Motion management optimization in radiotherapy

From the most common to the most uncommon patient

Mannerberg, Annika

2023

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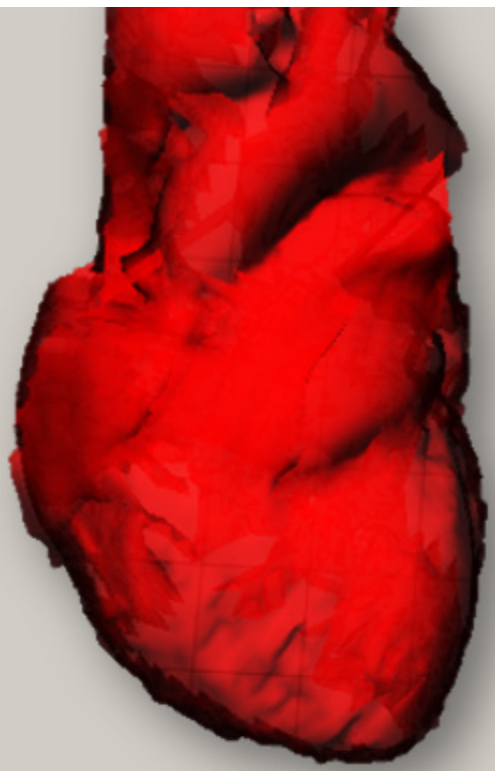

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Annika Mannerberg

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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To be publicly defended in the Torsten Landberg lecture hall, Radiotherapy building 3rd floor, Klinikgatan 5, Skåne University Hospital, Lund, on 3rd of November 2023 at 1.00 pm.

Faculty opponent
Professor Dirk Verellen
Faculty of Medicine and Health Sciences, Antwerp University, Antwerp, Belgium and
Iridium Netwerk, GZA Hospitals, Radiation Oncology Department, Antwerp, Belgium

Organization: LUND UNIVERSITY Department of Medical Radiation Physics Clinical Sciences, Lund Faculty of Science	**Document name:** DOCTORAL DISSERTATION
	Date of issue: 2023-11-03
Author(s): Annika Mannerberg	**Sponsoring organization:**

Title and subtitle: Motion management optimization in radiotherapy
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Various motion management techniques were analysed for different treatments and patient groups. Surface imaging (SI) and its potential to improve the workflow was assessed for both our most common patients (breast and prostate cancer patients) treated with conventional RT and for some of our most uncommon patients (canine patients) treated with the emerging RT technique FLASH-RT. The potential dosimetric effect of prostate motion and inadequate motion management in the magnetic resonance linear accelerator (MR-linac) workflow was investigated for three different planning target volume (PTV) margins. The dosimetric effects of different motion management methods were also evaluated for our most uncommon patients, ventricular tachycardia (VT) patients receiving stereotactic body RT (SBRT), by simulating treatment in breath-hold (BH) and treatment in free breathing with and without abdominal compression (AC). The potential of AC to decrease respiratory induced heart motion was also investigated.

This thesis demonstrated that SI can improve the initial patient setup accuracy and efficiency and is currently the only feasible motion management option for our FLASH-RT treatments. Further, it was shown that there is a risk of underdosage of the prostate in the MR-linac workflow if position correction is not carried out just before beam-on. Finally, we demonstrated that for most patients heart motion was reduced with AC, however it also increased motion for a few patients. It was shown that AC can reduce motion but also push the stomach closer towards the target, making AC dosimetrically unfavourable. Treatment in BH appeared to be dosimetrically preferable, however an induvial assessment of both BH and AC should be carried out for all VT patients.

In conclusion, this thesis has improved the initial patient setup accuracy and efficiency, implemented motion management for a new treatment technique, raised awareness of risks if proper motion management is left out and demonstrated dosimetric effects of different motion management techniques. This thesis has contributed to increased knowledge for future margin reductions, breathing adapted RT, and new motion management implementations and highlights the importance of continuous motion management optimization in conventional, novel, and emerging treatments.

Key words:		
Classification system and/or index terms (if any)		
Supplementary bibliographical information		**Language:** English
ISSN and key title:		**ISBN:** 978-91-8039-808-4 (print) 978-91-8039-807-7 (pdf)
Recipient's notes	**Number of pages: 74**	Price
	Security classification	

Signature Date 2023-10-05

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Cover: A surface scan of a heart anatomy model.

Cover by Annika Mannerberg

Faculty of Science

Department of Medical Radiation Physics

ISBN 978-91-8039-808-4 (print)

ISBN 978-91-8039-807-7 (pdf)

Printed in Sweden by Tryckeriet i E-huset, Lund University

"I knew exactly what to do. But in a much more real sense,
I had no idea what to do."

Michael Scott, The Office, Season 5, Episode 15

Table of Contents

Abstract

In radiotherapy (RT), the treatment is thoroughly planned and optimized to fulfil the goal of delivering a high dose to the target, while sparing as much normal tissue as possible. This implies that the patient position and anatomy should be the same as they were during the planning image acquisition. To achieve this, it is important to have motion management methods for predicting, monitoring, and mitigating patient motion. These methods involve for instance adding extra margins around the target accounting for motion uncertainties, treatment in breath-hold, and imaging before and during beam-on. Ultimately, these techniques enhance treatment accuracy by reducing discrepancies between the planned and delivered dose. The work in this thesis aimed to evaluate and optimize motion management for patients treated with RT.

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Populärvetenskaplig sammanfattning

Målet med strålbehandling är att ge en hög stråldos till ett sjukt område i kroppen, vanligtvis en tumör, samtidigt som man minimerar stråldosen till omkringliggande frisk vävnad. Strålbehandling baseras vanligen på en datortomografi av patienten, som innebär att man tar många röntgenbilder på en hel volym av patienten. I dessa röntgenbilder ritar läkare sedan in det område som ska behandlas, samt friska organ i närheten som man vill undvika att bestråla. Patientens strålbehandling planeras och simuleras i ett datorprogram. Det är ofta en iterativ process för att komma fram till en bra stråldosplan, där tumören får en hög stråldos, medan den friska vävnaden får så låg stråldos som möjligt. Ofta delas den totala stråldosen upp i mindre delar, så att man får en liten stråldos varje dag. Vid själva behandlingen ligger patienten på en brits under tiden som strålbehandlingsmaskinen snurrar runt patienten och strålar mot det sjuka området från olika vinklar. Stråldosen tar vanligtvis ett par minuter att leverera. Under behandlingen är det viktigt att patienten är positionerad på samma sätt som under röntgenbildtagningen, och att hen ligger stilla under tiden maskinen strålar. Viss patientrörelse är dock oundviklig. Rörelser som exempelvis andning, peristaltik, hjärtslag eller att det är omöjligt att positionera patienten exakt likdanat vid varje behandlingstillfälle leder till att det finns en del rörelserelaterade osäkerheter att ta hänsyn till, och dessa kan hanteras på olika sätt.

För att vara säker på att man inte missar att stråla på delar av den sjuka volymen är det vanligt att man lägger till extra marginaler runt om. I detta fall ökar man sannolikheten för att ge en adekvat stråldos till tumören även om patienten skulle röra sig under behandling. Detta betyder dock också att man inkluderar frisk vävnad i den volym som ska få den höga stråldosen. Det är därför eftersträvansvärt att ha så små extramarginaler som möjligt. Man kan även minska rörelseosäkerheterna, och därmed även extramarginalen, genom att minimera patientrörelserna.

I denna avhandling har olika metoder för rörelsehantering under strålbehandling undersökts. Ett system som kan användas för att kontrollera patientens position och rörelser under tiden man strålar har utvärderats. Detta system skannar av patientens yta med vanligt synligt ljus. En referensyta som berättar exakt hur patienten ska vara positionerad, jämförs mot en så kallad liveyta som visar hur patienten ligger just nu på britsen. Genom att få dessa ytor att överlappa säkerställer man att patienten är rätt positionerad på britsen. Systemet är sedan i gång under hela behandlingen och fortsätter skanna av patientens yta och liveytan jämförs kontinuerligt mot referenspositionen. För mycket rörelse gör så att strålningen bryts automatiskt. Arbeten i den här avhandlingen har visat att detta ytskanningssystem leder till en ökad noggrannhet och effektivitet i patientpositioneringen jämfört med konventionella metoder. I avhandlingen visades

också att ytskanningssystemet är tillräckligt snabbt för att kunna användas för att övervaka patientens rörelser vid en helt ny strålbehandlingsteknik där hela stråldosen levereras under en bråkdel av en sekund.

För vissa behandlingar kan det gå lång tid mellan att man positionerar patienten på britsen till att strålningen sätts i gång och det finns då en risk för att patienten rör sig. I denna avhandling undersöktes hur patientrörelser som sker under denna tid kan påverka stråldosen. Det visades att patientrörelserna kan leda till att tumören får för låg dos om man använder små extramarginaler runt tumören.

De senaste åren har strålbehandling av hjärtsjuka patienter med ventrikulär takykardi utforskats och resultaten är lovande. Dessa patienter har problem med arytmi och studier har nu visat att strålbehandling kan minska patienternas arytmiska episoder från 60 stycken/månad till inga episoder alls. Eftersom hjärtat rör sig med både hjärtslag och andning, finns det mycket rörelse att ta hänsyn till vid behandling. I denna avhandling jämfördes olika behandlingsmetoder med målet att avgöra vilken av metoderna som både tar hänsyn till rörelser samt resulterar i den bästa stråldosen till patienten. Resultaten visade att det kan vara fördelaktigt att ge behandling medan patienten håller andan, men fortsatt utvärdering behövs för att dra några slutsatser. Baserat på resultaten i denna avhandling rekommenderas att utvärdera alla metoder för varje individuell patient.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their roman numerals.

I. **Surface guided radiotherapy (SGRT) improves breast cancer patient setup accuracy**
Kügele M, Mannerberg A, Nørring Bekke S, Alkner S, Berg L, Mahmood F, Thornberg C, Edvardsson A, Bäck S Å J, Behrens C F, Ceberg S
Journal of Applied Clinical Medical Physics, 2019, 20(9): 61-68

II. **Faster and more accurate patient positioning with surface guided radiotherapy for ultra-hypofractionated prostate cancer patients**
Mannerberg A, Kügele M, Hamid S, Edvardsson A, Petersson K, Gunnlaugsson A, Bäck S Å J, Engelholm S, Ceberg S
Technical Innovations & Patient Support in Radiation Oncology, 2021, 19: 41-45

III. **Surface guided electron FLASH radiotherapy for canine cancer patients**
Mannerberg A, Konradsson E, Kügele M, Edvardsson A, Kadhim M, Ceberg C, Petersson K, Thomasson HM, Arendt M L, Børresen B, Bastholm Jensen K, Ceberg S
Medical Physics, 2023, 50(7): 4047-4054

IV. **Dosimetric effects of adaptive prostate cancer radiotherapy in an MR-linac workflow**
Mannerberg A, Persson E, Jonsson J, Jamtheim Gustafsson C, Gunnlaugsson A, Olsson L E, Ceberg S
Radiation Oncology, 2020, 15(1):168

V. **Abdominal compression as motion management for stereotactic radiotherapy of ventricular tachycardia**
Mannerberg A, Nilsson M P, Edvardsson A, Karlsson K, Ceberg S
Accepted for publication in *Physics and Imaging in Radiation Oncology*, 2023

VI. **Dosimetric impact of simulated motion management techniques for stereotactic body radiotherapy of ventricular tachycardia**
Mannerberg A, Nilsson M P, Edvardsson A, Karlsson K, van der Pals J, Ceberg S
Manuscript, 2023

Author's contribution to the papers

Below is a summary of my contributions to each original paper included in this thesis.

I. I collected all data related to the locoregional breast cancer patients and contributed to the data analysis. I reviewed and commented on the manuscript.

II. I contributed to the scientific question, conducted all data analysis, and wrote the manuscript. I was the corresponding author.

III. I contributed significantly to the scientific question and planning of the study. I conducted all measurements and was responsible for the surface imaging during all treatment sessions. I conducted all data acquisition and analysis. I wrote the manuscript and was the corresponding author.

IV. I contributed to the scientific question. I did all the treatment plans and performed all data analysis. I wrote the manuscript. I was the corresponding author.

V. I contributed significantly to the scientific question and the planning of the study. I did all delineations. I conducted all data acquisition and analysis. I wrote the manuscript and was the corresponding author.

VI. I contributed significantly to the scientific question and the planning of the study. I did part of the delineations and all treatment plans. I carried out the data analysis. I wrote the manuscript.

Abbreviations

3D	three-dimensional
3D-CRT	three-dimensional conformal radiotherapy
4DCT	four-dimensional computed tomography
AC	abdominal compression
A-P	anterior-posterior
ART	adaptive radiotherapy
BH	breath-hold
COM	center of mass
CT	computed tomography
CTV	clinical target volume
DIBH	deep inspiration breath-hold
DVH	dose volume histogram
EBH	expiration breath-hold
EPID	electronic portal imaging device
FB	free breathing
FFF	flattening filter free
FLASH-RT	FLASH radiotherapy
FOV	field of view
GTV	gross tumour volume
IBH	inspiration breath-hold
ICD	implantable cardioverter defibrillator
ICRU	International Commission on Radiation Units and Measurements
IGRT	image guided radiotherapy
ITV	internal target volume
kV	kilovoltage
lat	lateral

linac	linear accelerator
lng	longitudinal
L-R	left-right
MLC	multileaf collimator
MRI	magnetic resonance image
MR-linac	magnetic resonance linear accelerator
MV	megavoltage
OAR	organ at risk
PET	positron emission tomography
PTV	planning target volume
QA	quality assurance
ROI	region of interest
RT	radiotherapy
SBRT	stereotactic body radiotherapy
sCT	synthetic CT
SGRT	surface guided radiotherapy
S-I	superior-inferior
SI	surface imaging
SSD	source-to-surface distance
SSD100	SSD = 100 cm
SSD70	SSD = 70 cm
SUS	Skåne University Hospital
TPS	treatment planning system
VMAT	volumetric modulated arc therapy
vrt	vertical
VT	ventricular tachycardia

1. Introduction

The goal of radiotherapy (RT) is to deliver a high dose to the target volume, while sparing the surrounding healthy tissue as much as possible. To achieve this it is important that the delivered treatment is the same as the planned. One major factor that can cause differences between the planned and delivered dose distribution is patient motion. If patient motion during RT is not considered there is a high risk of a positional deviation of the target and surrounding organs at risk (OARs), which can have an adverse effect on the delivered dose distribution. These differences may result in the tumour receiving less dose than planned, while surrounding healthy tissue receives a higher dose than planned. Substantial differences could potentially lead to treatment failure of the tumour and/or the delivery of excessively high doses to OARs, leading to severe normal tissue complications. It is therefore crucial to have methods for predicting the motion that will occur during the RT treatment course. Further, the motion should be monitored to ensure that the motion between and during fractions is not exceeding the predictions. Ideally the motion is also minimized, facilitating irradiating the tumour while avoiding healthy tissue. These methods are so called motion management methods and are essential to fulfil the goal of RT and to prevent that the actual dose delivered to the patient differs from the planned dose.

There are numerous motion management techniques available in RT and often a combination of different techniques is used. One of the most commonly used approaches is to add a margin around the target volume to account for geometric uncertainties during treatment such as patient motion. Another straightforward method is to immobilize the patient. A good immobilization increases the position reproducibility, and it can also prevent excessive motion during irradiation. Before treatment delivery the patient position and internal anatomy can be verified by acquiring images which are used to adjust for deviations in both target position and other internal structures. Patient motion during irradiation can be monitored with real-time imaging and based on the extent of motion different measures can be taken. If the motion is larger than tolerated, the beam can either be held or adapted to the new target location. Alternatively, the treatment can be modified according to the patient's breathing by only irradiating at certain parts of the respiratory cycle. Regardless of the

motion management method applied, the common goal is that no patient motion that occurs during treatment will result in deviations from the planned dose distribution.

Different motion management can be combined with different RT delivery techniques. Radiotherapy techniques are continuously developing in order to increase treatment efficacy while minimizing side effects. Some of these advances have been technical, involving for instance the introduction of volumetric modulated arc therapy (VMAT) and more recently the magnetic resonance linear accelerator (MR-linac). Compared to three-dimensional conformal radiotherapy (3D-CRT), VMAT offers a more conform dose distribution as well as shorter treatment times. The MR-linac offers online imaging with superior soft tissue contrast. Other developments are the result of radiobiological findings, such as FLASH radiotherapy (FLASH-RT), which has been reported to increase normal tissue sparing while maintaining tumour control. During FLASH-RT the radiation is delivered at ultra-high dose rates and the total fraction dose is delivered in under a second.

With more conform and complex treatment delivery techniques, the planned dose distribution also becomes more sensitive to patient motion. With steeper dose gradients, hypofractionation or treatment delivery during extremely short beam-on time, there is an increased demand for accurate and effective motion management. To ensure that the patients benefit as much as possible from their treatments, it is important that the motion management follows a similar course of advancements as the treatment techniques.

1.1 Outline

This thesis is based on six papers, with focus on motion management optimization. In chapter 2 the conventional RT workflow is introduced and patient motion and its dosimetric effect is explained. Chapter 3 describes different motion management techniques used in RT, and both conventional and novel techniques are presented. The potential limitations associated with the different methods are also highlighted, to clarify the motivation for the papers in the thesis. In chapter 4 the methods and findings in the papers are presented and discussed. A general discussion and future perspectives are given in chapter 5 and the overall conclusions are presented in chapter 6.

This thesis was funded by the Faculty of Science, Lund University, Sweden and The Swedish Cancer Society, Sweden.

1.2 Aim

The overall aim of this thesis was to analyse, evaluate, and optimize motion management for patients receiving RT treatment, including both conventional as well as novel and emerging treatment techniques.

Specific aims for each study were:

Paper I

To evaluate if the initial patient setup was improved using surface imaging (SI) compared to conventional 3-point localization setup for breast cancer patients.

Paper II

To investigate if the initial patient setup was faster when using SI while still maintaining setup accuracy, compared to 3-point localization setup for prostate cancer patients.

Paper III

To evaluate if surface guided radiotherapy (SGRT) could effectively be used for canine patients receiving FLASH-RT, including investigating the SI system's capacity for fur-coated surfaces, decreased source-to-surface distance (SSD) and detection of very fast motion.

Paper IV

To evaluate the dosimetric effects of anatomical changes in ultra-hypofractionated prostate cancer treatments, comparing this to an MR-linac workflow.

Paper V

To evaluate if abdominal compression (AC) could decrease respiratory induced motion in substructures of the heart.

Paper VI

To dosimetrically compare the four motion management methods free breathing with AC, free breathing without AC, expiration breath-hold and inspiration breath-hold simulated for stereotactic body radiotherapy (SBRT) of ventricular tachycardia (VT).

2. Background

2.1 The conventional radiotherapy workflow

In the conventional radiotherapy workflow, there are certain steps that are carried out for most patients and several of these steps include procedures related to patient motion and motion management (Figure 2.1).

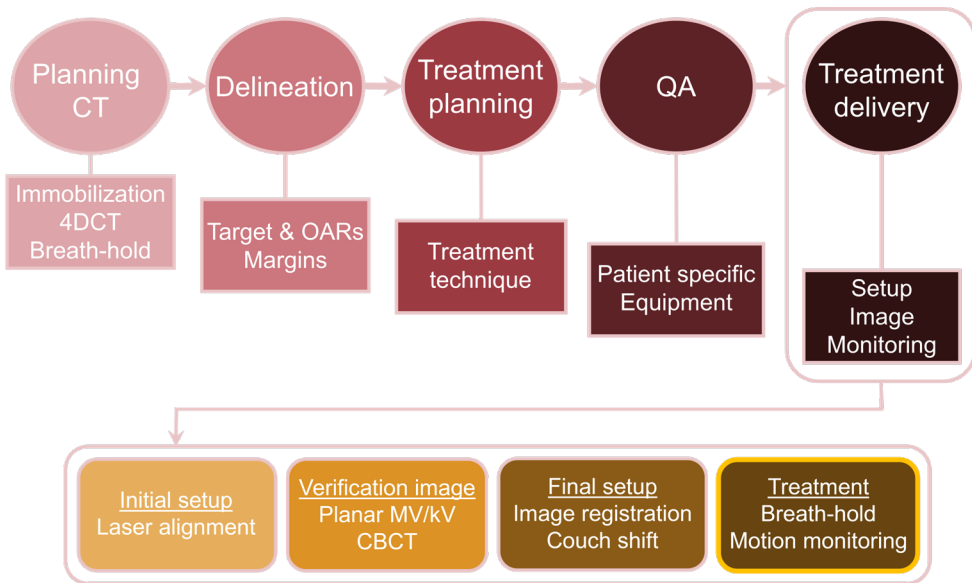


Figure 2.1. Schematic illustration of a standard radiotherapy workflow. The circles represent common steps in the radiotherapy workflow. The upper boxes shows important tasks related to patient motion that are carried out during each step. The treatment delivery procedure is illustrated in more detail in the lower boxes.

The first step in the workflows is typically acquiring a planning computed tomography (CT) of the patient. During this procedure the immobilization to be used during treatment is determined. Additional imaging can be performed, such as a four-dimensional CT (4DCT) for respiratory motion imaging or breath-hold (BH) CT for patients eligible for respiratory gated treatment. For additional information about

target boundary and functionality, the CT can be complemented with other imaging modalities such as magnetic resonance (MR) or positron emission tomography (PET) The CT is subsequently used during delineation of the target and OARs. At this stage the size of the margin accounting for geometrical uncertainties such as patient setup variations and patient motion is usually determined. The treatment planning involves making final decisions on treatment technique, such as choosing between photons or protons, and deciding whether to treat in free breathing (FB) or BH. Quality assurance (QA) is essential to ensure accurate delivery of the planned dose. Regular QA is carried out both for each specific treatment plan and for all systems used for treatment, including the linear accelerator (linac) and motion management systems such as kilovoltage (kV) imaging systems. During each treatment session initial patient setup is performed to resemble the setup during the planning CT acquisition as closely as possible. The initial setup is generally verified with verification images. The verification image is rigidly registered to the planning CT and the position of the patient is adjusted according to the registration result. When the patient is in the correct position treatment delivery can begin. Various real-time imaging techniques allow for the monitoring of patient motion during the treatment delivery.

2.2 Patient motion in radiotherapy

Patient motion during RT treatments will always be present in some form and is usually divided into being either interfractional or intrafractional.

Interfractional motion is the motion that occurs between treatment sessions, transpiring on a daily or weekly basis. Examples of interfractional motion are patient setup differences, weight gain/loss, tumour growth/shrinkage [1], variations in bladder and rectum filling [2] and a difference in breathing pattern [3].

Intrafractional motion refers to the motion occurring within a single treatment fraction, and one of the primary sources of such motion is respiration [2]. Other than respiration, cardiac motion, bladder filling, peristalsis, patient contracting/relaxing muscles, tumour drift and sudden patient shifts are examples of intrafractional motion [1]. This type of motion occurs within seconds or minutes. Some structures can exhibit both inter- and intrafractional motion. For instance, the bladder filling usually varies between fractions, while it also is continuously increasing during a fraction. Respiratory motion mainly occurs intrafractionally but can also be seen as a source to interfractional motion in situations where the breathing pattern varies between fractions [4].

2.3 Dosimetric effects of motion

The delivered dose distribution will differ from the planned dose distribution. The extent of difference primarily depends on how much unpredicted inter- and intrafractional motion that is present during treatment. There are two main ways for motion to affect the dose distribution; dose blurring and interplay affects [5].

Dose blurring is exactly what it sounds like, a blurring or smearing of the dose around the target volume. In the planned dose distribution, there are steep dose gradients and these gradients become smeared as an effect of both inter- and intrafractional motion. For interfractional motion, the gradients of the daily delivered dose distribution will still be sharp, however the whole dose distribution will be more or less shifted daily. If this shift is random, the shift will be different each fraction, and the cumulative effect of all interfractional shifts will be a blurred final dose distribution. In contrast, if the shift is completely systematic, the dose distribution would be shifted the same during each fraction. This would not result in blurring, but an underdosage of the target and potentially also overdosage to the OARs. For intrafractional motion it is instead the dose gradients in the dose distribution that is blurred each fraction [5].

Interplay effects can arise when treating with a dynamic technique, such as VMAT. During dynamic treatment delivery the linac is rotating while the multileaf collimators (MLCs) are moving and the dose rate is varied. This in combination with a moving target can result in a heterogeneous dose distribution with unforeseen cold- or hotspots in the target or OARs. The interplay effects tend to average out over multiple fractions, and can be neglected for treatments with many fractions [5]. However for few or individual fractions the interplay effects can influence the delivered dose distribution [6].

The effect of dose blurring on the target dose distribution can be reduced by increasing the margin around the target. Increased margins, however, will not reduce the interplay effects [6]. To reduce the interplay effects either the plan complexity or the target motion has to be reduced [7].

To minimize these dosimetric effects it is important to have motion management techniques in place throughout the radiotherapy workflow.

3. Motion management techniques

There are many approaches to managing motion in radiotherapy, not all of which will be covered in this thesis. This section therefore describes motion management techniques relevant for this thesis.

3.1 Margins

In 1978 the International Commission on Radiation Units and Measurements (ICRU) introduced the concept of target volume in external radiotherapy [8]. The ICRU later specified definitions for a gross tumour volume (GTV), clinical target volume (CTV) and planning target margin (PTV) [9]. The GTV constitutes the visible or palpable volume of the tumour and corresponds to the area with the highest concentration of tumour cells (Figure 3.1). Surrounding the GTV is the CTV which includes subclinical tumour cells (Figure 3.1). To ensure that the entire CTV receives the prescribed dose, a margin is added to generate the PTV (Figure 3.1). The PTV considers the geometric uncertainties arising from variations in patient positioning, organ movement, and beam geometry [9]. In addition, an internal target volume (ITV) can be used. The ITV includes the CTV and its expected physiological movements and variation in shape and size [10].

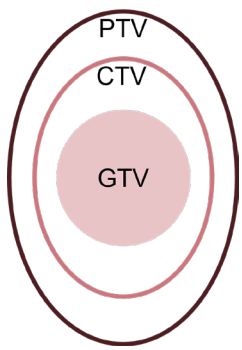


Figure 3.1. Schematic image of the gross tumour volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV).

The implementation of a PTV is a fundamental kind of motion management approach, as it compensates for inter- and intrafractional motion uncertainty [11]. Its concept is quite intuitive: with fewer geometric uncertainties, the PTV margin can be reduced, leading to healthy tissue sparing. Consequently, it is desirable to decrease sources of motion and minimize tumour position uncertainty. Novel motion mitigation and treatment techniques can create an opportunity to reduce the size of the PTV [12]. It has been shown that reduced PTV margin can reduce toxicity while maintaining outcome [13], however margin reduction can also impair outcome [14]. It is therefore important to thoroughly evaluate new margins to ensure that treatment outcome is either maintained or improved. The complete elimination of all uncertainties is very improbable, hence the PTV margin or any similar consideration of uncertainties will most likely never be zero.

In **Paper IV**, three different PTV margins were studied for localized prostate cancer patients, to analyse the resulting dosimetric effect of prostate motion for each margin. In **Paper VI**, simulated motion management approaches for stereotactic body RT (SBRT) for patients with ventricular tachycardia (VT) were evaluated. This evaluation entailed applying both CTVs and ITVs since treatment was simulated in both BH and FB.

3.2 Immobilization and patient positioning

During the planning CT acquisition, the immobilization and treatment position of the patient to be reproduced for every treatment fraction is determined. It is important for immobilization to effectively reduce motion and allow for easy reproducibility. A good immobilization can decrease both inter- and intrafractional motion [15-17]. This in turn can lead to the possibility to reduce the PTV margin [15, 18]. However, it is also important to ensure that the immobilization is comfortable enough for the patient to tolerate for the total duration of setup, verification imaging and treatment delivery. Failing to do so will increase the risk of patient motion [19, 20].

During the planning CT the patient also receives tattoos to be used as reference marks during the initial patient setup. During each fraction, in-room lasers are aligned with the tattoos, and the patient is thereafter moved to the planned isocenter position. Although this is a straightforward method for positioning the patient, it is also associated with challenges. Since the patient normally only receives three tattoos it can be difficult to detect rotational deviation [21]. It is also difficult to identify posture deviations in anatomies such as the arms, legs, and chin, where there are no tattoos. Further, there is a risk that only the skin is moved instead of the whole patient, to fulfil

laser alignment [21]. Tattoos placed in areas where there can be large daily variations, such as the stomach, can cause inaccurate positioning. Finally, for the patient the permanent tattoos can also be a visible eternal reminder of the burden associated with RT [22]. An alternative initial setup method involving surface imaging (SI) was evaluated in **Papers I** and **II** and used in **Paper III.**

3.2.1 Abdominal compression

The initial development of abdominal compression (AC) equipment dates back to 1994, and it was primarily used for patients undergoing stereotactic radiotherapy in the lung or liver [23]. Since then, it has become a common practice in many centers to employ AC for motion restriction in the thorax and abdomen [24]. Several studies have demonstrated the positive impact of using AC for lung- and liver tumours [17, 25-28]. However, there have also been studies indicating that AC may provide no or limited benefits in reducing respiratory motion [29, 30]. Even though AC is frequently used in RT, there are a limited number of studies demonstrating its effect on heart motion. This prompted **Paper V**, where the effect of AC on respiratory induced motion of the heart was evaluated in the context of SBRT for VT patients.

3.3 4DCT

The 4DCT was introduced in 2003 and is a method for assessing the expected extent of intrafractional target motion during treatment. This is achieved by adding a temporal dimension to the conventional CT scanning [31, 32]. In RT, a 4DCT is mainly used for imaging respiratory related movements and the imaging is based on acquiring images over multiple breathing cycles. 4DCT provides valuable information for individualization of RT treatment for patients with targets affected by respiratory motion. Before the introduction of 4DCT, PTV margins were mainly based on fluoroscopy, experience and/or published data and were often tumour site specific. This was inaccurate since the location of the tumour does not necessarily predict the tumour motion [33].

To be able to correlate the images to the patient's breathing cycle, the respiration is monitored with a respiratory motion surrogate simultaneously as the scanning. The respiration signal could be obtained from external surrogates such as SI, as well as internal surrogates from the acquired images or fiducial markers. The respiration signal is used to bin the acquired images into different breathing phases [34]. Either phase or amplitude binning can be applied (Figure 3.2). For phase binning the images are sorted

based on which breathing phase the respiration signal was in at image acquisition, with an equal amount of time dedicated for each bin. Amplitude binning is instead based on the amplitude of the respiration signal at the time of image acquisition [35]. Both binning methods have advantages and disadvantages. Since the bins are equally separated over time in phase binning, all bins are filled with CT slices and the entire range of breathing motion is covered. However, this method is also more prone to motion artefacts as it does not consider amplitude variations. Amplitude binning on the other hand is less susceptible to image distortions but may lead to missing slices in the reconstructed CT if the patient does not reach the full amplitude in all breaths [35].

In **Papers V** and **VI**, 4DCT images of lung cancer patients were utilized for evaluation of the potential of AC to reduce heart motion and to dosimetrically compare treatment in expiration breath-hold (EBH), inspiration breath-hold (IBH) and treatment with and without AC, simulated for SBRT of VT.

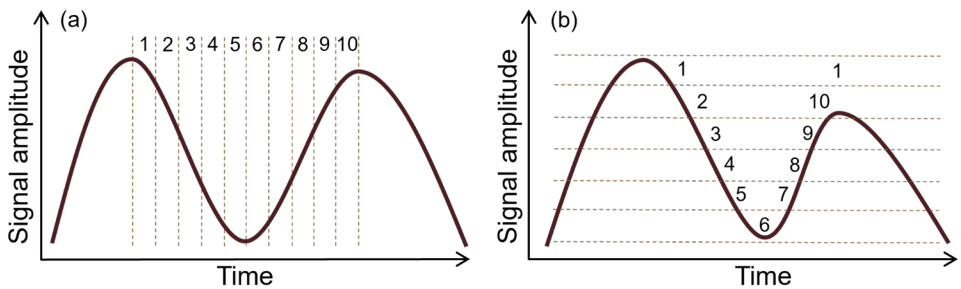


Figure 3.2. Schematic illustration of phase binning (a) and amplitude binning (b) for 4DCT reconstruction.

3.4 Respiratory gating and breath-hold treatment

Respiration affects most target sites in the thoracic and abdominal region [4]. Respiratory gating entails delivering the radiation during a portion of the respiratory cycle, enabling a smaller PTV. The patient's breathing is monitored, and the radiation is delivered only in a pre-determined part of the respiration [4]. Respiratory gating has been shown to reduce the lung dose in lung cancer patients [36].

BH treatment means that the radiation is delivered when the patient is holding their breath. A BH treatment can be delivered in either IBH, deep inspiration breath-hold (DIBH) or EBH [37]. Several studies have shown that the dose to the heart and lung and other OARs can be reduced with DIBH treatment for target sites in the thorax

[38-41]. EBH is more frequently used for targets in the abdomen, as EBH provides enhanced organ stability in the abdomen leading to improved BH reproducibility [42].

For gated RT or treatment in BH some challenges must be considered. It is important that the patient's breathing pattern stays the same throughout treatment. However, the breathing pattern can change both during and between fractions [4]. BH treatment is a demanding procedure for the patient, where the patient must be able to hold their breath for approximately 20 s and be able to reproduce the BH several times [42]. Further, it is not a guarantee that an external respiratory signal surrogate accurately corresponds to the tumour motion [4]. Finally, both gating and BH are associated with an increased total treatment time of up to 10 min [42, 43].

In **Paper VI**, EBH, IBH, treatment with AC and treatment without AC were dosimetrically compared to each other for SBRT of VT patients.

3.5 Image guided radiotherapy

With in-room imaging capabilities of the patient in treatment position, image guided radiotherapy (IGRT) introduced the possibility of obtaining important information about the patient anatomy and the position of the target. IGRT therefore substantially reduced the positional uncertainties and has consequently lead to a reduction of PTV margins [44]. IGRT has also made it possible to explore hypofractionation and non-uniform dose distributions. Further, it has been shown that IGRT can contribute to improved overall survival [45, 46]. Lastly, IGRT has paved the way for adaptive RT, allowing for treatment adjustments throughout the treatment as patient anatomy changes [47].

Verification of patient position started with using radiographic films. During the early 1990s the use of electronic portal imaging devices (EPIDs) became a widely adopted method for verifying the position. However, as EPID uses the linac megavoltage (MV) beam for imaging, the image quality is poor and the dose to the patient is high. This prompted the development of onboard kV imaging, with an X-ray source and detector mounted perpendicular to the treatment beam, having the same isocenter as the linac [48]. Placing kV imaging capabilities on the linac made it possible to also obtain 3D volumetric images of the patient, so called cone beam CT (CBCT) [49] (Figure 3.3a). This imaging technique is currently the most common one used for IGRT in RT centers [50]. The downside of CBCT is that the acquisition time is long, which contributes to blurring of structures affected by motion, and the soft tissue contrast is relatively poor, which can make it difficult to visualize the tumour [50]. Since 2012

MR guided RT is commercially available. An MR image (MRI) offers improved soft tissue contrast compared to X-ray images, enabling direct visualisation of the target and surrounding OARs [50] (Figure 3.3b). Furthermore, no additional dose is delivered to the patient.

The choice of imaging modality should be based on several factors. Aspects such as target site, expected motion, delivery technique, dose and fractionation should be considered. Planar X-rays can be adequate for treatment in the extremities or of the prostate where the fiducials correlate well to the prostate motion (Figure 3.3c, 3.3d), while stereotactic treatment often requires soft tissue imaging, preferably MRIs.

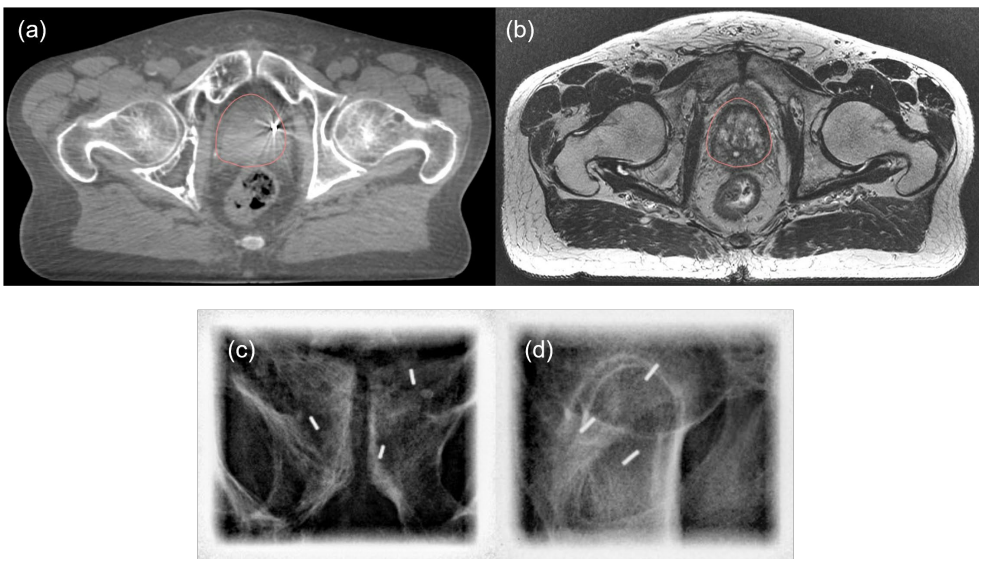


Figure 3.3. A CBCT (a), MRI (b), frontal planar kV X-ray (c) and side planar kV X-ray (d) of a prostate cancer patient. The prostate is delineated in pink in the CBCT and MRI. The soft tissue contrast can be compared between the images. Different soft tissue structures are distinguishable in the CBCT, but the MRI has the superior soft tissue contrast. Only bony anatomy and the fiducials are visible in the X-rays. One gold fiducial marker in the prostate is visible in the CBCT with some artefacts surrounding it. That fiducial marker can however not be seen in the MRI.

3.5.1 Pre-treatment IGRT

Pre-treatment IGRT is used for correcting for interfractional motion. During pre-treatment IGRT images are acquired just before treatment delivery, with the patient positioned on the couch to verify the patient position. The daily verification images are registered to a reference image corresponding to the patient's position during the planning CT. The landmarks used for evaluating the image registration varies depending on imaging modality and treatment site. For orthogonal kV images, for

instance, bony anatomy or fiducial markers are used since no soft tissue is visible (Figure 3.3c, 3.3d), while for CBCT both bony and soft tissue can be used (Figure 3.3a). Based on the image match, corrections for deviations between planned and actual patient position can be carried out. If only translational and small rotational setup deviations are present, a simple couch shift may be sufficient to correct for the deviations [51]. However, large deviations in the patient setup or anatomy which cannot be corrected for by couch shifts require manual adjustment of the patient position. Figure 3.4 shows a CBCT of a prostate cancer patient with a large gas bubble expanding into the delineated CTV. In this case the patient was instructed to use the restroom before the treatment was delivered.

In **Papers I** and **II**, the pre-treatment verification images were used as ground truth in order to determine if the initial patient setup was more accurate with SI or 3-point localization.

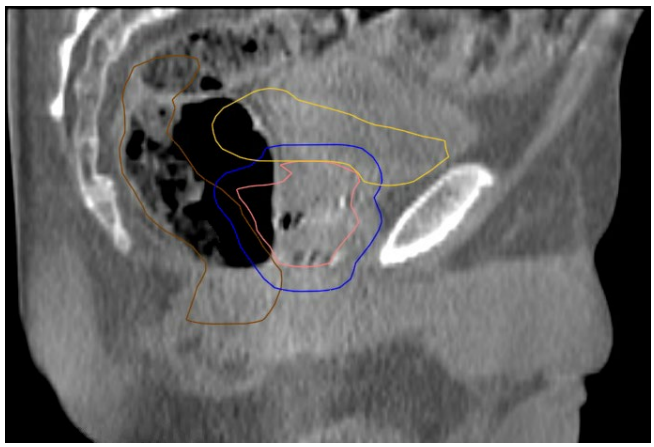


Figure 3.4. CBCT sagittal view of a prostate cancer patient. The pink, blue, yellow and brown delineations represent the CTV, PTV, bladder and rectum, respectively, and are based on the anatomy of the planning CT. A large gas bubble not present during the planning CT is visible in the CBCT. A small difference in the bladder filling can be seen as well.

3.5.2 Real-time IGRT

The intrafractional motion can be monitored with real-time IGRT, which means acquiring images during the treatment delivery. Based on the expected intrafractional motion, a tolerance for maximum motion allowed during irradiation can be set. If the target moves more than the tolerance level, the beam can be automatically held. Different techniques and imaging modalities can be used for real-time IGRT. Real-time monitoring of the respiration can be a good surrogate for targets that correlates

with the respiratory motion, such as lung or breast cancer. This could for example be achieved with SI. However, for targets located deep within the patient, monitoring of the surface is less suitable. In these cases, imaging with for instance kV, MV or MRIs is more appropriate. Both the target (or its surrogate) and its time scale for motion should be considered during real-time IGRT. For a prostate with implanted fiducial markers, kV imaging and a relatively slow beam hold latency would be acceptable, as the fiducials would be easily visualized, and the motion of the prostate is comparatively slow. For hypofractionation one could consider a higher imaging frequency. However, for targets exhibiting fast motion, such as respiratory motion, a short beam hold latency is required [1].

3.5.3 Adaptive radiotherapy

Adaptive radiotherapy (ART) was first introduced by Yan et al. in 1997 [52] and entails continuously adapting the treatment according to variations in patient anatomy throughout the course of treatment. In order to perform ART, IGRT has to be established to be able to monitor changes in the patient anatomy over time. The adaption can be carried out either offline, online or in real-time.

Offline ART is carried out between treatment sessions and primarily deals with gradual anatomical changes that transpire over the course of treatment, such as variations in body weight and tumour size. Offline ART is initiated after a treatment session and often entails repeating the whole workflow, including CT simulation, delineation, treatment planning and QA. The new treatment plan is introduced as soon as all steps in the workflow have been completed [53].

Online ART is instead performed before treatment delivery and addresses anatomical variations that occur on a day-to-day basis, such as bladder and rectum filling variations. The daily anatomy is evaluated with pre-treatment imaging and thereafter a new plan is created according to the anatomical changes of the day. Since online ART is performed with the patient lying on the treatment couch, the delineation, planning, optimization, quality assurance, and plan review procedures have to be faster than in the conventional workflow [53]. In **Paper IV** the dosimetric effects of patient motion occurring in the rather protracted MR-linac workflow was investigated.

In real-time ART the treatment plan is adapted according to anatomical changes occurring during treatment delivery. During real-time ART the position of the target is continuously monitored during irradiation and if a positional deviation of the target occurs the treatment delivery is automatically changed based on the images. Hence, the

beam “follows” the tumour. This real-time tumour tracking can be achieved with for instance robotic linacs or MLC tracking [54].

3.6 Surface guided radiotherapy

In recent years, the utilization of optical surface scanning as a means for patient setup, motion monitoring, and respiratory gating has gained substantial in interest and use. Surface guided radiotherapy (SGRT) has become an integral component of the standard radiotherapy workflow in many centers [55]. The technique involves projecting optical light onto the patient’s surface using a projector, while one or more cameras detect the dispersed light reflected from the patient [56]. A real-time 3D surface image of the patient can thereby be used for comparison with a reference surface and discrepancies between planned and live position can be detected.

SGRT have been shown to increase patient positioning accuracy and patient safety. It is also a useful tool for real-time motion monitoring as well as gated and BH treatments [56]. Limitations are for instance decreased accuracy for deep seated targets, large deformations of the real-time patient surface or potential difficulty to image patients with dark skin [57]. Another challenge associated with SGRT is the clinical implementation. To fully implement the SGRT workflow in the clinic can take a lot of time and effort [58].

In **Papers I**, **II** and **III** the optical surface scanning system Catalyst™ (C-Rad Positioning AB, Uppsala, Sweden) was used, and will therefore be the system in focus explaining surface guided motion management.

3.6.1 The Catalyst™ camera

The Catalyst™ camera is ceiling mounted and either one or three cameras can be used for patient positioning and monitoring. For the three-camera setup, the units are mounted with 120° between them. The Catalyst™ consists of a light emitting diode projector which projects structured light with a wavelength of 405 nm onto the patient surface. The light is scattered by the patient surface, and a camera detects the light that is reflected from the patient. With optical triangulation the system creates a 3D rendered surface of the patient [59]. The system has the imaging capability of acquiring 200 frames/s [60].

The reference surface to which the live surface is compared, could either be a 3D render of the body structure automatically created in the treatment planning system (TPS), or

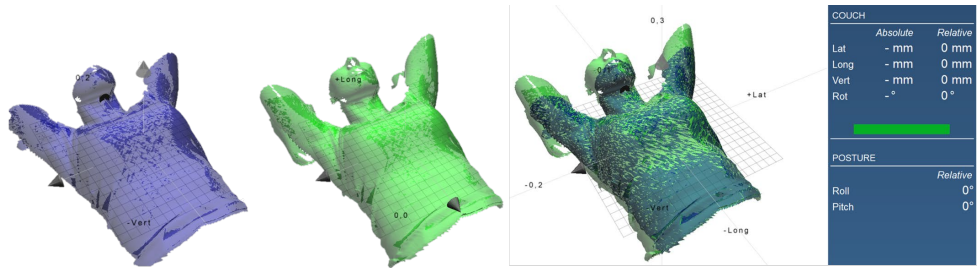
a surface captured by the SI system at the time of CT acquisition or during a treatment session. The Catalyst™ uses a deformable image registration algorithm for comparison between the reference and live surface [61].

3.6.2 Surface guided patient setup

SI with the Catalyst™ can be used for initial patient setup prior to treatment in the positioning mode. Before positioning begins, the live surface coverage should be optimized. This can be done by adjusting the integration time and gain. The integration time refers to the duration of light absorption while the gain represents the required number of captured electrons on a camera pixel to convert the light to a digital readout [62]. An appropriate scanning volume should also be set before positioning. For optimal positioning, the scanning volume should include the isocenter position and anatomical features that reflect light [61]. The maximal scanning field of view (FOV) is 110x140x240 cm in the lateral (lat), longitudinal (lng) and vertical (vrt) direction [57].

The live surface of the patient lying on the treatment couch is compared to the reference surface (Figure 3.5). To highlight deviations between the live and reference surface, the Catalyst™ projects a colourmap onto the patient's surface, indicating if any part of the patient should be positioned higher or lower vertically. Using the colourmap, patient rotation can therefore easily be detected and corrected for. Based on the surface match the system calculates the patient shift from the isocenter and suggests a positional correction in translations (lat, lng and vrt) and in rotations (rotation, roll and pitch) to shift the patient to the correct treatment position. The Catalyst™ offers a so-called "Adjust couch" functionality, which means that the couch can be automatically shifted into the correct position [63].

Pre-set tolerances for both the surface match and the calculated shift from treatment position can be used. These tolerances should correlate to the maximum accepted patient position deviation for each specific patient and treatment site. If setup deviations below tolerances are not achieved, the treatment cannot commence without the user overriding the positioning result.



(a) (b) (c)

Figure 3.5. A Catalyst™ reference (a) and live (b) surface image. These are overlapped (c) and the patient shift from isocenter position is calculated based on the surface match. A couch shift is suggested to position the patient in correct position. Here the patient is perfectly positioned without any translational or rotational deviations.

3.6.3 Surface guided motion monitoring

The Catalyst™ can also be used for motion monitoring during treatment delivery in the motion monitoring mode. Once the patient positioning is completed, the Catalyst™ treatment module can be entered, where the first captured live surface is saved as a temporary reference surface, for that particular treatment session. The Catalyst™ then continues to scan the patient, constantly comparing the live surface to the daily reference surface (Figure 3.6). As in the positioning mode, posture deviations are displayed with the colourmap and shifts from isocenter position is displayed in 6 degrees of freedom [63]. Thresholds for surface match deviations and shifts from isocenter can be used during monitoring as well. The chosen threshold for positional deviation from isocenter should correlate to estimated intrafractional motion [61]. If thresholds are exceeded the system will automatically hold the beam.

3.6.4 Surface guided respiratory gated treatment

The Catalyst™ can be used for respiratory gated treatment by monitoring the patient's respiratory motion with a region of interest (ROI) placed on the surface of the patient (Figure 3.6). The ROI surface should be representative of the breathing motion. The ROI is monitoring the respiratory motion in the vrt direction and can trigger both beam-on and beam-hold. A second ROI can be placed anywhere on the patient surface for extra visual monitoring (Figure 3.6). The secondary ROI will however not hold the beam. During a respiratory gated treatment, the beam is allowed by the Catalyst™ system when the live ROI surface is aligned with the reference surface and the ROI is within the gating window [63].

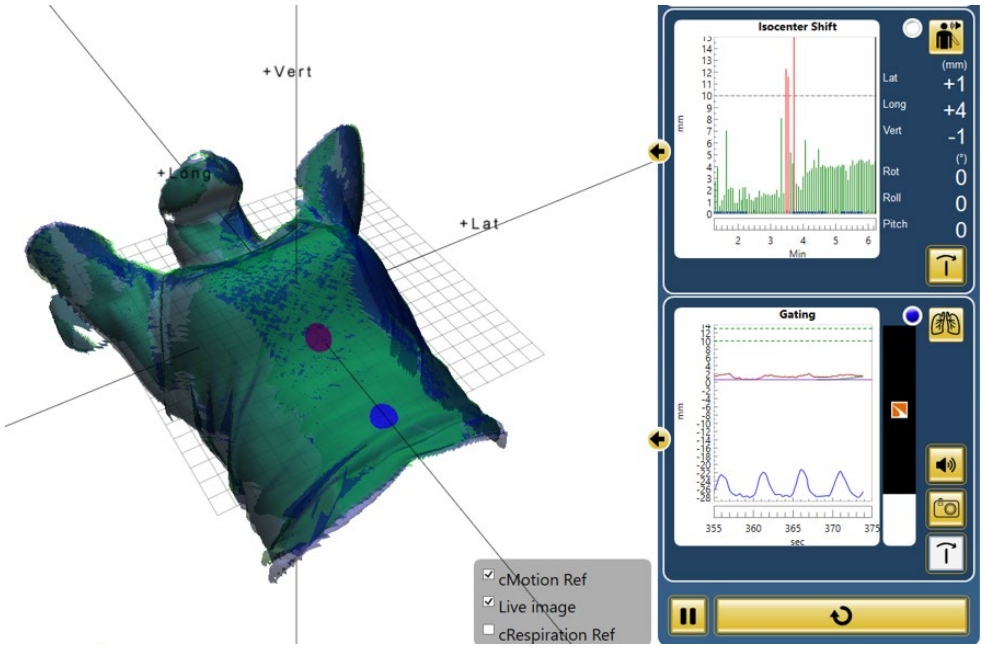


Figure 3.6. Monitoring of the patient using the Catalyst™ system. The match of the reference (blue) and live (green) surface is used for the isocenter shift calculation. The patient's position relative to the isocenter is displayed in numbers and as bars (upper right). If the patient position deviates from the isocenter position more than the pre-set tolerance (here 10 mm), red numbers and bars appear and the beam is automatically held. The red region of interest (ROI) used for respiratory gating is placed on the patient's chest. The secondary blue ROI is placed on the abdomen for extra respiratory motion monitoring. The patient is breathing at her baseline level and would have to inhale to get the gating ROI into the gating window, which is the area between the two green dashed lines (lower right).

4. Motion management optimization

The common motivation for all papers included in this thesis was the curiosity whether the motion management in the RT workflow of different treatments had potential to be optimized. We wanted to improve for both the large and smaller, new patient groups. For the most common patients (breast and prostate cancer patients) the treatments, technology, and routines are well-known and well-established. The treatment for these patients has already been evaluated and optimized several times and many different challenging patient cases have already been faced and solved. However, we believed that in our clinic the initial setup could be improved for breast cancer patients by using SI. After this was demonstrated in **Paper I**, we believed that SI also had the potential to improve the workflow efficiency. This was tested and demonstrated for prostate cancer patients in **Paper II**.

For the emerging treatment technique FLASH-RT, both the treatment and patients are uncommon, which entails facing entire new problems. For FLASH-RT, the motion management could definitely be optimized since it was basically non-existing. Although the delivery of FLASH-RT takes less than a second, it is important to be able to assure that the patient is not moving during that second. In our clinic the goal is to implement FLASH-RT for humans, but our current patients are canine. There were therefore two challenges: motion management for ultra-fast RT and motion management for canines. We believed that SI was a good motion management candidate for electron FLASH-RT of canines and therefore evaluated it in **Paper III**.

While treating prostate cancer patients is not new, treating them on the MR-linac with a completely new workflow is. Novel treatments involves new ways of working and can be associated with some risks, which was the motivation for **Paper IV**. Because of the long time required for adaptive replanning on the MR-linac, we thought there may be a risk of impaired delivered dose distribution when treating the patient with a plan that was adapted according to how the patient's anatomy looked 30 min earlier. We therefore wanted to investigate the dosimetric effect of neglecting position verification after plan adaption.

SBRT of VT is an emerging treatment and VT patients are some of our most uncommon patients. Since 2021, three patients have been treated with RT at Skåne

University Hospital (SUS), Lund. The treatment technique itself, VMAT SBRT, is not new, however the patient group and the target site are. Instead of avoiding the heart, the heart is now the target. In such a new treatment as this, there is no standard way of treating and there are still many questions to be answered. Some of these questions were attempted to be answered in **Papers V** and **VI**.

4.1 Surface guided radiotherapy

4.1.1 Surface guided setup of breast and prostate cancer patients

When considering the replacement of a well-established and widely recognized setup method such as 3-point localization for patient positioning, it becomes crucial to assess whether the new method contributes to enhanced positioning accuracy and improves the overall workflow. This was investigated for SI setup of breast and prostate cancer patients in **Papers I** and **II**, respectively. Breast and prostate cancer patients are the two largest patient groups treated with RT at SUS, so improving their workflows would have a large impact for many patients and for the clinic. **Paper I** aimed to enhance setup accuracy, while **Paper II** focused on assessing workflow improvements and ensuring that SI maintained the same setup accuracy as 3-point localization.

In **Paper I** breast cancer patients receiving tangential and locoregional treatment were included, and in **Paper II**, patients diagnosed with localized prostate cancer were included. In both **Papers I** and **II**, patients were initially setup with either 3-point localization or SI. For SI setup the colourmap tolerance was set to 5 mm in both studies. In **Paper I** the tolerance for positional deviation from isocenter was ≤2 mm for translations and ≤3° for rotations. In **Paper II**, the "Adjust couch" function was utilized and was applied until positional deviations were as close to zero as possible (Figure 4.1).

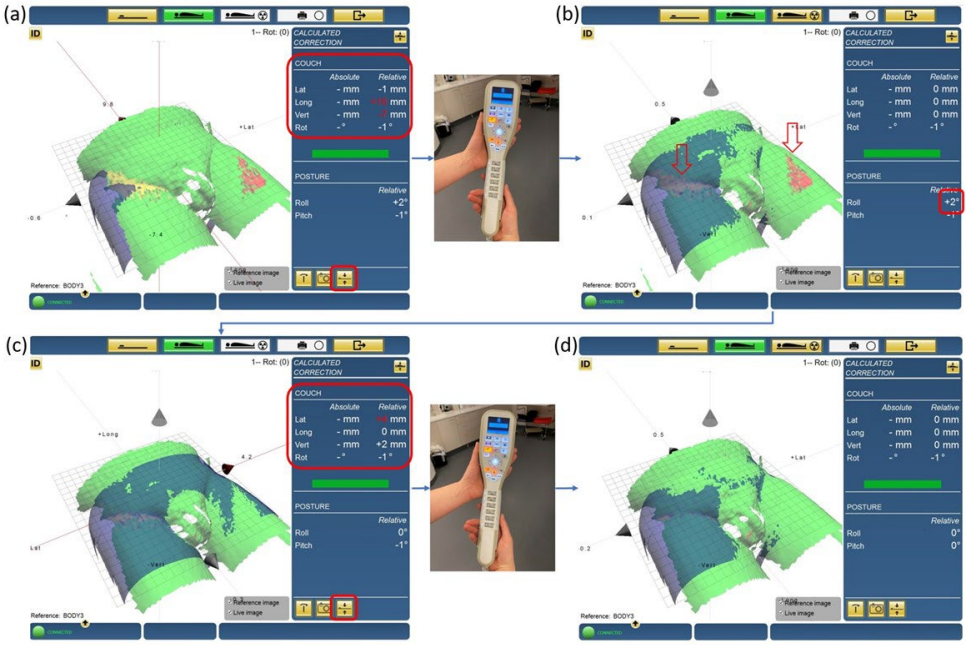


Figure 4.1. Example of the patient setup process with surface imaging using the "Adjust couch" function. The blue surface is the reference surface while the green surface is the live surface. The couch was first shifted to the saved couch parameters. The shift caluclated by the Catalyst™ based on the surface match (lat:-1 mm, lng:+10 mm, vrt: -7 mm) was then applied using the "Adjust couch" button (a). Subsequently, the Catalyst™ colourmap indicated a roll (b). After correcting for the roll, residual positional deviations (lat: +4 mm, lng: 0 mm, vrt: +2 mm) were corrected for (c). After the final couch shift the patient was positioned in the correct position (d). Figure from **Paper II**.

In both **Papers I** and **II** it was the initial patient setup that was investigated. Regardless of if the patients were setup with 3-point localization or SI, the patient position was verified with imaging prior to treatment and the verification images were considered gold standard. The size of positional deviations according to the verification image match in lat, lng and vrt and corresponding 3D vector offset ($\sqrt{lat^2 + lng^2 + vrt^2}$) was compared between 3-point localization and SI setup.

The results of **Paper I** and **Paper II** showed that SI significantly improved setup accuracy for both breast and prostate cancer patients (Figure 4.2). For tangential breast treatments the median vector offset was reduced from 4.2 mm for 3-point localization to 2.4 mm for SI (p<0.01, Wilcoxon rank sum test, α = 0.01). For locoregional treatments SI reduced the median vector offset from 4.7 mm to 4.0 mm (p<0.01, Wilcoxon rank sum test, α = 0.01). For prostate cancer patients the median vector offset was decreased from 5.2 mm to 4.7 mm with SI (p = 0.01, Wilcoxon rank sum test, α = 0.05).

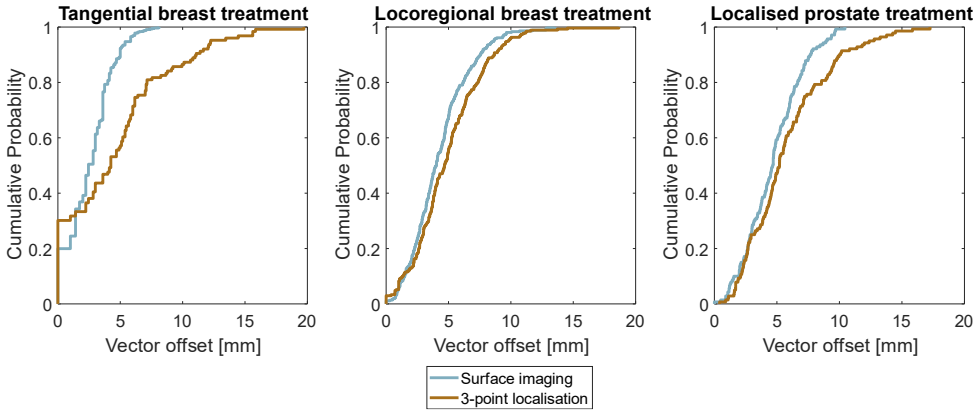


Figure 4.2. The cumulative vector offset probability for positioning of tangential and locoregional breast cancer patient positioning as well as prostate cancer patients. Figures adapted from **Paper I** and **Paper II**.

In both **Paper I** and **Paper II,** SI reduced the number of setup deviations exceeding 10 mm. Even though many radiotherapy centres move towards daily IGRT, the reduction of large setup deviations can still enhance treatment efficiency and patient safety. Large setup deviations can entail additional verification imaging, to ensure correct patient position following substantial position correction. Further, in scenarios involving human errors such as forgetting either to acquire verification images or to apply matching results, SI increases the probability for the initial patient setup to be adequate. In **Paper I** large setup deviations were mainly caused by incorrect arm position and surface loss over the bolus area, which is a vital area for the SI algorithm, since the treatment isocenter is usually located below the bolus. In **Paper II** it was not expected that SI would significantly improve setup accuracy since the prostate is located deep in the patient. The reason for the improvement can be because SI offers a million data points, while 3-point localization only provides three points for patient setup. Instead of aligning the tattoos with the lasers by unintentionally only adjusting the patient's skin, SI provided a more operator-independent check of the patient position, where the colourmap was used for rotational posture corrections. However, to fully take advantage of the setup accuracy demonstrated for SI, it is important to adjust the camera settings for an optimized surface coverage.

In **Paper II** the duration of setup was also compared between SI and 3-point localization, to evaluate the workflow efficiency for each setup method. For the time efficiency evaluation, the ARIA (Varian Medical Systems, Palo Alto, CA, USA) system log files were used. The time stamp for either pressing lasers on or moving the couch, whichever that occurred first, was determined as start of initial setup. The start of

verification image acquisition was set as the end of the initial setup. Results demonstrated that the initial patient setup effectiveness was improved when using SI setup. The median initial setup time per fraction was reduced from 3.5 min for 3-point localization setup, to 2.8 min for SI setup (Figure 4.3).

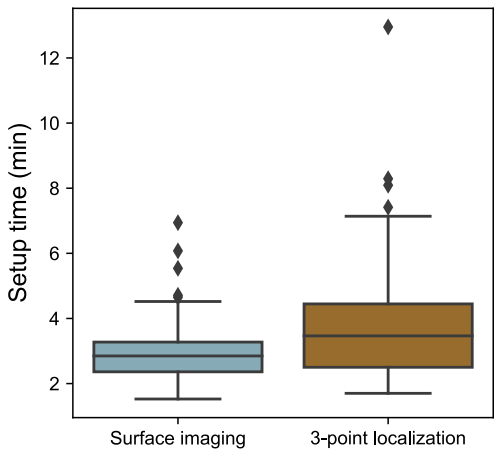


Figure 4.3. Boxplot of setup times for surface imaging and 3-point localization. The lower quartile is the 25th percentile and the upper quartile represents the 75th percentile. The horisontal lines within the boxes marks the median setup time. The whiskers shows the non-outlier minimum and maximum value. The black diamonds represent the outliers, which are values larger than 1.5 times the interquartile range. Figure adapted from **Paper II**.

To reduce the time that the patient is laying on the couch is desirable since studies have shown that the longer time the patient spends on the couch, the higher the risk is for intrafractional motion [64-68]. A faster setup procedure would also be beneficial from a patient comfort perspective as well as from an institutional perspective since it opens for the possibility to treat more patients every day. Langen et al. [64] showed that 5 min after initial setup a prostate displacement >3 mm was observed in 12,5% of the 550 prostate motion tracking sessions. After 10 min the corresponding number was 25%. The authors also urged the importance of minimizing the time between initial setup to beam-on. The reduction in initial setup time in **Paper II** can be attributed to the standardized setup workflow implemented for SI setup. Instead of investing time in aligning lasers and skin marks, which can be subjective, the patient position could be quickly adjusted using the colourmap and the "Adjust couch" feature.

4.1.2 Surface guided FLASH radiotherapy for canine patients

FLASH radiotherapy (FLASH-RT) involves delivering a radiation dose at ultra-high dose rates ≥40 Gy/s [69]. This new type of delivery technique stands as a potential groundbreaking advancement within radiation oncology. In early studies, it has been demonstrated that FLASH-RT have the potential to significantly reduce the adverse effects on normal tissue, while maintaining similar antitumour effects as conventional dose rate RT [70]. While the underlying radiobiological mechanisms of FLASH-RT remain unidentified, FLASH-RT has demonstrated feasibility in treating both veterinary [71-73] and human [74-76] cancer patients.

Together with an ultra-high dose rate, the so-called FLASH effect seems to be dependent on a high fractionation dose as well [77]. Because of the extremely short irradiation time (<500 ms) [70] and the high absorbed dose, the demand for precise and accurate dose delivery becomes even higher for FLASH-RT compared to conventional RT. Therefore, ensuring accurate target positioning during irradiation requires motion monitoring with a notably high time resolution, capable of detecting rapid and unforeseen movements. In **Paper III** the potential of utilizing SI for patient setup and motion monitoring during electron FLASH-RT for canine patients was investigated.

At SUS, Lund, a clinical linac has been modified to be able to deliver FLASH-RT [78]. The FLASH-RT treatment room is also equipped with a one-camera Catalyst^{TM} system. To verify that the Catalyst^{TM} system was capable of detecting and reproducing surfaces of fur, three furs with different colours and structures were tested (Figure 4.4a). Two different types of motion were simulated: breathing and sudden motion. The QUASAR Respiratory Motion Phantom (Modus Medical Devices, Canada) was employed to simulate breathing motion, while an in-house built phantom was utilized to simulate sudden patient motion. An SSD = 70 cm (SSD70) was used because of the increased dose rate compared to the conventional SSD = 100 cm (SSD100) [71]. Hence all measurements were carried out at both SSD70 and SSD100.

In both motion simulation measurements, the vertical motion was tracked by placing a circular ROI on the fur blanket. The radius of the ROI was up to 15 mm for breathing simulation (Figure 4.4b), whereas the radius of the ROI for sudden motion measurement was restricted to 5 mm (Figure 4.4c), prioritizing optimal speed of the SI system. The QUASAR phantom was set to move sinusoidally with an amplitude of 10 mm and 15 breaths/min. The motion of the in-house phantom was systematically changed, undergoing a stepwise movement at frequencies of 1, 2, 3, 4, 5, 6, 7, and 10 Hz. From the Catalyst^{TM} log files the vertical ROI position and its associated time stamp was retrieved, which was used to determine the sampling time.

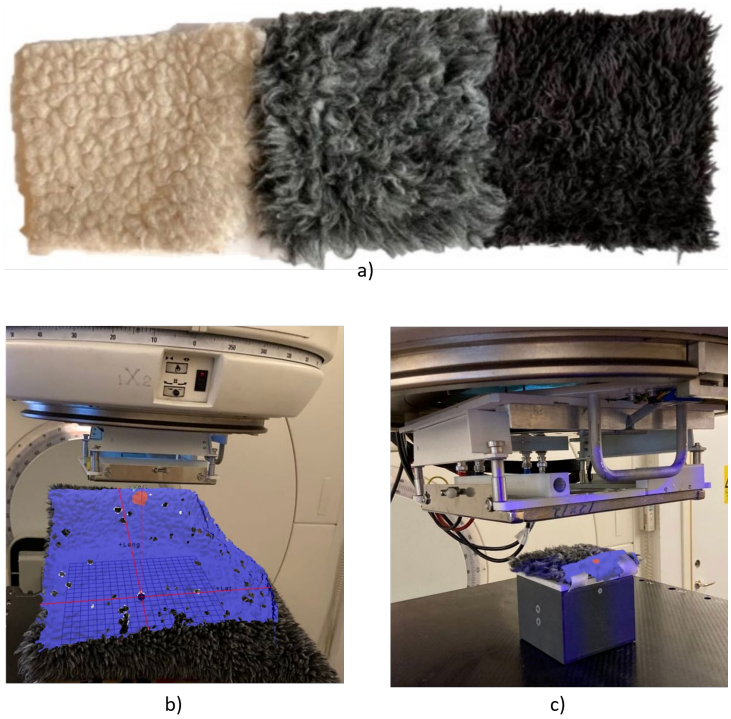


Figure 4.4. The fur blankets used for measurements of surface coverage, breathing motion and sudden motion (a) and the setup for breathing motion simulation (b) and sudden motion simulation (c). Some surface coverage loss is seen in (b) and the used ROI is diplayed as a red circle in (b) and (c). Figures adapted from **Paper III**.

All fur surfaces were detectable by the SI system and a surface was rendered for each fur colour within hardware limitations. The darker the fur, the higher the integration time and gain of the camera settings.

The SI system could accurately reproduce a breathing curve for all fur colours. The sampling time was comparable between the white and grey fur (approx. 62.5 ms), while it was slightly larger for the black fur (80.5 ms). For sudden motion the SI system could not distinguish all peaks for frequencies larger than 3 Hz (Figure 4.5a). For the majority of measured frequencies, the sampling time was under 65 ms (Figure 4.5b). For the black fur however, the sampling time was larger with sampling times over 100 ms for all frequencies but 1 Hz (Figure 4.5b).

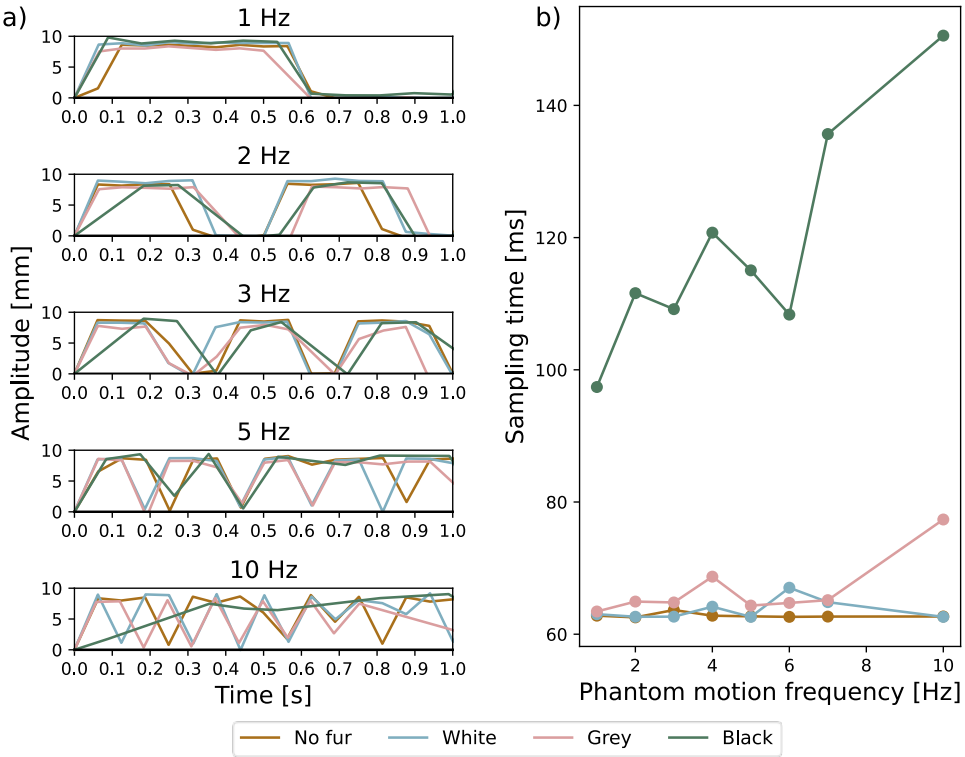


Figure 4.5. (a) The measured curves for the simulated sudden patient motion for frequencies 1, 2, 3, 5 and 10 Hz at SSD = 70 cm. (b) The mean sampling time for each simulated motion frequency at SSD = 70 cm (b). Figure adapted from **Paper III**.

The surface quality is influenced by both the colour and structure of the scanned object [57]. Hair and dark coloured objects have been observed to negatively affect the surface coverage [57, 79, 80]. However, **Paper III** presented evidence that with optimized camera settings, it was feasible to achieve surface coverage and motion tracking for all furs. Adequate surface coverage for the black fur was however at expense of reduced sampling time.

Unlike in conventional RT, a sudden temporary motion in FLASH-RT could mean that the total dose is delivered to the wrong location. This therefore puts a higher demand on a fast motion management technique. In **Paper III**, we demonstrated that patient position information can be obtained every 62.5 ms, which to our knowledge is the fastest system available. It has been previously shown that 158 – 1664 ms can pass between when the operator gives the beam-on clearance and when the irradiation actually begins [81-84]. With SGRT there is a possibility to detect motion during the beam-on time delay.

Although the SI system had trouble to accurately determine the amplitude and to distinguish all peaks at frequencies higher than 3 Hz for the simulated sudden motion, it at least detected *a* motion. While the estimated position offset might not be correct, SI could still be able to detect motion with a frequency of 10 Hz.

For clinical FLASH-RT treatments, SGRT was used and evaluated for 11 consecutive canine cancer patients. Ten patients received a single fraction of FLASH-RT, while one patient was treated in three fractions. Prescribed single fraction doses ranged between 15 and 40 Gy and the fractionated prescribed dose was 15 Gy/fraction. The camera settings were optimized for each patient, to achieve the best surface coverage. Once the setup was complete, a reference surface was captured in the positioning mode. The patient was then moved outside of the treatment field for FLASH-RT beam quality control. For real-time monitoring during this, a temporary surface reference was used in the motion monitoring mode. After quality control the patient was moved back to the approved couch position. The saved reference surface could then be used for assuring that the patient's current setup did not deviate from the approved setup. The motion of the patient was monitored and just before beam-on, the position of the patient was checked and if no clinically significant motion was observed, the treatment proceeded. The motion monitoring data was retrieved from the Catalyst™ system log files for motion analysis.

Good surface coverage was achieved for the majority of canine patients (Figure 4.6a,b). Only one patient had a total vector offset motion >2 mm immediately before and after beam-on (Figure 4.6c).

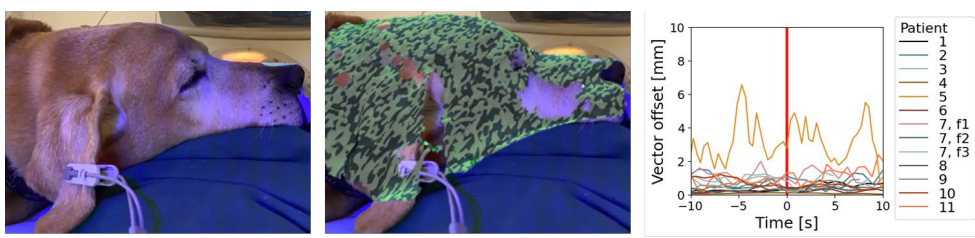


Figure 4.6. An example of a canine patient (a) and its surface overlayed on the patient (b). (c) The total vector offset motion data for the 11 canine patients.The motion 10 s before and after beam-on at 0 s (red bar) is displayed. Figures adapted from **Paper III**.

SI proved to be an valuable asset during the FLASH-RT treatments of canine cancer patients, without causing any treatment compromises or delays. For the fractionated treatment, it was practical to utilize the refence surface from the first fraction during the subsequent ones. Additionally, SI played a crucial role in averting incorrect treatment for one patient where the Catalyst™ detected large motion prior to radiation

delivery. This motion was due to that the patient had not been administered enough anaesthesia.

4.2 Prostate motion and the MR-linac workflow

The MR-linac workflow (Figure 4.7) differs from the conventional workflow, since the MR-linac is intended to be used for online ART. Generally, both a planning CT and a planning MRI are acquired for dose calculation and delineation purposes. During each fraction the patient anatomy and position are evaluated with a daily MRI. If the patient's position and anatomy closely match the planning CT, the adapt to position workflow can be applied. In this workflow the daily MRI is rigidly registered to the planning CT and a translation of the isocenter is carried out. The original treatment plan can then be either recalculated or reoptimized with the planning CT used for dose calculation [85]. For situations with large anatomical changes, the adapt to shape workflow can be selected instead. The daily MRI is then deformably registered to the CT and the structures are propagated to the daily MRI. The deformed structures are reviewed and can be edited if necessary. Reoptimization is then carried out based on the anatomy of the day in the daily MRI, using bulk electron densities for dose calculation [85]. Patient specific QA is performed both offline of the original plan before treatment and online after reoptimization [86]. Treatment delivery is preceded by another MRI to verify the patient anatomy. If the anatomy remains unchanged since the initial MRI, treatment can proceed. However, if there have been anatomical changes during the plan adaptation process, another adaption should be carried out [87].

Besides the possibility of online ART, the MR-linac also offers real-time imaging with superior soft tissue contrast. Further, the MR-linac has the ability to automatically hold the beam if the target is detected to be too far outside its PTV margin [88]. This means that target sites that are complicated to treat with conventional RT, such as pancreatic tumours in close proximity to the bowel, can instead be treated on the MR-linac [89].

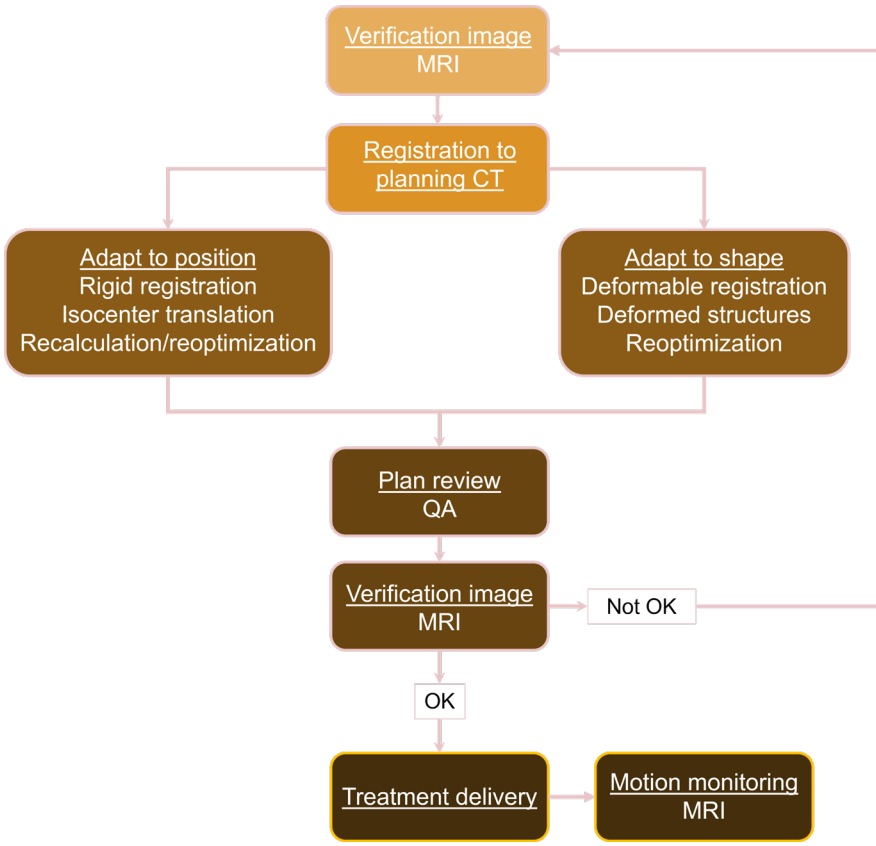


Figure 4.7. Schematic illustration of a typical MR-linac workflow from online verification imaging and forward. Depending on the patient position and anatomy, either the adapt to position or adapt to shape workflow can be selected.

A major drawback of the MR-linac is the time-consuming workflow [88]. The time between daily MR acquisition and beam-on is typically around 25-30 min [90-94], with times up to 45 min recorded [94]. This suggests that the patient is treated with a plan adapted to the anatomy of 30 minutes earlier. As mentioned in section 4.1.1, prostate motion increases with time [64, 65, 68], which may pose an even greater challenge when treating prostate cancer patients on the MR-linac instead of a conventional linac. If it is not ensured that the adapted plan is still valid just before beam-on, there is a risk of adverse dosimetric effects. In **Paper IV** we therefore assessed the dosimetric impact of prostate motion and anatomical changes during the time frame representative of the adaptive replanning procedure on the MR-linac. This was carried out because we were specifically interested in understanding the dosimetric

effects that may arise in an MR-linac treatment when beam-on is not preceded by a thorough verification of the patient anatomy.

The 35 patients with localized prostate cancer included in the study had all been treated according to an MRI-only RT workflow [95]. All patients had therefore undergone MR examination in treatment position. During the MR imaging two large FOV T2-weighted MRIs (MR1 and MR2) were acquired 30 min apart. Synthetic CT (sCT) images were created for both MRIs for dose calculation (sCT1 and sCT2). All delineations were carried out based on the anatomy of MR1. Treatment plans were created in Eclipse v 13.6.23 (Varian Medical Systems, Palo Alto, CA, USA) with a prescribed dose of 42.7 Gy in 7 fractions using two full arc 6 MV flattening filter free (FFF) VMAT beams. For each patient treatment plans for three different PTV margins (3 mm, 5 mm, and 7 mm) were created. The 7 mm margin is the one currently used in our clinic. A PTV margin of 5 mm have been reported for hypofractionated localized prostate cancer RT [96] and a 3 mm margin have been used for treatment on the MR-linac [93, 97]. The treatment plans were created for the anatomy of MR1 and calculated on sCT1. This dose distribution (D1) was then recalculated on sCT2 with the same monitor units, generating D2. Anatomical changes were quantified in MICE Toolkit (NONPI Medical, Umeå, Sweden) using deformable registration between MR1 and MR2. Dose volume histogram (DVH) comparison was enabled by warping D2 to the geometry of D1. In an MR-linac workflow D1 represented the online adapted treatment plan, while D2 represented the resulting dose distribution delivered to the patient if no motion correction was carried out just before beam-on. The dosimetric effects were evaluated for one fraction.

The 30 min between MR imaging resulted in a mean (range) CTV center of mass (COM) vector shift of 1.92 mm (0.13 – 9.79 mm). Motion occurred primarily in anterior-posterior (A-P) and superior-inferior (S-I) directions, with largest motion in A-P. Anterior shifts were mainly caused by rectal gas and posterior shifts were caused by the bladder or the patient relaxing his muscles from MR1 to MR2. The probability of a displacement ≥3 mm and ≥7 mm during 30 min was 20% and 2.9%, respectively. A decrease larger than 2% in the CTV D_{min} from D1 to D2 was present in 1, 4 and 11 patients for the 7 mm, 5 mm, and 3 mm margin respectively (Figure 4.8). Using the Wilcoxon signed-rank test with a significance level of 0.05, statistically significant difference in CTV D_{min} between D1 and D2 was found for the 3 mm margin.

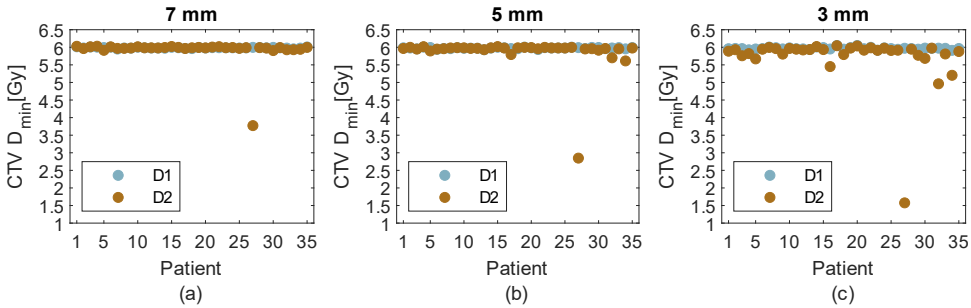


Figure 4.8. The CTV D_{min} dose for one fraction in dose distribution D1 (blue) and resulting dose distribution after 30 min, D2 (brown), without correcting for motion, for a 7 mm (a), 5 mm (b), and 3 mm (c) PTV margin. Figure adapted from **Paper IV**.

As demonstrated in **Paper IV** there is a risk of prostate motion and anatomical changes occurring during the time of the online ART procedure on the MR-linac. **Paper IV** highlights the importance of verifying the prostate position and the surrounding anatomy just before treatment is delivered and that this step should not be neglected in the MR-linac workflow. A two-dimensional image in only one or two planes might not be enough to get the full picture of how the anatomy has changed since the first MRI and how these changes can affect the dose distribution.

A smaller PTV margin led to lower rectum dose, which can be expected. Promising outcome results have been published showing low acute toxicity and good early outcome for MR-linac treatment of prostate cancer [97, 98]. This is presumably the result of a smaller PTV margin and real-time imaging of the prostate motion. However, since the MR-linac still is relatively new, long term follow up data on tumour control and late toxicity are still limited [98].

4.3 Stereotactic body radiotherapy of ventricular tachycardia

VT is defined as a heart rate exceeding 120 beats per minute with at least 3 consecutive beats, arising from the ventricles [99]. It often originates from scar tissue which has developed following a previous myocardial infarction. VT patients often have an implantable cardioverter defibrillator (ICD) to interrupt the VT episodes [100]. Standard treatment of VT also includes catheter ablation and anti-arrhythmic medicine [99]. Recently, SBRT has been explored as an alternative treatment for VT. Early

studies have shown that by delivering a high dose of 25 Gy in one fraction to the VT substrate, the amount of VT episodes can be substantially reduced [101-103].

In order to precisely locate the VT substrate and subsequently define a target volume, a combination of imaging techniques is employed. Electrophysiological imaging is utilized to map the electrical activity in the heart, allowing for the precise determination of the arrhythmogenic source. These electrical maps can be complemented with various imaging modalities, including MRIs, 4DCT scans capturing both cardiac and respiratory motion, nuclear medicine images such as single-photon emission computed tomography or PET, and a planning CT. All the acquired images contribute to localization and characterization of the VT substrate, which is denominated CTV in the context of RT [104].

Inter-and intrafractional motion is accounted for by adding a PTV margin to the CTV. The size of the PTV margin has varied among the reported studies [105]. Some groups have only considered the cardiac and respiratory motion, while others have also included other uncertainties such as setup errors and anatomical changes in the OARs [105]. Regardless of size, the PTV margin will include healthy tissue, and may also overlap with OARs in close proximity to the target. Minimizing the PTV margin is important for sparing as much heart and other OARs as possible.

If motion was reduced, it should also be possible to reduce the PTV margin. However, SBRT of VT is a new treatment, and it should not be assumed that motion mitigation methods proven effective for well-established RT treatments can be directly applied to VT treatment. It is therefore important to evaluate the currently available motion management strategies once again for emerging treatments, and accordingly, the objective in **Paper V** was to investigate if AC is an effective method for reducing respiratory induced heart motion.

Since VT patients receiving RT are some of the most uncommon patients in our clinic, a surrogate patient cohort was used to increase the sample size. The cohort consisted of 30 lung cancer patients who all had undergone one 4DCT scan with AC and one without AC. Each 4DCT consisted of 10 phases and the respiratory signal was captured with the Sentinel system (C-Rad Positioning AB, Uppsala, Sweden). The AC plate in combination with the stereotactic body frame (Elekta, Stockholm, Sweden) was used for compression. Twelve patients had to be excluded from the study because of either substantial image artefacts or incomplete heart coverage within the scanning volume.

Since VT RT targets most frequently are located in the left ventricle [104], the left ventricle and its motion relative to other substructures and surrounding heart tissues of the heart was of particular interest. Therefore, the left coronary artery (LCA), the left anterior descending artery (LAD), the lateral wall of the left ventricle, the apex of the

heart, the carina, and the right and left diaphragm were delineated. The LCA, LAD, carina and diaphragm were all delineated as small point structures. The apex was delineated in the two most inferior CT planes of the heart and the left ventricle wall was delineated from most superior to most inferior part (Figure 4.9). All structures were delineated in both max expiration phase and max inspiration phase in both available 4DCTs, and all delineations were carried out in the Eclipse (v 15.6) TPS.

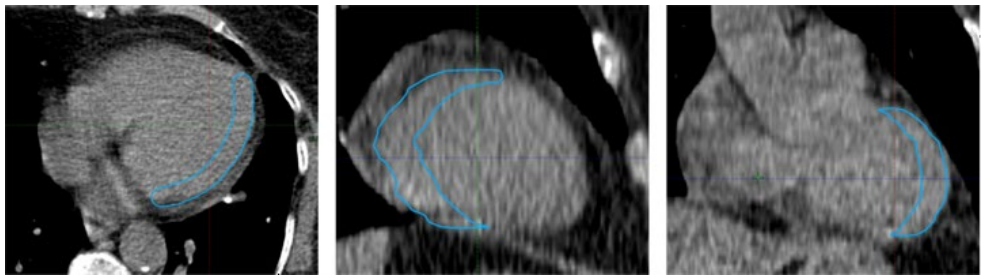


Figure 4.9. Example of delineated left ventricle wall in the transversal (left), sagittal (middle) and coronal (right) plane. Figure from **Paper V**.

In Eclipse the COM shift in L-R, A-P, and S-I direction was retrieved from the statistics tool. The individual translational shifts and the total 3D vector shift from max expiration to max inspiration were compared between the 4DCT with AC and the 4DCT without AC.

The results showed that AC reduced the median 3D vector COM shift from max expiration to max inspiration by 1.9 mm, 0.5 mm, 1.8 mm, 4.1 mm, 1.0 mm, 7.6 mm and 5.5 mm for the LCA, LAD, left ventricular wall, apex, carina, right diaphragm, and left diaphragm, respectively (Table 4.1). AC reduced respiratory induced motion most in the S-I direction. For 14 out of 18 patients, the motion in the left ventricle wall was reduced when AC was used (Figure 4.10). However, for four patients the motion increased, with 3.3 mm being the largest increase (Figure 4.10).

Table 4.1. The median (range) 3D vector center of mass (COM) shift from max expiration to max inspiration for all delineated structures, for both with and without abdominal compression (AC). Statistically significant difference was tested using the Wilcoxon signed rank test ($\alpha = 0.05$) and significant difference is marked with an asterisk.

Structure	Without AC	With AC	*p*
LCA	6.2 (3.5 – 16.6)	4.3 (1.9 – 11.0)	<0.01*
LAD	6.8 (3.8 – 12.5)	6.3 (1.9 – 10.9)	0.14
Left ventricle wall	7.4 (1.8 – 16.3)	5.7 (0.3 – 12.7)	0.01*
Apex	10.2 (4.8 – 20.2)	6.1 (2.2 – 22.8)	0.01*
Carina	5.4 (0.7 – 11.9)	4.4 (0.0 – 7.2)	0.09
Right diaphragm	15.7 (6.0 – 30.0)	8.1 (2.9 – 28.9)	<0.01*
Left diaphragm	13.5 (6.3 – 23.1)	8.0 (3.6 – 19.0)	<0.01*

LCA = left coronary artery, LAD = left anterior descending artery

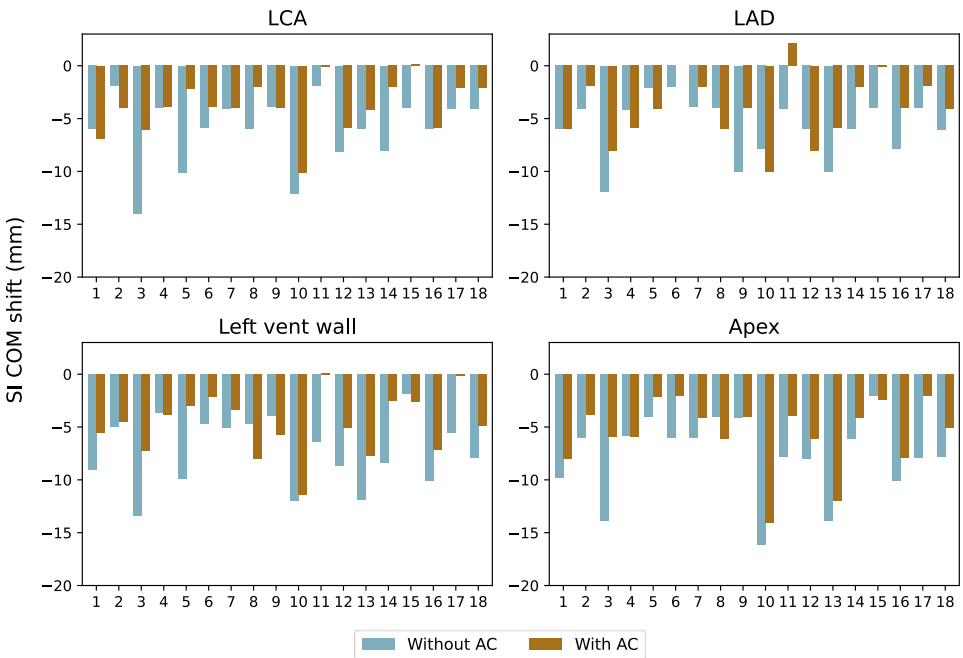


Figure 4.10. Center of mass (COM) shift from max expiration to max inspiration in 4DCT without abdominal compression (AC) (blue) and with AC (brown) in the superior-inferior direction for the left coronary artery (LCA), left anterior descending artery (LAD), left ventricle wall (left vent wall) and the heart apex. Negative values correspond to an inferior shift from expiration to inspiration. Figure adapted from **Paper V**.

The results indicated that the median respiratory motion of the heart was decreased by 1-3 mm when using AC. This might seem like a small effect but can still be of clinical significance in the case of SBRT of VT where a very high dose is delivered in just one fraction. It is however important to note that even if the respiratory induced motion of the heart decreased ≥3 mm for 10 of the patients in the S-I direction, the motion also increased for four patients. This is an indication that the potential benefit of AC has to be individually assessed.

Few studies have reported the effect of AC on the heart. Rasheed et al. [106] found no significant reduction in motion of the heart when using AC in lung cancer patients. The authors did demonstrate that while the motion decreases in one region of the thorax it can increase in another, similar to our results (Figure 4.10). This further underscores the importance of individually evaluating the effect of AC.

Although we showed in **Paper V** that a majority of the patients exhibited a reduction in respiratory induced heart motion, we did hypothesize that AC might not always be dosimetrically preferable even if motion is reduced. We suspected that the AC might push the stomach towards the target in some cases, possibly leading to an overlap between the stomach and the PTV. An overlap that would not have existed without the AC. Additionally, in a case report by Cha et al. [107] it was demonstrated that the distance between the stomach and PTV was 0 cm when AC was applied. The patient was instead treated in DIBH, where the separation between the stomach and PTV was 0.67 cm. Further, several studies have described treatment in either DIBH [107, 108] or expiration gating/EBH [109, 110], but none of the studies have compared the different BH techniques between each other. The effect on OAR doses and target coverage of using AC, EBH and IBH remains to be comprehensively evaluated. Therefore, **Paper VI** aimed to dosimetrically compare EBH, IBH and treatment with and without AC for SBRT of VT patients.

Paper VI was carried out using the same patient cohort as in **Paper V**. In **Paper VI** we wanted to examine the dosimetric effect for patients with largest motion, since they would have the most benefit of either of the motion management strategies. Patients with a diaphragm motion <1.5 cm in the SI direction were therefore excluded. A total of 10 patients met this criterion. However, one of these patients had a deviant anatomy because of previous surgery and was therefore also excluded.

The objective throughout the study was to follow our clinical routine that is in place for SBRT of VT patients. The simulated target represented a realistic and standardized target for VT patients, corresponding to an occlusion in the LAD (Figure 4.11) and was delineated following the same method for all patients. The target volume, denominated CTV, was first delineated in the mid-position phase in the 4DCT

without AC (CTV_{NAC}). In the same 4DCT, a CTV_{EBH} and a CTV_{IBH} were delineated in the max expiration and max inspiration phase respectively. A CTV_{AC} was delineated in the mid-position phase of the 4DCT with AC. Both CTV_{NAC} and CTV_{AC} were expanded to ITVs according to the motion in respective 4DCT. The CTV-PTV margin was 3 mm for the FB treatments and 5 mm for the BH treatments. Cardiac motion was considered to be included in the ITVs, hence the smaller PTV margin for the FB plans. The OARs that were delineated were the heart, esophagus, stomach, bowel and both lungs.

The dosimetric effect of proximity to an OAR was of interest and the five patients with PTV in closest proximity to the stomach were considered as most interesting and treatment plans were therefore created for them. The treatment plans consisted of two half arc (0° - 179°) 10 MV FFF beams, with a prescribed dose of 25 Gy in 1 fraction. They were normalized so that 95% of the PTV received 100% of the prescribed dose. The dose constraints for the OARs were met for all treatment plans since it was strict a requirement and was prioritized higher than dose coverage of the target.

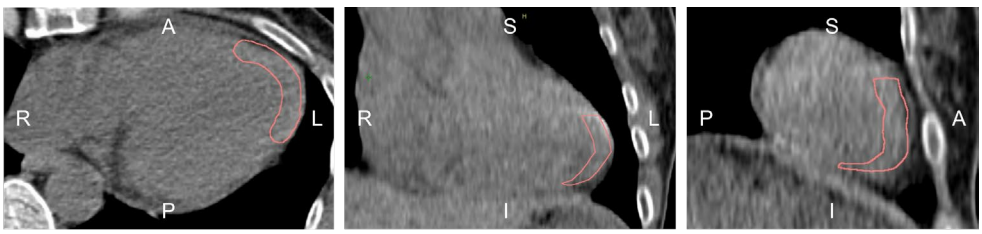


Figure 4.11. An example of the CTV in the transversal (a), coronal (b) and sagittal (c) plane. Figure from **Paper VI**.

For most simulated treatments the target coverage was maintained. However, for two treatment plans a substantial compromise of PTV coverage was observed; Patient 1 had impaired PTV coverage in the treatment plan *without* compression (PTV_{NAC}) and Patient 4 had impaired PTV coverage in the treatment plan *with* AC (PTV_{AC}) (Figure 4.12, Table 4.2). Patient 1 and Patient 4 both had an overlap between the stomach and the PTV (Table 4.2).

The stomach affected the treatment plans the most because it was the OAR in closest proximity to the PTV. The separation between the PTV and stomach ($d_{(PTV\text{-}Stomach)}$) was generally larger for BH treatment (Table 4.2). This contributed to a slightly lower dose to the stomach in the BH plans compared to the FB plans and smaller PTV volumes receiving <25 Gy and <20 Gy (Table 4.2).

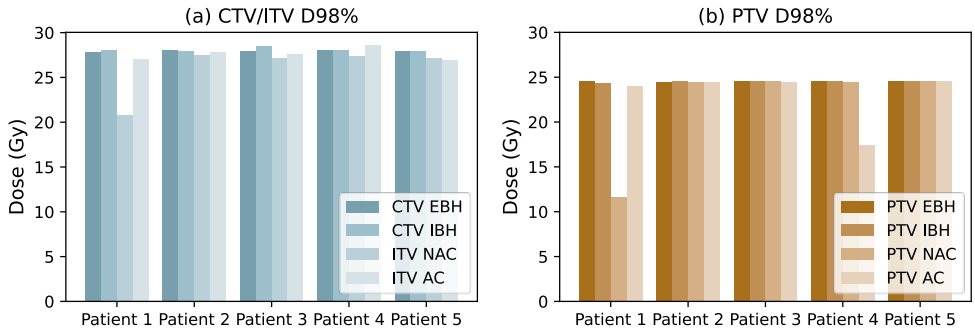


Figure 4.12. The $D_{98\%}$ to the CTV/ITV (a) and PTV (b) for simulated treatment plans in expiration breath-hold (EBH), inspration breath-hold (IBH), without abdominal compression (NAC) and with abdominal compression (AC). Patient 1 and Patient 4 both had compromised PTV coverage. Figure adapted from **Paper VI**.

Table 4.2. The distance between the PTV and stomach ($d_{(PTV\text{-}Stomach)}$), the PTV volume, PTV $D_{95\%}$ and PTV volume receiving <20 Gy for treatment simulation in expiration breath-hold (EBH), inspration breath-hold (IBH), without abdominal compression (NAC) and with abdominal compression (AC).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
$d_{EBH(PTV\text{-}Stomach)}$ (mm)	1.5	2.0	5.9	5.7	7.0
$d_{IBH(PTV\text{-}Stomach)}$ (mm)	-3.9	4.3	5.1	1.5	6.0
$d_{NAC(PTV\text{-}Stomach)}$ (mm)	-7.2	1.7	4.0	1.8	2.6
$d_{AC(PTV\text{-}Stomach)}$ (mm)	0	0	0	-2.3	3.5
PTV_{EBH} Volume (cc)	53.1	73.7	55.0	49.3	69.6
PTV_{IBH} Volume (cc)	56.7	75.0	53.6	48.9	68.4
PTV_{NAC} Volume (cc)	71.5	88.8	60.3	57.1	90.2
PTV_{AC} Volume (cc)	55.4	75.0	53.2	50.5	87.8
PTV_{EBH} $D_{95\%}$ (Gy)	25.0	25.0	25.0	25.0	25.0
PTV_{IBH} $D_{95\%}$ (Gy)	24.3	25.0	25.0	25.0	25.0
PTV_{NAC} $D_{95\%}$ (Gy)	19.8	25.0	25.0	25.0	25.0
PTV_{AC} $D_{95\%}$ (Gy)	24.5	24.6	25.0	23.8	25.0
PTV_{EBH} $V_{<20Gy}$ (cc)	0	0	0	0	0
PTV_{IBH} $V_{<20Gy}$ (cc)	1.2	0	0	0	0
PTV_{NAC} $V_{<20Gy}$ (cc)	3.7	0	0	0	0
PTV_{AC} $V_{<20Gy}$ (cc)	0.1	0.3	0	1.5	0

The results suggested that BH may be dosimetrically preferable compared to FB for patients where the stomach is close to the target. There was a clinically significant difference between the FB plans for Patient 1 and Patient 4, where AC increased the distance to the stomach for Patient 1 but decreased the distance for Patient 4. Noteworthy is, that for both these patients the AC reduced their heart motion in **Paper V** (Figure 4.10, Patient 1 in **Paper VI** = Patient 13 in **Paper V**, Patient 4 in **Paper VI** = Patient 1 in **Paper V**). The AC reduced the motion of the left ventricle wall in S-I direction with 3.5 mm for Patient 4, however it also pushed the stomach towards the stomach, resulting in reduced target coverage.

As it appears that target coverage is linked to the proximity of the stomach to the PTV, measuring the simple distance between the PTV and nearest OAR can provide valuable information about which of the motion management strategies would be dosimetrically favourable, either for an individual patient in a clinical setting or for a cohort of patients in a research setting. However, our findings also demonstrated that a separation of only 2-3 mm can be enough to be able to keep the target coverage. A larger distance would solely result in a lower dose to the OARs. One patient (Patient 3) had large separation between the PTV and stomach for all simulated treatments except with AC, where the distance was 0 mm. Despite this, the target coverage was acceptable in all plans, including the one with AC.

To summarize, the results from **Paper V** and **Paper VI** indicate that AC can be beneficial in means of reducing respiratory induced heart motion. However, the effect on motion in combination with the effect on distance between target and OARs must be evaluated Further, BH appears to increase the distance between the PTV and the stomach, which can mean a dosimetric advantage. Based on our results we would recommend an individual comparison between BH vs. FB as well as treatment with or without AC for all VT patients.

5. General discussion and future perspectives

It is now a few years since the study in **Paper I** was carried out. At the time of data collection, SGRT was not the standard workflow in the radiotherapy department at SUS, Lund and SI was used mainly for DIBH RT of breast cancer patients. Many in the treatment staff who operated the system in the study, were still inexperienced with the Catalyst™ system, while they had several years of experience of positioning the patients with 3-point localization. Furthermore, only a limited number of linacs were equipped with the three-camera setup at that time. **Paper I** did however initiate the clinical implementation of using SI setup for all breast cancer patients in our clinic. At the time of **Paper II,** there still remained some inexperience in using the Catalyst™ system. The access to the three-camera setup was also still limited. Today however the picture is completely different in our clinic and SGRT is an important part of our workflows. All clinical linacs with C-Rad systems are now installed with a three-camera setup and all patients are initially positioned with SI and are no longer tattooed. Surface motion monitoring is generally also used for all patients and is a central tool for patient safety and accurate treatment delivery. It would be interesting to conduct a similar study as in **Paper I** and **Paper II** to evaluate how several years of clinical practice of using SGRT for all patients have influenced the initial setup accuracy. However, daily imaging of all patients is now common practice in our clinic, which it was not at the time of **Papers I** and **II**, so the initial setup is always verified with images. Therefore, it might be even more interesting to further investigate the effectiveness of applying the SGRT workflow, as new data probably would show an even larger reduction in setup time now when the staff is more experienced and comfortable with using the system.

Another interesting finding from **Paper II** was that the treatment personnel noticed an improved physical work environment with the SGRT workflow. There was less need for manual hands-on positioning of the patient in uncomfortable or awkward positions for the staff, resulting in reduced back and shoulder pain. While this is beyond the scope of my research it would still be interesting and important to follow up on these findings.

Fast motion management will be crucial for FLASH-RT of human patients. Although **Paper III** focused on SGRT for FLASH-RT of canine patients, the work can still be applicable to human patients. Mascia et al. [76] reported on proton FLASH-RT for 10 patients whose position prior to beam-on was verified with X-ray images. However, in FLASH-RT it is important to be able to verify the patient position as close to beam-on as possible and acquire and match X-ray images may be too slow for detecting sudden motion. Additionally, for non-isocentric FLASH treatments SI would right now be our best option for imaging the patient in treatment position, because of the large FOV and fast imaging capabilities of SI. SI will continue to be used for motion monitoring of our canine patients receiving FLASH-RT. Many patients have been treated off-isocenter and with various couch rotations, which makes it difficult to obtain surface coverage over or near the target site with only one camera. For full surface coverage in all angles and SSDs, a three-camera setup would be warranted. However, three cameras also involve processing more data, which could potentially result in a reduction in the speed of the system. It would also be of interest to explore other fast motion management options for FLASH-RT. For instance, the potential of Cherenkov imaging during FLASH-RT delivery has been published by Rahman et al. [111].

When **Paper IV** was conducted, we were wondering what the effects would be for a prostate cancer patient where the intended MR-linac workflow was not followed. This question arose from hearing that a few RT centers that just had started treating with an MR-linac, did not acquire verification images after the adaption procedure, just before beam-on. We thought that there would probably be dosimetric effects of treating with a plan adapted to the anatomy valid 30 min earlier. Although the field of MR-linac has seen rapid growth since **Paper IV** [112], the question of the dosimetric impact of different MR-linac workflows is still relevant. In a recent study by Lawes et al. [113] the authors described their workflow for doing an adapt to position before beam-on, after an adapt to shape replanning had been carried out. The results showed that for patients where intrafractional motion had occurred during the daily replanning, it was dosimetrically beneficial to also adapt to position after the first adaption. This is in coherence with our conclusion in **Paper IV**, that positional verification is important immediately before beam-on. Since a major drawback of **Paper IV** is that it was not carried out on an MR-linac, it would in the future be interesting to do a similar investigation on an actual MR-linac.

The advantages and disadvantages of using AC during SBRT of VT should be further investigated. Based on our results the AC can reduce motion (**Paper V**) and impair the dose distribution (**Paper VI**) at the same time. However, this was only apparent for one patient, and it would therefore be interesting to include more patients in a future evaluation. One drawback of both **Paper V** and **Paper VI** is that they were carried out

using lung cancer patient data. We wanted to evaluate all motion management strategies for each individual but also between individuals and chose a relevant and large patient cohort where each patient had undergone two thorax 4DCT examinations. We included 30 patients and in the end nine were left for evaluation in **Paper VI,** which was fewer than anticipated. It would therefore be interesting to in the future include more patients. Additionally, it would be of interest to also investigate the dosimetric effects of the motion management techniques for other locations in the left ventricle.

Another drawback of **Paper VI** is that the BH treatment is simulated on phases from the 4DCT. It would be more accurate to evaluate the difference between EBH and IBH, or even DIBH, on actual BH CTs. Unfortunately, we did not have access to a large data set where both EBH and DIBH had been imaged for the same patient. An option to further compare EBH to DIBH would be to utilize CT images of breast cancer patients. A few years ago, the breast cancer patients planned for DIBH treatment in our clinic were always CT scanned in both DIBH and FB. By creating VT SBRT treatment plans on both these images the benefits and disadvantages of DIBH might become more apparent. However, this would still include approximations. FB is not the same as EBH and breast cancer patients are not VT patients.

Of course, the most interesting would be to do future investigations on our actual VT patients. Since 2021, three VT patients have been treated with SBRT at SUS, Lund. At present, it would be difficult to show any clinical significance or even trends based on this small patient cohort. When the number of patients is larger, motion management optimization will be carried out on the VT patients.

6. Conclusions

This thesis aimed to analyse, evaluate, and optimize motion management techniques for radiotherapy (RT) patients receiving conventional, novel or emerging treatment techniques. The work in this thesis has improved the initial patient setup accuracy and efficiency, implemented motion management for a completely new treatment, raised awareness of risks if proper motion management is left out and demonstrated dosimetric effects of different motion management techniques.

Specifically, it was concluded that:

- Initial setup using surface imaging (SI) instead of 3-point localization improved the positioning accuracy for both breast and prostate cancer patients. (**Papers I** and **II**)
- The initial setup time was reduced by approximately 1 min per fraction when SI was used instead of 3-point localization for prostate cancer patients. (**Paper II**)
- SI can be used for motion monitoring of canine patients in a clinical electron FLASH-RT setup. Surface coverage was achieved for several fur colours. The sampling time of the SI system was fast enough to detect sudden motion, enabling beam hold immediately prior to treatment delivery. (**Paper III**)
- Due to anatomical variations in prostate cancer patients occurring during the time of daily adaptive replanning in the MR-linac workflow, there is a risk of target underdosage if anatomical changes are not corrected for before beam-on. (**Paper IV**)
- Abdominal compression (AC) decreased the respiratory induced heart motion for the majority of patients. However, for a few patients the AC increased the heart motion, which indicates that the effect of AC should be individually assessed. (**Paper V**)
- For ventricular tachycardia (VT) patients with the stomach in close proximity to the target there appeared to be an inclination towards a more preferable dose distribution in the simulated breath-hold (BH) treatment plans compared to

treatment in free breathing (FB). Based on the small data set we would recommend comparing treatment in BH and FB as well as treatment with or without AC individually for each VT patient. (**Paper VI**)

Acknowledgements

This thesis would never have been finished without all the help and support that I have received over the years from so many people. I am grateful to each and every one who, in some way or the other, contributed to this work. Some of these incredible people deserve a special thanks.

First, I would like to thank my main supervisor *Sofie Ceberg*. This journey would not have been half as fun and rewarding without you there, constantly cheering me on. Thank you for sharing all your knowledge and for showing me how fun research can be. Thank you for all your support, for always being available and for always believing in me. Your endless encouragement and positive outlook on everything will keep me inspired for life.

I would also like to thank my co-supervisor *Anneli Edvardsson*. You have been a role model of mine since you were my lab supervisor during my undergraduate studies. You really have the best combination of knowledge, curiosity, and critical thinking, and your feedback is always golden! Thank you for always listening and offering to help.

My co-supervisor *Martin Nilsson*, thank you for your support and for sharing your knowledge and perspective as an oncologist. I have really enjoyed working closely together with you on the two last projects and I am amazed by your structured way of working and your pedagogical skills.

My co-supervisor *Crister Ceberg*, thank you for sharing your endless wisdom in all matters and for always having valuable input. I am very grateful that you have taken time from your busy schedule to be my supervisor.

I would also like to thank all my co-authors. A special thanks to: *Malin Kügele*, it has been so much fun working together with you and I have learnt a lot from you and all your expertise. You are like a breath of fresh air with your limitless energy and positivity! The *MRinRT group*, thank you for the fun and fruitful collaboration and *Emilia Persson*, a special thanks to you for guiding me so well towards my first first-name publication and for all the fun times, both in and outside the clinic. *Elise Konradsson*, thank you for helping with the measurements that led to our first joint paper, and for being my brilliant teammate during this whole thing, at meetings, presentations,

courses, and conferences (and conference parties!). *Kristin Karlsson*, thank you so much for all your many contributions to the two last papers. I really hope that our collaboration continues.

Thank you to all my colleagues at Medical Radiation Physics in Lund. A special thanks to all past and present fellow PhD students. Thank you for all the fun times, including lunches, coffee breaks and after works. I wish you all the best. *Anina Seidemo*, thank you for being the best office roomie during both productive and not so productive times.

Thank you to everyone, including physicists, oncologists, engineers, and nurses, at the Radiotherapy department at Skåne University Hospital, Lund. I am especially grateful to all my fantastic physicist colleagues, you guys make it a wonderful place to work, and a special thanks to *Sven Bäck*, who has always had my back.

To all my friends, thank you immensely for all the dinners, beers, fikas, parties, conversations and other activities we have shared and thank you for always letting me vent about work, even if some of you have had no idea what I have been going on about.

To my family. *Christina*, my sister and one of the smartest and loveliest people I know, thank you for everything you have done for me over the years. Seeing you always leaves me happier than I was before. *Mamma* and *Pappa* thank you for your never-ending love and support. Thank you for letting me choose my own way in life and for always being there to help no matter what.

To all the children in my life, thank you for putting things in some much-needed perspective. And thanks to *Sixten*, for forcing me to take breaks and go outside every now and then.

However, the biggest thank you of them all goes to *Jonas*. My best person. I could not have done this without you. While I have been writing this thesis you have been supporting me, listening to me, comforting me, encouraging me, and feeding me without complaining once. And even if research is fun, there is nothing as fun as spending time with you. You are everything to me.

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Printed by Tryckeriet i E-huset, Lund 2023

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Medical Radiation Physics
Faculty of Science
ISBN 978-91-8039-808-4 (print)
ISBN 978-91-8039-807-7 (pdf)