing energy loss $\mathrm{d}E$ per distance $\mathrm{d}x$. Consequently, the stopping power strongly increases towards the maximum particle range (which is determined by the initial kinetic energy) and results in a highly localized *Bragg-peak* with a maximum dose deposition, see Figure 1.1.
Due to the different positions of the maximum dose depositions in photon therapy (maximum near the entrance) and particle therapy (maximum at the penetrating range of the particles, determined by the initial kinetic energy), the depth-dose curve of particles is often referred to as an *inverse dose profile*, compared to the photon dose profile. This inverse dose profile allows a better sparing of healthy tissues in particle therapy, compared to photon irradiation. By combinations of multiple particle beams with different energies and intensities, a spread-out Bragg peak (SOBP) can be obtained, that covers the entire tumor depth.

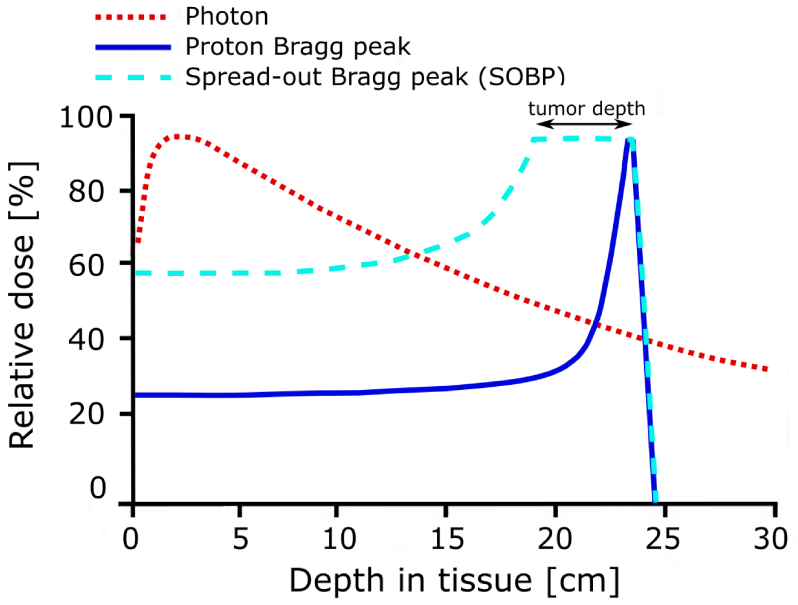

Figure 1.1: Schematic depth-dose curves of photons and protons, adapted from [11].

For pancreatic cancer, which is one of the most severe types of cancer with a mean 5-year survival rate of only 5-20% [12, 13], toxicity of OARs is a considerable challenge for radiation therapy. Since the pancreas is surrounded by many adjacent OARs such as stom-

ach, bowel, duodenum and the kidneys, particle therapy is considered a potentially more effective treatment than photon therapy by exploiting the Bragg-peak characteristics [14].

Being an abdominal organ, however, the pancreas is exposed to respiration-induced motion and pancreatic tumors are likely to move during every breathing cycle due to the close vicinity to the diaphragm. Such abdominal organ motion counteracts the precision of charged particle irradiation and may lead to significant range uncertainties with the risk of over- and undershooting of the target [15].
Moreover, particle irradiation beams are usually delivered using pencil-beam scanning techniques, where the tumor is raster-scanned by a narrow particle beam that is moved over the entire tumor volume [16]. Consequently, in presence of respiratory motion, a so-called *interplay effect* occurs between the motion of the scanning beam and the moving tumor [17] which may lead to undesired pronounced dose heterogeneity and dosimetric hot and cold spots in the target volume. Due to the highly localized dose deposition in the Bragg peak, abdominal organ motion has a more severe impact in particle therapy than in X-ray therapy, as in the latter, the rather smooth depth-dose curves are less susceptible to anatomical changes.
In order to fully exploit the potential of particle therapy and to achieve a homogeneous conformal dose deposition in the tumor with sufficient tumor coverage, organ motion and its resulting dosimetric impact need to be quantified and taken into account in the process of treatment planning. For such purposes, both the tumor localization and its motion patterns need to be known. This requires (time-resolved) medical imaging techniques and consecutive image-guided radiation therapy (IGRT).

1.2 Imaging in Radiation Therapy

1.2.1 Overview

Different medical imaging technologies exist that are used for diagnosis, tumor staging and treatment planning purposes. They can be divided into anatomical modalities, such as computed tomography (CT), magnetic resonance imaging (MRI) or ultrasonography (US), which yield information on the patients' anatomy, and physiological imaging modalities such as positron emission tomography (PET) or single photon emission computed tomography (SPECT) that provide information on the functionality of certain mechanisms in the human body.
Computed tomography (CT) utilizes X-ray radiation to visualize the attenuation properties of different tissue materials and provides anatomical images from which the resulting

CT Hounsfield Units (HU) can be directly converted into electron densities for radiation treatment planning purposes. CT imaging has the advantage of being a fast and geometrically accuracte imaging modality. However, it comes along with additional dose exposure to the patients and suffers from low soft-tissue contrast, which is especially unfavourable in the abdominal region.
In contrary, magnetic resonance imaging (MRI), which makes use of quantum mechanical spin properties of mainly protons in external magnetic fields, does not involve any additional dose deposition by ionizing irradiation and additionally provides a high soft-tissue contrast [18, 19].
As this thesis focuses on MRI applications for radiation therapy purposes, a short introduction to MRI is presented in the following.

1.2.2 Magnetic Resonance Imaging

If an object or patient is placed in an external static magnetic field $\vec{B_0}$, the number of proton spins oriented parallel or anti-parallel to $\vec{B_0}$ is unequal, with the difference being determined by the Boltzmann statistics. This results in a macroscopic net magnetization $\vec{M_0}$, that is oriented parallel to $\vec{B_0}$, conventionally defined as the z-direction. By means of transmitted radiofrequency (RF) pulses with an appropriate frequency close to the Larmor frequency $\omega_0 = \gamma \cdot B_0$, where γ denotes the gyromagnetic ratio, $\vec{M_0}$ can be flipped by a flipping angle α due to spin resonance effects. This leads to a reduced longitudinal magnetization component M_z in z-direction, and an increased magnetization component M_{xy} in the xy-plane.

The contrast in MR images is determined by the tissue-specific relaxation times $T1$, $T2$ and $T2^*$, which are defined by the phenomenological Bloch equations [20] that describe the time evolution of a net magnetization vector $\vec{M_0}$.
The longitudinal relaxation time $T1$ denotes the characteristic tissue-specific time constant that describes the time M_z needs to recover to its full amplitude $|\vec{M_0}|$ in thermal equilibrium after an RF excitation. For $M_z = 0$ at the time $t = 0$, the time evolution of M_z is given by

$$M_z(t) = |\vec{M_0}| \cdot (1 - e^{-t/T1}). \tag{1.1}$$

MR imaging sequences, i.e. a specific series of RF pulses and gradients, in which the MR parameters are selected such as that the differences in $T1$-values between different tissues determine the predominant image contrast, are called $T1$-weighted sequences.

On the other hand, the tissue-specific characteristic transversal relaxation time constant $T2$ describes the dephasing time of the transversal magnetization component M_{xy} in the xy-plane. Such dephasing effects occur due to spin-spin interactions at the atomic level. Furthermore, T1 relaxation is another cause for T2 relaxation.
For $M_{xy} = M_{xy,0}$ at $t = 0$, this dephasing process is described by an exponential decay:

$$M_{xy} = M_{xy,0} \cdot e^{-t/T2}. \tag{1.2}$$

MR sequences that highlight the tissue-specific differences in $T2$ are called $T2$-weighted sequences.
A third important relaxation time, $T2^*$, additionally considers inhomogeneities of the magnetic field, which lead to a faster transversal spin dephasing in reality, than described by $T2$, i.e. $T2^* \leq T2$.

Generally, in MRI, the signal intensities and contrasts between different tissue properties can be manipulated by adjusting MRI-specific sequence parameters such as the repetition time TR, the echo time TE and the flip angle α. The repetition time TR determines the time between two consecutive radiofrequency pulses that are transmitted into the patient to cause the magnetization $\vec{M}_0$ to be tilted away by the flip angle α from the longitudinal z-axis. In so-called *gradient echo sequences*, a gradient magnetic field is overlayed to the static magnetic field after an RF excitation of the spins, which leads to a decaying signal by dephasing of the spins. By reversing the process using a rephasing gradient with opposite polarity, an echo signal is evoked, which is then measured by the read-out coil. This time between the radiofrequency pulse and the echo of the signal, that is received by the read-out coil, is called the echo time TE.

For MR-based motion quantification purposes, the repetition time TR is commonly chosen in the time range of a few milliseconds to obtain a high time resolution. In combination with novel 4D reconstruction techniques using dedicated sampling strategies of the frequency space (k-space), in which MR images are acquired, time-resolved volumetric MR images (4D-MRI) can be obtained that cover multiple breathing cycles of the patient.
In this thesis, a gradient echo sequence using radial k-space sampling with golden angle spacing was utilized with a subsequent iterative 4D reconstruction of the raw data. The reconstruction is based on a k-space-center self-gating signal that provides up to 20 reconstructed overlapping breathing phases [21].

1.2.3 MR-guided Radiation Therapy

Apart from the MRI advantage of providing a high soft-tissue contrast with no imaging dose, MR images hold the disadvantage, compared to CT scans, of not providing any material density information, as the MR intensities are determined by the pulse sequence and the MR parameter settings. For dose calculation purposes in treatment planning, such material density information is, however, essential and needs to be incorporated in MR-only planning approaches, where the entire planning is done on MR images. Different approaches have been developed to generate MR-based synthetic CTs [22–24] to integrate this relevant material density information into MR-based treatment planning.
The high MR image quality, combined with the prevention of additional imaging dose to the patient, makes MRI a powerful imaging modality. Especially the development of cine MR sequences, i.e. multiple rapidly acquired 2D MR images, and 4D-MRI reconstruction algorithms that allow spatial motion extraction over multiple breathing cycles (while conventional 4D-CT imaging illustrates only a single snapshot of a breathing cycle) outline the high potential of MRI with respect to motion characterization and quantification for radiation therapy purposes [21,25,26]. Radiation therapy, that is "guided" by MR images, is called MR-guided radiation therapy (MRgRT) or, with respect to proton irradiation, MR-guided proton therapy (MRgPT).

In an ideal MR-guided radiotherapy scenario, real-time MR imaging could potentially be performed during irradiation to include the online imaging feedback of the current tumor position and anatomical changes in the beam path into the irradiation delivery. In photon radiation therapy, hybrid MR-LINAC devices that combine online cine MR imaging with X-ray irradiation of a linear accelerator, have recently been developed and put into clinical practice [27–30]. However, such devices do not yet exist for high-precision particle irradiation, but may be available in the future [31].
Therefore, pre-treatment imaging needs to be included in the treatment planning at the moment to investigate the motion-induced impacts on dosimetry and to determine strategies to reduce either tumor motion or mitigate its impact. Dedicated 4D dose evaluation studies are essential to assess such information on motion-induced dosimetric impacts and can help to determine suitable treatment strategies.

In this thesis, repeated time-resolved volumetric MRI data sets (4D-MRI) were utilized to investigate and quantify pancreatic motion patterns and the resulting dosimetric impact on proton therapy of pancreatic cancer. Based on high-contrast 4D-MRI and novel methods to quantify such motion-induced dosimetric uncertainties along the treatment course, different motion mitigation strategies were analyzed to determine suitable treatment approaches to improve particle therapy of pancreatic cancer.

The methods are developed with respect to current pre-treatment MR imaging strategies, but could also be applied in prospective MR-guided proton therapy scenarios with real-time MR imaging.

2. Thematic Allocation of Publications

In this thesis, 4D-MRI applications were utilized to investigate pancreatic motion patterns and the motion-induced dosimetric impact on proton therapy of pancreatic cancer patients by means of 4D dose calculations. In this chapter, the six peer-reviewed publications (I-VI) that are comprised in this cumulative thesis are put into the overall context of particle therapy of pancreatic cancer. Moreover, the major developed methods and the obtained results are summarized. The topics covered in this thesis are illustrated in figure 2.1. The original publications are included in chapter 3.

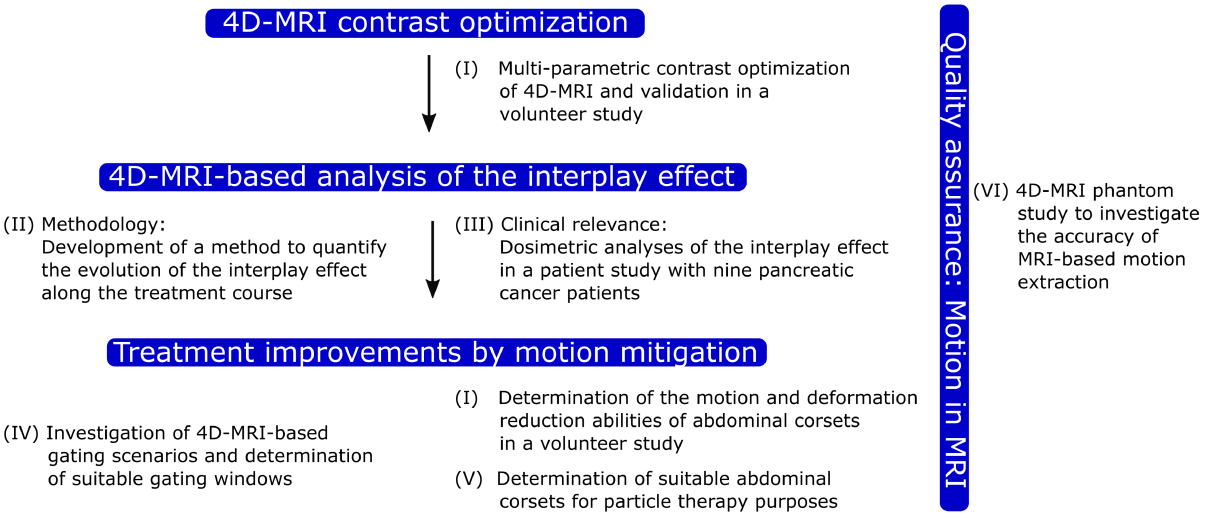

Figure 2.1: Diagram of the thematic allocation of the six publications (I-VI) that are comprised in this cumulative thesis.

2.1 4D-MRI Contrast Optimization

4D-MRI-based analyses of pancreatic motion require high-contrast MR images with a good visibility of the pancreas. For this reason, a first study (I) was dedicated to a comprehensive multi-parametric 4D-MRI contrast optimization.

The 4D-MRI data in this thesis were acquired by means of a $T1$-weighted gradient echo sequence. The tissue-specific signal intensity S of such an MR sequence is given by [32]

$$S \propto \frac{1 - e^{-TR/T1}}{1 - \cos\alpha \cdot e^{-TR/T1}} \cdot e^{-TE/T2^*} \cdot \sin\alpha \tag{2.1}$$

with the tissue-specific relaxation times $T1$ and $T2^*$, and the MRI-specific adjustable parameters repetition time TR, echo time TE and flip angle α, which were introduced in section 1.2.2.

The contrast optimization was performed in two steps: first, the optimum parameter settings were determined in a simulation study, based on tissue-specific relaxation times of the pancreas and surrounding organs ($TR = 3.3$ ms, $TE = 1.5$ ms, $\alpha = 10 - 12°$). Second, a validation of the optimal parameter settings was performed by a volunteer study. 4D-MRI data sets were acquired for nine volunteers with different parameter settings of the gradient echo sequence. A delineation-based contrast analysis of the resulting 4D-MR images confirmed the resulting high contrast in the optimized setting determined in the simulation study. These results were additionally confirmed in a blind analysis by three physicians, who rated the images of the volunteer study based on the visual contrast of the pancreas to its adjacent organs.

2.2 4D-MRI-based Analysis of the Interplay Effect

Based on high-contrast 4D-MR images, a patient study with nine pancreatic cancer patients, who underwent particle therapy at the Heidelberg Ion-Beam Therapy Center (HIT), was initiated. Up to six repeated 4D-MRI scans of the patients were acquired along their respective treatment course to visualize and investigate tumor motion patterns and to quantify the resulting dosimetric impact on fractionated proton therapy, in which the entire treatment is divided into multiple irradiation sessions on different days. In collaboration with the *Paul-Scherrer Institute (Villigen/Switzerland)*, a method was developed to quantify the evolution of the motion-induced interplay effect along the treatment course for pencil-beam scanning proton therapy of pancreatic cancer (II). In this workflow, static treatment planning CTs of these nine patients were deformed by means of deformation vector fields (DVFs), extracted from multiple 4D-MRI data sets of the patients, to generate multiple synthetic 4D-CTs. Static irradiation treatment plans were calculated on the static CTs and the impact of motion was determined by a comprehensive 4D dose calculation study on the synthetic 4D-CTs. In this study, the multiple synthetic

4D-CTs for each patient with variable tumor motion patterns were then utilized as samples for an estimation of the evolution of the interplay effect along the entire treatment course with 28 fractions.

A clinical-oriented study (III) revealed pronounced inter-patient variations of the interplay effect with remarkable dose heterogeneity and low coverage of the tumor volume in single treatment fractions. Significant correlations between the interplay effect and tumor motion quantities were determined and clinically relevant pre-treatment imaging strategies were investigated to estimate the interplay effect.

The novel developed methods based on repeated 4D-MRI data sets allowed a statistical analysis of the motion-induced dosimetric impacts as a function of the numbers of treatment fractions. The studies revealed a pronounced statistical mitigation of the interplay effect by fractionation with sufficient tumor coverage after on average seven fractions for the underlying patient cohort. However, for small numbers of treatment fractions (hypofractionated treatments) or patients with large tumor motion amplitudes, the 4D analyses showed that further motion mitigation would be required to reduce the dosimetric impact of abdominal organ motion to meet clinical requirements.

2.3 Dosimetric Improvements by Motion Mitigation

Consecutive studies were performed with respect to motion reduction and mitigation techniques such as beam-gating (IV) and the usage of abdominal corsets (I,V).
In beam-gating scenarios, the irradiation beam is only turned on while the tumor position fulfills certain pre-selected criteria and is turned off otherwise. Assuming online 4D-MR imaging during prospective MR-guided proton treatments, a comprehensive gating study was performed for a cohort of pancreatic cancer patients. The effectiveness (assessed as low residual interplay effects) and efficiency (high duty cycles, i.e. low treatment times) of various gating criteria were investigated, which were either based on absolute and relative tumor motion amplitudes or on image-based tumor overlap criteria.
An effective interplay mitigation with a highly homogeneous dose throughout the tumor was observed for small gating windows, i.e. small residual motion amplitudes, which, however, lead to pronounced longer treatment times. Relative gating criteria, based on patient-specific 30% tumor motion amplitudes, showed to be most effective while still revealing a sufficient efficiency in single fractions. Inferior results were obtained for fixed gating thresholds or overlap criteria. Considering the entire treatment course, gating with variable initial breathing phases resulted in a highly effective combination of mitigation of the interplay effect by fractionation and intrinsically less hot- and cold-spots in each

individual treatment fraction.

Since the interplay effect was found to correlate with tumor motion amplitudes, physically reduced abdominal motion offers another possibility for a direct mitigation of the interplay effect. Such a physical motion restriction can be achieved by means of abdominal corsets. A first corset study (I) revealed a remarkable reduction of pancreatic motion and deformation by means of abdominal corsets and showed an improved reproducibility of motion patterns on different days. In a second corset study (V), three different types of abdominal corsets were compared to determine their suitability with respect to particle therapy applications, taking into account the more stringent material requirements posed by particle therapy over conventional photon-based radiation therapy. Polyethylene-based corsets were found to be suitable due to their homogeneous composition and constant thickness, while polyurethane-based corsets, which have been already used in photon radiation therapy, revealed to be non eligible in particle therapy.

2.4 Quality Assurance of MRI-based Motion Extraction

All studies in this thesis utilized MRI-based extraction of abdominal organ motion. To quantify the accuracy of the extracted motion parameters in cine-MRI and 4D-MRI, a 4D-MRI motion phantom was first commissioned in collaboration with *OncoRay (Dresden/Germany)* and then utilized at an MR scanner with different multi-dimensional motion patterns of the phantom target (VI). The motion uncertainties in fast cine-MRI and 4D-MRI were determined to be < 0.5 mm in the phantom measurements.

3. Publications

This cumulative thesis comprises six peer-reviewed publications that have been published in internationally recognized journals. The publications are numbered by roman numbers from I-VI.

I 4DMRI-based analysis of inter- and inter-fractional pancreas motion and deformation with different immobilization devices

Authors: Kai Dolde, Christian Dávid, Gernot Echner, Ralf Floca, Clemens Hentschke, Florian Maier, Nina Niebuhr, Kai Ohmstedt, Nami Saito, Merkur Alimusaj, Beate Fluegel, Patrick Naumann, Constantin Dreher, Martin Freitag, Asja Pfaffenberger.

Publications status (05/2019): Published.

Journal reference: *Biomedical Physics and Engineering Express*, 2019; 5, 025012

DOI: 10.1088/2057-1976/aaf9ae

Authors' contributions: KD organized and performed most of the 4D-MRI measurements, and performed both the image processing and the data analysis. GE engineered the setup board, NN supported in the MR measurements, CDá supported in the 4D-MRI reconstructions. RF and CH provided support in image registration with the AVID framework. PN, CDr and MF provided clinical input and evaluated the MR image data. KO performed the delineations. MA and BF collaborated with respect to corset selection and adjustments. AP, NS and FM supported the integration of the study into the overall project strategy. KD drafted and revised the manuscript with critical review from AP, PN, NS, FM, CH and RF.

II 4D dose calculation for pencil beam scanning proton therapy of pancreatic cancer using repeated 4DMRI datasets

Authors: Kai Dolde, Patrick Naumann, Christian Dávid, Regula Gnirs, Marc Kachelrieß, Antony Lomax, Nami Saito, Damien Weber, Asja Pfaffenberger[§], Ye Zhang[§].
[§] Both authors share last authorship.

Publications status (05/2019): Published.

Journal reference: *Physics in Medicine and Biology*, 2018; 63,165005

DOI: 10.1088/1361-6560/aad43f

Authors' contributions: KD developed the method to quantify the evolution of the interplay effect along the treatment course. PN recruited the patient for this pilot study. KD and RG performed the MR measurements. CD and MK provided both software and support for the 4D-MRI reconstructions, which were executed by KD. KD and YZ generated the synthetic 4D-CTs and performed the 4D dose calculations. AP, DCW, AJL and NS contributed with fruitful discussions, coordination and, as well as PN and YZ, with critical revisions of the manuscript. AP and YZ supported the integration of the study into the overall project strategy. KD performed the data analysis, drafted and revised the manuscript.

III 4DMRI-based investigation on the interplay effect for pencil beam scanning proton therapy of pancreatic cancer patients

Authors: Kai Dolde*, Ye Zhang*, Naved Chaudhri, Christian Dávid, Marc Kachelrieß, Antony Lomax, Damien Weber, Nami Saito, Asja Pfaffenberger.
* Both authors share first authorship

Publications status (05/2019): Published.

Journal reference: *Radiation Oncology*, 2019; 14:30

DOI: 10.1186/s13014-019-1231-2

Authors' contributions: KD organized the MR measurements, was involved in the data acquisition and processed the images. PN recruited the patients for this pilot study. CD and MK provided both software and support for the 4D-MRI reconstructions. NC provided important information on the treatment plans. KD and YZ generated the synthetic 4D-CTs and performed the 4D dose calculations. KD performed the simulations of fractionated treatments and the statistical data analysis. AP, DCW, AJL and NS contributed with fruitful discussions, coordination and, as well as PN and YZ, with critical revisions of the manuscript. AP and YZ supported the integration of the study into the overall project strategy. KD drafted and revised the manuscript.

IV Comparing the effectiveness and efficiency of various gating approaches for PBS proton therapy of pancreatic cancer using 4DMRI datasets

Authors: Kai Dolde, Patrick Naumann, Christian Dávid, Marc Kachelrieß, Antony Lomax, Damien Weber, Nami Saito, Lucas Burigo, Asja Pfaffenberger, Ye Zhang.

Publications status (05/2019): Published.

Journal reference: *Physics in Medicine and Biology*, 2019; 64,085011

DOI: 10.1088/1361-6560/ab1175

Authors' contributions: KD conceived the idea of this comparison study and defined the different gating strategies together with AP, NS and YZ. KD organized the MR measurements, was involved in the data acquisition and processed the images. PN recruited the patients for this pilot study. CD and MK provided both software and support for the 4D-MRI reconstructions. KD and YZ generated the synthetic 4D-CTs and performed the 4D dose calculations. KD performed the simulations and analysis of the different gating scenarios. AP, LB, DCW, AJL and NS contributed with fruitful discussions, coordination and, as well as PN and YZ, with critical revisions of the manuscript. AP and YZ supported the integration of the study into the overall project strategy. KD drafted and revised the manuscript.

V Comparison of pancreatic respiratory motion management with three abdominal corsets for particle radiation therapy

Authors: Kai Dolde*, Sergej Schneider*, Sarah Stefanowicz, Merkur Alimusaj, Beate Fluegel, Nami Saito, Esther Troost, Asja Pfaffenberger§, Aswin Hoffmann§.
* Both authors share first authorship
§ Both authors share last authorship

Publications status (05/2019): In press.

Journal reference: *Journal of Applied Clinical Medical Physics*, 2019; xx:x,1-9

DOI: 10.1002/acm2.12613

Authors' contributions: KD and SSc conceived the idea of the corset comparison study and performed the MRI measurements. MA and BF collaborated with respect to corset adjustments. AP and AH supported the integration of the study into the overall project strategy. KD performed the 4D-MRI measurements and the motion analysis, SSc performed the WER analysis. KD and SSc drafted and revised the manuscript, KD submitted the manuscript. AP, AH, NS, ET and SSt provided further ideas with respect to the study and critically revised the manuscript.

VI Commissioning of a 4D MRI phantom for use in MR-guided radiotherapy

Authors: Sergej Schneider[*], Kai Dolde[*], Johanna Engler, Aswin Hoffmann[§], Asja Pfaffenberger.[§]
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[§] Both authors share last authorship

Publications status (05/2019): Published.

Journal reference: *Medical Physics*, 2019; 46(1): 25-33

DOI: 10.1002/mp.13261

Authors' contributions: SS was devoted to the phantom setup, filling and operation. KD and SS executed the phantom measurements together with AH and AP and performed the motion analysis. JE and SS evaluated the distortion grid, SS further evaluated the relaxation times. AP and AH supported the integration of the study into the overall project strategy. SS and KD drafted and revised the manuscript with critical review by AH and AP.

4. Discussion

4.1 Benefits and Limitations of 4D-MRI

4D-MRI is a promising and useful imaging modality to extract abdominal organ motion and deformation. First, compared to conventional 4D-CT imaging, MRI offers an intrinsic superior soft-tissue contrast and thus enables an improved differentiation between abdominal organs. Dedicated MRI contrast optimizations by determination of suitable MR-specific parameter sets (I) allow further improvements in the soft-tissue contrast and set the basis for this 4D-MRI study on the impact of pancreatic motion in proton therapy. Second, 4D-MRI does not expose patients to additional imaging dose by ionizing radiation in contrary to 4D-CT imaging with radiation doses between 20-200 mGy [33]. This benefit can be exploited by acquiring repeated MRI data sets or longer imaging sessions that provide more comprehensive motion information than single snapshots of a specific breathing cycle in a 4D-CT scan. Such repeated imaging is beneficial to obtain information on day-to-day motion variations and allows a more realistic estimation of motion-induced impacts on dosimetry during an entire treatment course (II,III).

The 4D-MRI data in this thesis were obtained by utilizing a $T1$-weighted MR sequence with radial stack-of-stars sampling at the golden angle, followed by a subsequent iterative reconstruction algorithm that provide up to 20 overlapping breathing phases [21]. Such an iterative reconstruction procedure allows to utilize all raw image data, acquired within different breathing phases to reconstruct the image of a certain breathing phase. In particular, the reconstruction alternates between image reconstruction and motion estimation. It iteratively reconstructs 3D images for each breathing phase, followed by the estimation of deformation vector fields (DVFs) between different breathing phases. The entire image reconstruction procedure is based on deformable image registration (DIR) and the Demons algorithm [34].

DIR is generally used to match a moving image to a fixed image by determination of a suitable DVFs between the two images. DIR itself, however, constitutes an intrinsically ill-posed problem [35] and comes along with certain uncertainties. For instance, the obtained DVFs and thus the extracted motion quantities strongly depend on the chosen registration algorithm [36, 37]. Therefore, it is generally difficult to determine precise

motion quantities from patient measurements by DIR as generally no ground-truth information of organ motion or deformation is available.
To quantify the accuracy of MR-extracted motion amplitudes, in this thesis a 4D-MRI phantom was utilized (VI). First, the phantom was commissioned to determine the intrinsic accuracy between pre-set and actual motion patterns and then utilized on a clinical MR scanner to assess the motion accuracy in cine-MRI and 4D-MRI data sets. While the results showed a high motion accuracy with deviations < 0.5 mm, it needs to be noted that these results were obtained for a purely rigid target motion. In patients, however, organ deformations occur and low tissue contrasts or image artefacts can challenge motion extractions in a more severe way than it is the case in 4D motion phantoms. One way to further investigate these additional uncertainties would be the usage of anthropomorphic 4D phantoms, that allow to generate motion patterns within a patient-like environment [38, 39]. Such phantoms have been used in previous studies to validate 4D-MRI-based motion extraction, however, these phantoms usually reveal less reproducible motion patterns than geometric, non-anthropomorphic phantoms due to more complex setups [39].
For DIR evaluations of the real patient data, DIR quality assurance needs to be performed by calculations of DIR-specific quantities such as Dice coefficients, Jacobian determinants and inverse consistency errors (ICE) [40]. They allow the determination of registration uncertainties by, for instance, validation of contours (Dice) and DVFs (Jacobian, ICE) and allow to keep the registration uncertainties at a tolerable level (I,II,III).
Alternatively to 4D-MRI, abdominal organ motion is often determined by cine-MRI, that allows a fast real-time imaging modality in usually two dimensions [41]. Estimations of 3D motion patterns by cine-MRI can be achieved by stacking of 2D slices, acquired at different time points, by the acquisition of inter-leaved (orthogonal) 2D slices [42] or by dedicated motion models that volumetrically interpolate 2D results based on offline 4D models [43]. In contrary, 4D-MRI allows a voxelwise extraction of 3D DVFs to quantify the spatial motion of each individual voxel. However, this additional useful information comes along with a longer reconstruction time, compared to cine-MRI, which currently limits the usability of 4D-MRI for real-time imaging. Nonetheless, novel approaches based on deep learning algorithms [44, 45] have already shown high potential in achieving a short reconstruction time during the actual MR data acquisition opposite to a longer pre-treatment learning phase. Such approaches may finally enable real-time 4D-MRI data acquisition and reconstruction.

4.2 Motion-induced Impact on Dosimetry

Abdominal organ motion leads to pronounced underdosage and heterogeneous dose distributions in pancreatic tumors due to the interplay effect between the moving organ and the scanning beam (II, III). In this thesis, a novel method was developed to quantify the evolution of this interplay effect along the treatment course by sampling the underlying motion patterns, derived from DVFs of repeated 4D-MRI data sets.
The developed method, based on acquisitions of repeated 4D-MRI data sets, offers the benefit of integrating both intra- and interfractional motion variations into the 4D dose calculation. It further enables the utilization of pre-treatment 4D-MRI to estimate the evolution of the interplay effect along the treatment course and may provide support in selection of suitable treatment strategies with respect to potentially necessary motion mitigation.
The 4D dose calculation studies revealed a remarkable mitigation of the interplay effect in highly fractionated treatments due to redistribution of hot and cold spots along different treatment fractions. However, it should be noted that such a statistical wash-out may not compensate the biological effect of tumor underdosage in each single fraction. This effect should be investigated separately in a dedicated dose or effect accumulation study.
Significant correlations between tumor motion amplitudes and the interplay effect were observed and for patients with larger motion amplitudes, more fractions were required for a sufficient mitigation of the interplay effect. On average, after seven fractions a sufficient tumor coverage was observed. This result may be affected, however, by the rather small tumor motion amplitudes in the underlying patient cohort with maximum amplitudes of < 15 mm, while our volunteer study (I) as well as previous published studies reported larger pancreatic motion of > 30 mm [41]. Such patients with large tumor motion amplitudes may require additional motion mitigation to exploit the full potential of proton therapy.

4.3 Motion Mitigation Strategies

In this thesis, physical motion reduction by abdominal corsets (I,V) and residual motion reduction by beam-gating (IV) were investigated. Abdominal corsets were observed to remarkably reduce pancreatic motion and deformation in inferior-superior and anterior-posterior direction. Consequently, the interplay effect, which correlates to the motion amplitudes, could be reduced by the use of abdominal corsets.
Additionally, abdominal corsets further enabled an increased reproducibility of motion patterns within different days with lower day-to-day motion variations. Lower organ motion and more reproducible motion patterns could be beneficial for the integration of

organ motion into 4D treatment planning process [46] and would be advantageous with respect to tumor motion predictions in gating or tracking scenarios.
While different kinds of corsets were found to reduce pancreatic motion, not all of them were observed to be suitable for particle therapy, as particle therapy sets more stringent material requirements in comparison to conventional photon-based radiation therapy. For instance, density variations in the beam path are a considerable source of range uncertainties in particle therapy [47]. While the applied polyethylene-based corsets showed a homogeneous thickness and material composition, foam-based polyurethane corsets showed a highly variable thickness with multiple air inclusions within the foam (V). Therefore, although foam-based corsets are already used in photon radiation therapy [48] and can easily be patient-specificly adjusted, they were found to be unsuitable for particle therapy purposes. In contrary, polyethylene-based corsets were found to be suitable and could be easily included into the process of treatment planning due to their homogeneity and known water-equivalent thickness. It should be noted that abdominal compression by corsets may not be tolerable by certain patients because of abdominal pain. However, first preliminary results of a clinical trial at our partner facility *OncoRay (Dresden/Germany)* indicated that such corsets are well-tolerated by pancreatic cancer patients (V).

Alternatively to active motion reduction by abdominal compression, a passive reduction of the residual motion during irradiation by beam-gating was investigated. In this case, irradiation only occurs while certain pre-selected gating criteria are fulfilled, e.g. within certain breathing phases with low residual motion. In clinical practice, such gating trigger signals are often derived from external surrogates such as pressure belts [49] or optical surface monitoring devices [50] that detect the movement of the abdominal wall. However, possible correlations between external surrogate signals and tumor motion need to be investigated with caution and may not be reliable [51, 52].
For this reason, in this thesis 4D-MRI-based gating scenarios were investigated with regard to possible prospective real-time MR imaging during proton irradiation. By allowing a direct visualization of spatial tumor motion, it could be possible to avoid the dependency on external surrogate signals or correlation models. In photon radiation therapy, image-based gating approaches are already performed on hybrid MR-LINAC devices [27–30]. However, these are currently based on single-slice cine-MR images which do not provide spatial motion information.
In this thesis, 4D-MRI-based gating criteria, based on patient-specific relative 30% CTV (clinical target volume) motion amplitudes, showed the significantly lowest residual interplay effect with still sufficient duty cycles, in contrast to inferior results by either fixed gating thresholds or CTV overlap criteria. Further improvements of the effectiveness in the mitigation of the interplay effect along the treatment course were achieved by addi-

tional variations of initial breathing phases in different fractions.
If the start of beam delivery is not correlated with a specific breathing phase, the gating advantages of lower interplay effects in every single fraction were shown to come along with a further effective fractionation-induced mitigation of the interplay effect (IV).
However, the performed gating analysis did not consider possible baseline shifts or irregular breathing patterns. Both factors may prolong the duty cycles and may require adaptations of the treatments. For such purposes, 4DDC simulations could give useful guidance, to determine suitable adaptation strategies. Possible combinations of abdominal corsets and beam-gating could potentially further combine the advantages of more reproducible and reduced abdominal motion by corsets with further interplay mitigation by beam-gating.

Alternatively to the investigated motion mitigation approaches in this study, fast rescanning techniques have shown huge potential to smear-out hot and cold spots in the dose distributions [53]. Apart from that, irradiation during breath-hold of the patients could potentially eliminate the interplay effect, but would require highly reproducible breath-hold positions of the tumor. End-exhalation instead of end-inhalation breath-hold have shown to be advantageous with this respect [54]. Alternatively, high dose rates would be needed that enable a fast irradiation of an entire field during a single breath-hold.
Future sophisticated options like real-time target tracking [55] for proton therapy of pancreatic cancer would require real-time volumetric imaging and precise information on density variations in the beam path to handle range uncertainties which are currently technically challenging.

4.4 MR-guided Proton Therapy

This thesis was dedicated to 4D-MRI applications towards prospective MR-guided proton therapy (MRgPT) with real-time MR imaging during proton irradiation. Due to its longer history, image-guidance in photon therapy is far ahead of proton therapy. However, especially the advantages of MR-guidance are expected to yield higher benefits to proton therapy than the hybrid MR-LINAC devices offer in photon therapy due to the steep dose gradients in proton irradiation [31]. Online integration of MR imaging during proton therapy is therefore expected to improve the treatments and reduce toxicity by fully exploiting the clinical potential of high-precision proton irradiation [31].
First simulations on proton dosimetry in magnetic fields showed that in small magnetic fields of 0.5 T, lateral beam deflections > 1 cm could occur. However, these deflections are predictable and therefore could be accounted for in the treatment planning [56]. Moreover, it was reported that the dosimetric impact of magnetic fields in MR-guided proton

therapy is rather small due to the low energy of the secondary electrons, generated by protons [57]. Even for higher magnetic fields of 1.5 T, no dosimetric obstacles are expected [58]. Still, several major steps need to be taken to finally accomplish MR-guided proton therapy, especially with respect to design, hardware and engineering of such a device with its individual components and interactions between the MRI scanner and the beam transport magnets [59]. Moreover, software developments for treatment planning and target tracking in an MR-guided environment are essential in further developments.

In real-time MRgPT, 4D-MRI could potentially be acquired during the irradiation and used for spatial target tracking for image-based gating or tracking applications. Furthermore, by means of the proposed method in this study of warping a static CT by DVFs from 4D-MRI, the actual 4D dose distribution of the day could be calculated as a control measure of the dose delivery after every fraction.
In current proton therapy with pre-treatment MR imaging, in a possible clinical workflow, pre-treatment 4D-MRI data sets could be acquired and utilized for a subsequent 4D interplay analysis along the estimated treatment course. Based on such an analysis and pre-defined criteria, patients who require dedicated motion reduction could potentially be identified and treatment strategies, utilizing beam-gating, abdominal corsets or other motion mitigation strategies, could be patient-specific adapted.

All in all, this thesis demonstrated the benefits of 4D-MRI in proton therapy of pancreatic cancer. 4D-MRI provides high soft-tissue contrast images without any imaging dose and offers various beneficial applications in both prospective real-time and current pre-treatment imaging scenarios. 4D-MRI constitutes a useful imaging tool as a basis to analyze motion-induced dosimetric impacts and to determine suitable treatment strategies for proton therapy of pancreatic cancer.

5. Conclusion

Time-resolved volumetric magnetic resonance imaging (4D-MRI) enables spatial motion extraction of respiration-induced abdominal organ motion while providing high soft-tissue contrast and avoiding any imaging dose to patients.
Based on contrast-optimized data sets, this thesis utilized repeated 4D-MRI measurements of pancreatic cancer patients and healthy volunteers to quantify pancreatic motion, investigate motion-induced impacts on dosimetry (*interplay effect*) and determine suitable treatment strategies for proton therapy of pancreatic cancer.
A novel 4D-MRI-based method was developed in this thesis to evaluate the evolution of the interplay effect along an entire treatment course. The results from 4D dose calculations showed pronounced tumor underdosage and heterogeneous dose distributions with cold and hot spots in the tumor for single fractions. For patients with small tumor motion amplitudes (< 15 mm), these motion-induced effect can be mitigated in fractionated treatments due to the redistribution of the dosimetric hot and cold spots by day-to-day variations of both motion patterns and initial breathing phases.
However, correlations between the interplay effect and tumor motion amplitudes pointed at the necessity of further motion mitigation for patients with larger motion amplitudes or hypofractionated treatments. For such cases, homogeneously composed abdominal corsets were identified to be suitable for particle therapy purposes. They remarkably reduce pancreatic motion and deformation, while at the same time, improve the reproducibility of motion patterns on different days which is beneficial for motion prediction models in 4D treatment planning.
Alternatively, beam-gating with pre-selected gating windows during which the irradiation occurs, showed to effectively and efficiently reduce the residual interplay effect, especially when using gating windows based on relative tumor motion amplitudes and allowing variable initial breathing phases in different fractions.
4D-MRI offers several beneficial possible applications for both offline (pre-treatment) and online (real-time) MR-guided proton therapy of pancreatic cancer. The developed 4D-MRI-based methods and analysis strategies can be utilized for motion quantification, pre-treatment estimations of the interplay effect and determination of suitable treatment strategies for pancreatic cancer patients.

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