PhD thesis
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Real-time motion management of prostate cancer radiotherapy

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Abstract

The aim of radiation therapy is to deliver a radiation dose to the tumour that is high enough for all cancer cells to be killed, while sparing healthy organs to such an extent that the side effects are as low as possible. Prostate cancer is the most common type of cancer among men in Denmark, and for prostate cancer treatments, the proximity of the bladder and rectum makes radiotherapy treatment of this site a challenging task. Furthermore, the prostate may move during the radiation delivery and treatment margins are necessary to ensure that it is still receiving the intended dose.

The main aim of this thesis is to manage prostate motion in real-time by aligning the radiation beam to the prostate using the novel dynamic multileaf collimator (DMLC) tracking method. Specifically, the delivered dose with tracking was compared to the planned dose, and the impact of treatment plan complexity and limitations of the MLC on the performance of DMLC tracking were investigated. We found that for prostate motion, the main tracking error arose from the finite leaf width affecting the MLCs ability to construct the desired shape.

Furthermore, we also attempted to model prostate motion using a random walk model. We found that for the slow and drifting motion, the model could satisfactory replicate the motion of the prostate, while the rapid and transient prostate motion observed in some cases was challenging for the model. We therefore added simulated transient motion to the random walk model, which slightly improved the results.

Using simulations of prostate treatments with motion, we estimated the impact of uncompensated motion during hypofractionated treatments, where the therapeutic dose is delivered during a small number of treatments. The vast majority of prostate motion was found to have a small impact on the dose to the prostate, while the dose to the risk organs varied as the motion either moved them towards or away from the irradiated region.

Finally, we investigated the usefulness of plan complexity metrics for untracked treatments. We found clear relationships between plan complexity and the agreement between delivered and calculated dose. Using plan complexity metrics is therefore potentially useful for predicting if plans are too complex for the dose calculation and delivery to be accurate.
Dansk resumé (Danish summary)

Prostatakæft er den hyppigste form af kræft hos mænd, og cirka 4000 mænd i Danmark får hvert år sygdommen. Radioterapi er en god behandling for prostatakæft, men på grund af tætheden til blæren og rectum så er det svært at undgå at disse organer også får en høj dosis. Problemet bliver større i det at prostata bevæger sig mens patienten ligger på lejet. For at sikre at prostata får den ønskede dosis er det nødvendigt at udvide det behandlede volumen. En anden mulighed er at kompensere for bevægelsen i realtid ved at lade strålefeltet følge prostata, såkaldt dynamic multifileaf collimator tracking (DMLC tracking). Teknikken kan potentielt bruges på de fleste strålemaskiner og er netop begyndt at blive anvendt ved prostatabehandlinger.

Formålet med denne afhandling er at undersøge overensstemmelsen mellem den beregnede dosis for et statisk målefantom og den målte dosis med bevægelse og DMLC tracking. Vi undersøgte betydningen MLC-bladens tykkelse, da tykkelsen giver en grænse for hvor godt MLC kan tilpasses den ønskede formen. Vi fandt at teknikken kunne genskabe den beregnede dosis selvom der var bevægelse, og at bladtykkelsen var den parameter der forårsagede den største fejl ved brug af tracking.

Vi brugte en Markovproces (eller random walk model) til at beskrive bevægelsen af prostata. Vi fandt at det virkede godt for de tilfælde hvor prostata kun bevægede sig langsomt. For at modellere hurtig bevægelse simulerede vi udover random walk også hurtige og store skridt, og fandt at de gav en noget bedre overensstemmelse med de virkelige bevægelser.

Derudover undersøgte vi de dosimetriske effekter af ukompenseret bevægelse ved at simulere adskillige behandlinger med såkaldte hypofraktionerede behandlinger, hvor hele dosis gives med et mindre antal behandlinger i stedet for de cirka fyrre behandlinger der er standard i dag. Vi fandt at for den store majoritet er marginer på 5 mm (3 mm mod rectum) omkring prostata nok til at undgå underdosering til prostata. Derimod varierede dosis til risikoorganerne i det at bevægelsen flyttet dem tættere på eller væk fra højdosisområdet (studie fire). Til sidst brugte vi et mål af plankompleksiteten som tidligere har været brug ved tracking, til at forudsige hvor god overensstemmelsen vil være mellem den beregnede dosis og målte dosis for almindelige strålerapi-behandlinger (uden tracking).
This thesis is based on the following five manuscripts which are based on research carried out from 2011 to 2014. The manuscripts are placed in an order relevant for the thesis and not in the order of production or conception.


List of papers not included in the thesis


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1. Introduction

1.1. External beam radiotherapy

The aim of radiotherapy is to kill tumour cancer cells so that the growth of the tumours is permanently stopped. Meanwhile, normal tissue should be spared to such a degree that any side effects are manageable. When the tumour is located close to organs whose function is critical, so called organs at risk (OARs), achieving both goals is extra challenging. When the tumour also has a tendency to move during the treatment, the challenge becomes even greater. For prostate cancer patients, the whole prostate is usually considered the tumour, and irradiated to the full radiation dose. Meanwhile the OARs include the bladder, rectum, and the femoral heads. A common approach in prostate radiotherapy is to aim high energy x-rays from an external source towards the prostate, so called external beam radiotherapy (EBRT). Using EBRT for cancer treatment is well grounded in current evidence and approximately every other cancer patient would need radiation in an optimal treatment regime [1]. To utilize different biological properties between tumour cells and healthy tissue, radiotherapy is usually fractionated and delivered daily during several weeks. Each treatment is then called a fraction.

1.2. The linear accelerator

A linear accelerator (linac) is used to create the high-energy x-rays [2]. In the linac, electrons are accelerated to energies in the megavoltage (MV) range in a straight (or linear) waveguide. The electrons are then directed towards a metal structure called a target. When hitting the target, the electrons are slowed down and x-rays are produced in a bremsstrahlung process. After passing through a primary collimator, the x-ray beam is made uniform with a flattening filter. The flattening filter is cone shaped so that it absorbs more energy in the centre, where the beam has higher energy fluence than in the periphery. On some linacs, the flattening filter can be removed, allowing higher dose rate and shortening of the treatment time. Finally, the jaws (the secondary collimator) and a multileaf collimator (MLC) form the x-ray beam to the desired geometrical shape. The jaws are two pairs of thick metal blocks that shape a rectangular field. The MLC is placed beneath the jaws and consists of a number of narrow interleaved metal collimators (leaves) placed in pairs among two leaf banks. The leaves move independently of each other to create semi-arbitrary shapes, limited by the maximum leaf travel from carriages holding the leaves. The collimators are mounted on a gantry that can rotate around the patient, and the collimators can also be rotated so that the alignment between the MLC leaves and the patient can be changed. The intersection of the gantry’s axis of rotation is called the isocenter.

1.3. The evolution of prostate radiotherapy

3DCRT
In the 1970s and 1980s, computed tomography (CT) scanning was introduced and allowed for three dimensional (3D) representations of patient anatomy. Together with dose calculation algorithms, CT scanning made it possible to first visualize and then to calculate the expected dose distribution given to the tumour and surrounding healthy tissue [3]. When the MLC was developed, it was used to shape the radiation field to the tumour and to shield OARs [4]. The technique was called 3D conformal radiation therapy (3DCRT). Basically, 3DCRT is a number of beams that are shaped based on the 2D projection of the patient anatomy as seen from the gantry. The projection is referred to as the beam’s eye view (BEV).

IMRT
The main limitation of 3DCRT is that it is difficult to achieve complex dose distributions, such as sparing the rectum while treating the partially surround-
Quality assurance

When IMRT and IMAT were introduced, the method of dose delivery was changed substantially from the static 3DCRT technique with open fields, to a dynamic technique where the MLC and gantry continuously move during irradiation [7]. The complexity of the dose calculation also increased, from a summation of a small number of open beams, to a summation of a large number of small and irregular fields delivered from up to 360 degrees around the patient [11]. In all, this motivated the implementation of patient-specific quality assurance (QA), i.e. measuring the plan delivered by the linac before treating the patient. Several options for patient-specific QA exist, including ionization chambers placed in phantoms [7], film measurements [13], diode and ionization chamber arrays [14–16] and x-ray imaging [17].

1 Otto called the technique volumetric modulated arc therapy (VMAT) but since Elekta uses the abbreviation commercially, IMAT is used throughout this thesis as to avoid manufacturer-specific terms.
The gross and clinical tumour volumes (GTV and CTV respectively) are volumes contoured by a physician to which a certain radiation dose is prescribed. For prostate radiotherapy, the GTV is often not delineated separately and instead the prostate (and, depending on clinical risk factors, parts of the seminal vesicles) are drawn, representing the CTV. The target volumes are then expanded with a margin to create the planning target volume (PTV), which is the volume used for subsequent treatment planning. The prostate is known to move sporadically, influenced by rectum and bladder changes [20]. Decreasing the geometrical uncertainties would allow reduction of treatment margins and thus a decreased volume receiving the prescribed dose [18].

1.5. Uncertainties and margins in radiotherapy

Due to calculation and mechanical imperfections of the linear accelerator and MLC, there will always be a difference between the calculated and the actually delivered dose in reference conditions. Basic dosimetry and quality controls ensure that the uncertainties are kept within acceptable levels. However, when treating patients, there are several geometric uncertainties that need to be addressed, including the following [18]:

- uncertainties in tumour delineation
- uncertainties in patient setup
- day-to-day differences in patient anatomy
- anatomical changes during a treatment fraction

The uncertainties (or errors, the terms are often used interchangeably) are usually divided into systematic and random errors, where systematic errors occur in the same way for each treatment fraction and random errors are different (and random) for each treatment fraction. It is useful to separate changes between treatment fractions (interfraction) from changes during actual delivery (intrafraction). Recommendations from the International Commission on Radiation Units and Measurements (ICRU) state that margins should be used to account for these uncertainties [19]. In practise, this is achieved by using different target volumes.

1.6. Cancer of the prostate

Prostate cancer is the most common form of cancer among men in Denmark and more than 4000 Danes are each year diagnosed with the disease. The mortality rate is relatively low and the 5-year survival is 82%³. Despite a clear increase in the number of diagnosed cases in the late 1990s, the number of deaths caused by prostate cancer has remained stable (figure 2). The primary options for treatment are surgery and radiotherapy, although active surveillance is also an option for tumours at less advanced stages.

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2 Not to be confused with the target in the linac, where the electrons are stopped and x-rays produced; here “target” refers to the volume that the x-rays are aimed at.

INTRODUCTION

Cancer of the prostate
2. Aim of the thesis

The general aim of this thesis was to investigate the feasibility and potential of dynamic multileaf collimator (DMLC) tracking of prostate radiotherapy, and specifically, to investigate the nature of prostate motion and the impact of uncompensated prostate motion on the dosimetric accuracy of radiotherapy.

The thesis is divided into three main parts; real-time motion management, prostate motion in radiotherapy and plan complexity in advanced radiotherapy. The specific aims of the three parts were as follows:

1. To investigate the possibility of compensating for prostate motion in real-time using the emerging DMLC tracking method and specifically determine the impact of plan complexity, MLC leaf width and motion characteristics on its performance (Study I, Study II).

2. To simulate prostate motion in an effort to further understand its features and to quantify the dosimetric impact of uncompensated prostate motion (Study III, Study IV).

3. To apply plan complexity metrics used in (1) on the agreement between planned and delivered dose in radiotherapy (Study V).
AIM OF THE THESIS

Cancer of the prostate
Motion management in radiotherapy is a general term used for all approaches that attempt to reduce or even eliminate the clinical impact of organ motion. Motion during delivery of a radiotherapy fraction is called intrafraction motion, while motion that occurs between fractions is called interfraction motion. Even though the same underlying processes (such as bladder filling) may cause both effects, the time scales are different. While interfraction motion can be corrected based on the tumour’s position before each fraction, intrafraction motion requires motion management on a time scale of seconds, i.e. real-time motion management (RTMM) [21].

Real-time motion management requires two, basically independent, steps: (1) real-time estimation of the tumour’s position, and (2) real-time compensation of the observed displacement [22]. In this section, an overview is given of current research regarding tumour localization and existing RTMM techniques, with specific focus on DMLC tracking, the technique used in Study I and Study II.

3.1. Localizing the tumour in real-time

Any real-time motion compensation approach requires that the position of the tumour is known with a sufficient accuracy both in time and space. That is, the position needs to be accurate for any compensation to be beneficial, and the position needs to be current or else the tumour may move before the motion compensation takes place. There are a number of options that, to certain degrees, fulfill both these criteria. These are discussed further here.

Megavoltage imaging

A straightforward way to image the patient on the couch is to use the treatment megavoltage (MV) beam and place a detector (called an EPID – electronic portal imaging device) on the opposite side of the patient. This is called portal imaging and has the advantage of using the same geometry as the treatment fields. The high energy reduces the image contrast compared to conventional x-ray imaging in the kilovoltage (kV) range, making soft-tissue localization difficult [23]. Implanting radiopaque markers (e.g. gold markers) in the prostate allows its position to be visualized regardless of the energy used. Although 2D images can give a position in 3D if obtained from different directions, there will when using portal images be a time delay between the first and the last image used for the 3D estimation. A single 2D image can still be suitable for RTMM since the physical properties of high energy x-rays means that motion along the direction of the beam has a small impact on the delivered dose, compared to motion towards the field edges [24]. One of the first examples of MV-imaging of implanted markers in the prostate was described by Balter et al. in 1995 [25]. The authors performed phantom studies and limited patient studies. Using a template from the first fraction and orthogonal images (i.e. two images taken perpendicular to each other), they were able to automatically extract the markers and calculate their, and thus the prostate’s, position in 3D. Continuous megavoltage imaging during treatment, using the therapeutic beam, has been investigated both with and without implanted markers. Yue et al. showed that with a general knowledge of the expected type of motion, a small number of continuous MV projections during an arc treatment were needed to estimate the 3D position with $< 1$ mm root mean square (RMS) error [26]. Mao et al. demonstrated how the treatment beam can be used to calculate the tumour position in 3D, using the EPID to image three implanted markers during IMRT. Images from one angle allowed calculating a 2D position, and images from several gantry angles were used to calculate a pseudo-3D-position [27]. Suh et al. showed that using MV-images, unresolved thoracic and abdominal motion can be limited with a mean RMS error of 0.12 cm [28]. For lung treatments, Rottmann et al. demonstrated marker-less
Localizing the tumour in real-time

REAL-TIME MOTION MANAGEMENT

MV-imaging, with < 2 mm error when compared to human observer, requiring one breathing cycle of training images [29]. Rottmann et al. later showed markerless MV-imaging in real-time with 1 mm RMS tracking error [30]. Park et al. were able to automatically detect implanted markers in liver for five patients, with good agreement to manual delineation. Their method utilized image processing and CT information to determine the expected marker positions [31].

The positions of three cylindrical fiducial markers implanted in the prostate have shown to be stable by Kupelian et al., who concluded, after examination of 56 patients, that any intra-marker variation is likely caused by prostate deformation [32]. In 2002, Kitamura et al. demonstrated the stability of implanted spherical gold markers in prostate (14 patients) and liver (4 patients), as the observed difference between the markers before and after a course of radiotherapy was on the same scale as the measurement uncertainty [33].

Lin et al. demonstrated automatic segmentation of prostate markers using the treatment beam, with consideration of whether the MLC would block a marker [34]. The method required training examples. In 2010, Liu et al. investigated the effect of MLC blocking the markers in prostate treatments, with approximately 55-60% marker detection rate (defined as at least one of three markers visible) during beam-on. Still, the amount of motion larger than a 3 mm threshold was more than halved (among the approximately 40% of traces that contained motion > 3 mm) [35]. Ma et al. showed that IMRT plans can be optimized so that markers are not blocked by the MLC, with a small loss of plan quality [36]. This has not yet been investigated for IMAT treatments. In 2009, Azcona et al. demonstrated localization of prostate implanted markers that could potentially be used in real-time during IMAT [37,38]. In a study of 10 patients, the fraction of images where at least one of three fiducial was visible varied greatly, from 10.9% for one patient to 94.5% for another [37]. In another study of five patients, the corresponding fraction ranged from 40% to 95%, with an average detection error (once a fiducial was visible) was less than 1 mm [38].

External markers

External markers are fiducial markers placed on the patient’s skin. For breast and skin cancer treatments, the markers are in close proximity to the treated volume and can therefore be used as is. For other tumours, some sort of correlation between the internal and external motion needs to be established [44]. For thoracic tumours, combined use of external markers, which move with the patients breathing, and kV imaging is a method to establish a correlation [45,46]. However, based on simultaneous fluoroscopy at 30 Hz and monitoring of the abdominal surface, Ionascu et al. observed a maximum miss-match in AP direction of 4.7 mm, caused by lack of correlation between the motion of the tumour and the abdomen [45]. Two independent studies have shown that using only external surrogates gives unsatisfactory uncertainties in tumour position [47,48]. In all, if using external markers for RTMM, it is necessary to periodically correlate the external motion with the tumour motion.

Kilovoltage imaging

Kilovoltage images have better tissue contrast than MV images, making them more suitable for determining the correct patient set-up. Also, the dose required for single image is lower [23]. For prostate radiotherapy, however, localizing the prostate still requires implanted markers. The downside compared to MV-imaging is that the geometry is different than the treatment geometry (a kV source and detector are commonly placed perpendicularly to the gantry and MV detector), and that MV images can be obtained from the treatment beam, i.e. with no extra radiation dose. Kilovoltage imaging for patient setup verification was investigated in the 1990s using gantry mounted [23] and room-mounted [39] x-ray sources and detectors. Combined MV and kV imaging for 3D localization of a marker have been demonstrated during arc radiotherapy [40]. Continuous kV-imaging during treatment can cause non-negligible extra radiation dose. Evolutions of a combined kV-MV approach allowed for primarily using MV-imaging and adding kV-imaging when needed [35,41]. In 2010, Liu et al. demonstrated combined MV and kV imaging for prostate arc therapy with implanted markers using phantom experiments and simulations studies. They used the kV imager only when the detected motion in the MV images was larger than a certain threshold, and used MV images from different gantry angles to calculate the semi-current 3D position of the markers [42]. The authors showed that a failure detection method detected prostate motion quicker than imaging with certain time intervals and with fewer kV images (and thus lower dose) than continuous imaging. In 2012, Li et al. demonstrated IMAT gating of lung with kV imaging for verification, with an external marker used to determine when to irradiate the tumour [43]. Implanted markers were identified and compared to the expected position to determine the tracking error.
Electromagnetic transponders
Electromagnetic transponders can be used to localize tumours without using any ionizing radiation. The transponders are implanted either in or near the tumour, or placed on the skin to act as an external marker. An external coil with a known location is placed in proximity to the patient in the treatment room. The coil induces resonance in the transponders that relax while transmitting a signal. The signal is received by the coil and determines the location and orientation of the transponders, and, by association, the tumour [49]. The technique is used in at least three commercial products that allow both patient setup and subsequent intrafraction monitoring. The most widely used system, Calypso, have been used extensively for prostate and prostate bed localization [50–54], and in limited studies for lung tumours [55]. The latter faces concerns of side-effects such as pneumothorax. In 2009, another commercial system called Micropos was demonstrated for clinical use for prostate patients [56]. In 2012, Cherpak et al. demonstrated an electromagnetic position sensor integrated with a dosimeter and studied its clinical use by placing detectors on the skin of lung cancer patients [57].

Volumetric imaging
Volumetric (i.e. 3D) imaging can be obtained by using 2D images from multiple angles. It is commonly used for pre-treatment setup, and the called cone-beam CT (CBCT). Intrafraction CBCT-imaging was demonstrated by Choi et al. who reconstructed the patient anatomy using a limited number of kV images during respiratory gated IMAT [58]. Options for volumetric imaging that do not use ionizing radiation include ultrasound and magnetic resonance (MR) imaging [20]. Ultrasound has, especially for prostate, the potential for 3D localization in real-time [59,60]. The usefulness of MR for RTMM is limited as combined MR-scanners and linacs (so called MR-linacs), is an emerging technology [61].

3.2. Beam gating, couch and source tracking
Once the tumour’s location is known, actions can be taken to ensure that any motion does not degrade the dosimetric accuracy of the treatment. There are two (conceptually) simple ways to do this in real-time. One is to stop the treatment if the tumour moves beyond a certain threshold and resume it once it moves back (called gating the beam), the other to align the tumour and the radiation field while the tumour moves (sometimes referred to as real-time tumour tracking). The latter can either be accomplished by aligning the beam to the tumour or by aligning the tumour (i.e. the patient) to the beam. In this section, a brief overview is given of beam gating, source tracking and couch tracking techniques.

Gating the beam
The principle of beam gating is very simple. If the tumour moves outside of a predefined volume, pause the treatment and wait until it moves back. With the tumour location known, all that is further needed is integration with the linac to automate the process [62]. For prostate treatments, the gated volume would likely surround the prostate with similar size in all directions [63]. For thorax treatments (e.g. breast, lung and liver), the gated volume can be chosen in a carefully prepared way to minimize residual motion within the gated volume, or to maximize the distance between the tumour and organs at risk [64]. The latter include deep inspiration breath hold for breast cancer patients [64]. The advantages of gating include its relative simplicity and the possibility of utilizing favourable patient anatomy (not applicable for prostate, however), while the main disadvantage is a prolonged treatment time.

Couch compensation
It is common practise to move the treatment couch before the start of radiotherapy treatment to align the target and organs at risk to its planned position [65]. If the tumour location is known, the correction can also be applied on a field-by-field basis [35]. The next natural step would therefore be to use the couch to correct for motion during the delivery as well. This has been successfully demonstrated in phantom studies with a modified conventional treatment couch by Buzurovic et al. [66] and for the Hexapod robotic couch by Wilbert et al. [67]. Couch tracking has been shown to be well tolerated by patients [68]. Advantages of couch tracking include high resolution and that no modification of the treatment plan is required. The main disadvantage is that the ability to correct for rotation is inherently limited (as the patient needs to lie relatively horizontally), and that deformations of the patients anatomy cannot be corrected for [66,67].

Moving the source
Moving the radiation source to account for tumour motion may seem unpractical, and it is impossible for a conventional linac. However, there are currently two commercial systems that allows such a strategy; Cyberknife and Vero.
The Cyberknife is a linear accelerator mounted on a robotic arm that can move with six degrees of freedom, i.e. it can both move and rotate in/towards any direction. It was designed for radiosurgery, i.e. very precise radiotherapy to a high dose [69]. Traditionally, radiosurgery was limited to cranial treatments as the patient’s head was fixed in a so-called radiosurgery frame, to maximize the treatment accuracy. The Cyberknife system instead used kV imaging to ensure the treatment accuracy, and thus allowed for extracranial treatments [69]. Besides kV imaging for patient setup, the system allowed for real-time tumour tracking using kV imaging combined with external markers (for compensation of breathing-correlated motion) [46,70] or only kV imaging for intermittent tracking (e.g. for prostate treatments) [71]. For breathing motion, a prediction algorithm is used to account for the system latency of 115 ms [70].

The Vero system consists of a small linear accelerator and a MLC mounted in an O-ring gantry (similarly to a conventional CT-scanner). Two gimbals hold the linac and MLC, allowing both to tilt and pan up to 2.5°, corresponding to 4.4 cm at isocenter, and for tumour tracking. The MLC is thus decoupled from the tracking system and can be used solely for intensity modulation. Two kV imaging systems are also mounted to the gantry, allowing for intrafraction kV-monitoring and tumour localization [72]. The RTMM part of the system was tested in a dry-run setup by Depuydt et al. in 2013, finding an acceptable level of skin dose from imaging when using external markers combined with kV imaging to build a correlation model between lung motion and chest wall motion [73]. The tracking error was found to be < 0.5 mm on average, with standard deviations (SDs) < 1 mm in both the pan and tilt directions. The tracking accuracy during lung cancer treatments for ten patients was reported recently [74].

### 3.3. DMLC tracking

Shaping the MLC in real-time to compensate for tumour motion is called dynamic MLC tracking (DMLC tracking). In contrast to the robotic and gimballed systems described above, DMLC track-

4 The word “tracking” when used in the literature can mean either to continuously observe the tumours position, “keeping track”, or to actively align the radiation beam to the tumour’s movement. Unfortunately, this causes some confusion and makes literature searches more challenging.

ing can be performed on a conventional linac. The development of DMLC tracking traces back to a publication by Keall et al. from 2001, where IMRT fields were pre-modified to account for sinusoidal motion and delivered to a moving phantom [75]. The treatment was started manually at a specific point in the motion pattern and the motion was limited to one direction, parallel to the direction of motion of the MLC leaves. The delivered dose with motion and with tracking (although that term was not yet used) was compared to the dose from a delivery without motion, yielding excellent agreement. Dynamic MLC tracking has since been demonstrated in real-time experiments and in November 2013, the first patient treatment with DMLC tracking was performed [76]. After 2001, the number of publications relating DMLC tracking, either theoretically, with simulations or experimentally, increased dramatically (figure 3). In figure 4, a visual overview is given of the most important milestones in the evolution of DMLC tracking, which are described in detail in this section.

#### Theoretical justification and simulations

The theoretical background for DMLC tracking for IMRT was established in a number of publications. Steve Webb initially described a theoretical implementation for motion correction in 1D (although the underlying target motion was in 2D) in 2005 [77] and McQuaid and Webb expanded the algorithm to 2D in 2006 [78]. Lech Papiez initially proposed a solution for tracking oscillating motion during IMRT in 1D for a rigid target [79]. McMahon et al. later described an algorithm for real-time tracking IMRT in 2D (in the BEV), allowing leaves to shift to account for motion perpendicular to the leaf travel, and also correcting in real-time for errors occurring in the process [80]. Since IMRT is delivered with a static gantry, the desired fluence in the BEV can be calculated and such a correction applied. For IMAT treatments however, due to the rotation of the gantry, the calculation is far from trivial and no solution has, to my knowledge, been described.

In 2007, a treatment planning study by Keall et al. investigated the dosimetric effect of aligning the MLC to different prostate displacements and correcting the number of MUs to account for inverse square law- and off-axis effects [81]. The study simulated DMLC tracking during 3DCRT treatments with a constant internal shift of the prostate, rectum and bladder of up to 2 cm. Despite the shifts, target coverage and OAR doses were maintained, except for the femoral heads for which the absorbed dose...
varied. A similar study was conducted by Ludlum et al., who considered IMRT treatments targeting the prostate and the pelvic nodes [82]. The pelvic nodes are considered to be fixed relative to the spine and an alignment of the field to a moving prostate introduces a risk of missing the nodes. The authors studied the effect of only adjusting the MLC leaves were used for prostate coverage and found it to be a feasible approach. In 2009, Suh et al. applied a DMLC tracking algorithm to 4DCT scans of 12 lung cancer patients. An IMRT plan was optimized for a reference phase on each scan, and then transformed to the other phases using the tracking algorithm, thus simulating what would occur during an actual treatment. The summed doses for all phases were similar to the dose for each phase, suggesting that the DMLC tracking approach would be viable for lung cancer patients [83].

In 2010 Sun et al. simulated DMLC tracking of IMAT treatments by considering motion known a priori and took machine limitations into account to modify the treatment plan to allow the MLC to track the motion and slow down the gantry if the MLC leaves needed to catch up [84]. Although increasing the treatment time, the algorithm should ensure accurate delivery of the planned dose in the presence of motion. No experimental verification of the algorithm has been published at this time. The method might mitigate one of the primary problems with the DMLC tracking implementation used in Study I and Study II, in which no consideration was taken to dosimetric errors caused by the MLC leaves not being able to arrive to their desired position in time to compensate for the observed motion.

Experimental tracking with motion known a priori

Two years after the publication by Keall et al. in 2001, Neicu et al. published a similar method that also used a priori target motion and a modified MLC sequence to correct for motion [85]. An option for using gating should the tumour not move according to the average pattern was also available. One year later, an adaption of the method by Keall et al. was investigated further in phantom studies simulating lung motion [86]. The first experimental DMLC tracking delivery on an Elekta linac was published in 2009 by McQuaid et al. [87] who applied a 4D tracking algorithm with a priori known motion.

A preparatory step that was needed before real-time DMLC tracking was possible to experimentally determine the physical limitations of the MLC with respect to maximum velocity and acceleration. This was done by Wijesooriya et al. in 2005 who found some variability between the three investigated MLCs and impact from gravity (tested by rotating the gantry parallel to the floor and varying the collimator angle). The author found an average maximum leaf velocity and acceleration/deceleration of > 3.3 cm/s and > 46 cm/s², respectively, considered sufficient for all but the fastest moving lung tumours [88].
Real-time DMLC tracking

In a review of motion in radiotherapy in 2006, Steve Webb, stated:

“In principle image extraction and feedback should allow the correction of the dMLC technique for intrafraction motion within a few years from now.” [89]

It turned out that he was correct, although this occurred sooner than he expected, as Keall et al. published the first experimental setup for real-time DMLC tracking just months later [90]. Their laboratory setup was limited to motion in the leaf travel direction and was not used during beam-on. A camera monitored reflective markers placed on a moving phantom, and sent their position to a DMLC tracking software, which calculated new positions for the MLC (that defined a circular field). Another camera simultaneously recorded the MLC and the phantom, visualizing the agreement between the target motion and the compensation with the MLC.

Two years later, in 2008, Sawant et al. published the first results of real-time DMLC tracking on a clinical linac for both 3DCRT, IMRT and IMAT plans [22]. A phantom moved 20 mm parallel and 5 mm perpendicular to the leaf travel direction with 4 s cycle time. A dosimeter placed on the phantom allowed for dosimetric evaluation of the effect of the motion, with and without DMLC tracking. Also, the geometrical accuracy was investigated with a camera setup. Submillimeter geometric tracking accuracy (< 1 mm RMS error) was observed for all techniques, and the dosimetric agreement to the dose corresponding to a static phantom increased as well. The authors also provided a detailed description of the DMLC tracking algorithm. Briefly, the algorithm performed a geometric correction of the MLC leaf positions based on the target position as reported by a monitoring system. For the motion component parallel to the leaf travel, the leaves were adjusted while the overall shape was maintained. For motion perpendicular to the leaf travel, the entire MLC shape was shifted the appropriate number of leaves. Finally, motion along the beam axis was corrected by magnifying or minifying the MLC shape. For technical reasons, no inverse-square law correction was applied, in contrast to the simulation study by Keall et al. [75]. At the time, correction of rotation and deformation was not implemented in the algorithm although it was noted that such corrections should be feasible. These features have since been added (see the section future prospects in DMLC tracking below). The authors observed that motion perpendicular to the MLC leaf travel direction was harder to manage, partly since the smallest correction step is one MLC leaf, and partly because of the MLC shape sometimes caused the distance to the next (i.e. adjacent) leaf to be too large for it to be able to rapidly reach the desired position.
An overall quality assurance programme for DMLC tracking was described by Sawant et al. in 2010 [91]. The authors specifically described DMLC tracking combined with the Calypso system, but the general approach had the potential to be used for other localization methods as well. A failure mode and effect analysis was used to quantify all potential errors during DMLC tracking based in its likelihood of occurrence, likelihood of detection (and thus avoidance) and the severity should the error occur unnoticed.

**Integration with different localization systems**

A substantial part of the research regarding DMLC tracking has focused on integrating the tracking software with different target localization systems (c.f. section 3.1). The following section summarizes the effort.

In 2009, a large number of articles reported on integration between DMLC tracking and different target localization systems. Sawant et al. reported on the first integration of DMLC tracking with the Calypso system [92]. The geometric accuracy and system latency were investigated, the former found to be < 2 mm (measured as RMS error) and the latter 220 ms. Smith et al. expanded the investigation to include IMRT plans and used film to determine the dosimetric accuracy [93]. Besides DMLC tracking, a spatial gating system was also used for motion management. Using the gamma index for evaluation (3%, 3 mm criteria), the failure rate with DMLC tracking was 0.7%, slightly worse than gating (0.2%) but better than no motion compensation (2.0%). Cho et al. demonstrated combined kV and MV imaging for target localization [94]. A gold marker was imaged at 6.7 Hz and segmented in real-time. Triangulation was used to calculate the markers position in 3D, which was then sent to the tracking software and used for motion compensation. The latency of the system was approximately 450 ms, but the tracking performance for sinusoidal motion and a circular MLC field was acceptable by applying a prediction algorithm, resulting in 0.2% gamma failure rate with tracking and 22.5% without tracking. Also in 2009, Poulsen et al. used a kV-imager placed perpendicularly to the treatment for DMLC tracking [95]. Continuous kV-imaging at 5 Hz during an arc was used to create a probability density function that described the most likely position of the target, which was then sent to the DMLC tracking system. The 3D RMS error of the target localization was 0.6 mm, while the geometric accuracy of tracking (with a circular field) was 0.7 mm.

The next year, Poulsen et al. expanded the use of kV-imaging only to respiratory motion during an arc delivery of a circular MLC field [96]. Both the target localization error and the tracking error increased to 1.8 mm and 1.1 mm respectively, compared to the prostate motion investigated the year before. A relatively high system latency of 570 ms contributed to the errors. Later that year, the kV-imaging approach was applied to IMRT and 3DCRT treatments delivered with a static gantry, with the kV-imager used both during irradiation and when the gantry moved between treatment fields [97].

In 2011, Keall et al. further expanded on the integration of DMLC tracking and Calypso in an experimental study using IMAT and eight motion traces, four prostate traces and four lung motion traces [98]. Two plans were delivered for each site, one with low modulation and one with high modulation, with the collimator aligned with the SI motion direction. Lung motion was slightly more difficult to track accurately (1.6% of the dose points failed the 3%, 3 mm gamma criteria, compared to 1.2% for prostate motion). Also in 2011, Krauss et al. integrated Calypso localization with DMLC tracking on a Siemens treatment machine, achieving good geometric accuracy but a relatively high latency of 500 ms [99]. The same year, Ravkilde et al. integrated electromagnetic localization using the Micropos system with DMLC tracking [100]. Similarly to Sawant et al. [92], a circular MLC field was used with a motion phantom reproducing lung and prostate motion. The localization error and tracking errors were 0.53 mm and 0.69 mm (RMS) respectively for lung motion, and 0.54 mm and 0.98 mm, respectively, for prostate motion. Also in 2011, Cho et al. investigated the novel approach of using combined kV/MV-imaging together with external markers [101]. The rationale for such an approach, although not applicable for prostate treatments, is that the external markers can be localized continuously with no extra dose to the patient, while kV/MV-imaging can be used intermittently to verify the correlation between the patient’s external motion and the tumour motion. The tracking error using this combined approach was < 1.5 mm (RMS), except during the initial building of a correlation model. The year after, the same authors adapted the method for only kV-imaging in combination with external markers for single arc and five-field treatments [102]. The tracking error was on average 1.0 ± 0.2 mm (one SD), compared with 4.9 ± 1.0 mm (one SD) without motion compensation. The same year, a new method for image readout that utilized
DMLC tracking and IMAT plan complexity

The first demonstration of DMLC tracking combined with RapidArc, the commercial implementation of IMAT by Varian Medical Systems, was published by Zimmerman et al. in 2009 [105], testing one lung plan and one prostate plan. A motion platform performed sinusoidal motion with 1.5 cm amplitude and 6 s cycle time [105]. A follow-up study by Falk et al. one year later varied the collimator angle by using 45° and 90°, either aligning perfectly or at a 45° angle the leaf travel direction and the phantom motion), and the motion amplitude, from 5 mm to 25 mm (peak-to-peak) [106]. Interestingly, and in contrast to earlier studies [22], the alignment between the motion and leaf travel had only a small impact on the dosimetric accuracy of DMLC tracking. Although not explicitly quantified, the investigated plans seemed to have rather low complexity, using 370 MU and 410 MU (this put the plans in the lower range of MU/Gy for clinical RapidArc plans, c.f. Study V) for collimator angle 45° and 90°, respectively. The low modulation likely reduced the complexity of the MLC shapes and thus the likelihood of adjacent leaves being too far away to enable accurate motion compensation.

The impact of IMAT plan complexity on DMLC tracking accuracy was explicitly investigated in another study by Falk et al., in 2012 [107]. Using a similar setup as in the 2010 paper, the maximum allowed distance to adjacent leaves was varied with the help of a leaf position constraint (LPC). For each of three lung cancer patients, five plans were optimized with a range of maximum allowed distances, including no constraint. The collimator was angled by 45° compared to the target motion (considered to give the best plan quality for IMAT), which was sinusoidal with 2 cm peak-to-peak distance and 6 s cycle time. Significant correlation was found between DMLC tracking accuracy and the dose weighted average adjacent leaf distance (ALDw), with plans with no constraint performing worse than plans with increasingly stringent constraints. The seemingly conflicting results from Falk et al. 2010 and Falk et al. 2012 with regards to the impact of motion perpendicular to the leaf travel can therefore be attributed to the impact of plan complexity.

In Study I, prostate treatments with or without a dose escalation to an intra-prostatic lesions (IPL) within the prostate (so called IPL boosted) were delivered with and without DMLC tracking [108]. A moving phantom reproduced six prostate motion traces that spanned a range of motion, from very limited to the worst case in a database of 548 prostate motion traces. The study aimed to investigate the following:

1. whether IPL-boosted plans could be optimized with a LPC that stringently limited the distance to adjacent MLC leaves (figure 5)
2. if DMLC tracking would be more challenging for dose escalated plans and if the accuracy would depend on the average prostate displacement
3. if IPL-boosted plans were more sensitive to uncompensated motion than standard plans

A novel approach used in the study was comparing the delivered dose with tracking to the planned dose, i.e. the dose calculated in the treatment planning system (TPS). Previously, the delivered dose with tracking was compared to the delivered dose while tracking a static phantom, isolating the effect of motion from other sources of uncertainty such as phantom setup and dose calculation accuracy. However, the agreement to the planned dose is in the end the clinical relevant comparison, and an aspect that had to be investigated before clinical use of DMLC tracking. The comparison with the planned dose was done in two ways; (1) the delivered dose to the phantom was compared to the calculated dose for a delivery without tracking and to a static phantom, and (2) the deliveries with and without tracking were afterwards reconstructed in the TPS, using a novel dose reconstruction method [109] (c.f. section 3.4). The study showed that while using the LPC caused a decrease in plan quality, the difference was small. The study was however limited to four patients. Also, the addition of an IPL boost did not increase the dose to the organs at risk (rectum and bladder), either with or without the LPC applied. Without motion compensation, the motion traces with the largest amplitude that moved to phantom anteriorly, caused a further increase in
rectum dose for the IPL-boosted plans compared to the standard plans. When comparing the delivered dose with tracking to the dose with a static phantom, the motion amplitude (quantified as the average 3D displacement from isocenter, where all traces started) had a very small impact, regardless of whether IPL boosting was done or not. Without tracking, a somewhat linear relationship between gamma index pass rate and target displacement occurred. However, when comparing the delivered dose with the planned dose, no tracking was better than tracking with a static phantom and the motion trace with 1.0 mm average displacement. For the trace with 1.8 mm average displacement, the two methods were equivalent, and with larger motion, tracking was favourable. Consequently, connecting the DMLC tracking system slightly deteriorated the delivered dose. This was investigated in detail by using a data file (instead of the monitoring system) as positional input, thus eliminating uncertainty due to noise. Then, the tracking software was modified so that it mimicked delivery without tracking (for example, the tracking system otherwise moves unused leaves to a position beneath the jaws). Even though the emulation increased the agreement between the delivered dose with and without tracking, the authors analysed the residual error during the different steps in the tracking software. Essentially, the ideal motion compensation would be the planned MLC shape shifted and magnified/minified according to the target’s current position. However, the following factors caused deviation from the ideal shape:

- target localization error: the error caused by imperfect localization of the target, by latency due to image processing and by error in target prediction (used for lung but not for prostate motion)
- leaf fitting error: the error caused by the physical limitations of the MLC, preventing it from achieving exactly the desired shape
- leaf adjustment error: the error caused by the MLC leaves not being able to reach the desired position

The area from the BEV that was irradiated when it ideally should not have been, and vice versa, was termed the overexposed area and the underexposed area. The sum of the two areas was shown to correlate with decreased dosimetric accuracy.

Figure 5. Example of two MLC shapes, one relatively complex (left) and one somewhat simpler (right). The MLC shape on the right was obtained using a leaf position constraint.
In **Study II**, we investigated further the impact of plan complexity for prostate treatments, using the ALDw metric while also investigating the importance of MLC leaf width and quantifying the tracking error [111]. Contrary to simulated lung motion [107], when using motion of the prostate recorded during radiotherapy, the plan complexity had a much smaller impact on DMLC tracking performance. Instead, the leaf width was the most important factor (besides using DMLC tracking in the first place) for managing prostate motion. Four prostate motion trajectories were measured with plans optimized for two MLCs with 0.25 cm and 0.50 cm central leaf width, respectively. Plans were optimized for two patients and with five different maximum allowed adjacent leaf distances using the LPC, creating a range of plan complexities. Also, the leaf width was isolated by converting plans from one MLC to the other for one of the patients. When comparing the delivered dose when tracking a motion phantom with the delivered dose when tracking a static phantom, plans with lower ALD had better agreement (although the difference was small). However, when comparing with the planned dose, the difference was not significant. In contrast, the choice of MLC was significant as the MLC with thinner leaves increased the dosimetric agreement. The detailed analysis of the contributing elements to the combined DMLC tracking error revealed that the major contributor was the leaf width. The different characteristics of prostate and lung motion are the likely reason that the results differed so clearly from Falk et al. 2010. Prostate motion is generally slower and drifting, placing a smaller requirement of quick leaf motion compared to the possibility of the MLC shape to shift by small amounts.

**In-vivo tracking and first patient treatment**

In 2011, Poulsen et al. reported on the first in vivo use of DMLC tracking [112]. Three minipigs had a stent implanted in the bronchia and were treated with a single fraction with DMLC tracking. Continuous MV-imaging was used to monitor the stent position and direct the tracking. Afterwards, the tracking error was calculated to estimate the systematic and random errors. The systematic error decreased from 1.7 mm / 1.4 mm (in two imager directions) to 0.5 mm / 0.4 mm by use of DMLC tracking, while the random error decreased from 0.8 mm / 1.4 mm to 0.5 mm / 1.1 mm.

In 2014, Keall et al. reported on the first patient treatments with DMLC tracking [76]. A prostate cancer patient had Calypso transponders implanted in the prostate and used for positional input to a DMLC tracking system. The tracking program was still pre-clinical and was not a commercial product. An IMAT treatment plan with two arcs was used for a total beam-on time of 2 min, which was not prolonged by the use of DMLC tracking.

**Future prospects of DMLC tracking**

The initial demonstration of real-time DMLC tracking by Sawant et al. [22] was limited to corrections of translations, and rotations and deformations were not corrected. In 2011, Wu et al. added rotational correction to the DMLC tracking software, and investigated the performance by rotating the couch between 0° and 60° [113]. The average difference between the target rotation and the beam rotation (measured using a D-shaped MLC field and static couch), was -0.3° ±0.6° (1 SD). For IMRT plans, decent agreement to the dose to a non-rotated delivery was seen, with 11% average gamma failure rate (using 3%, 3 mm). The first investigation of correction of deformations was recently published by Ge et al. [114]. The authors investigated deformation during DMLC tracking using two simple phantoms: (1) a rubber ball held by a clamp and compressed and (2) two golf balls whose separation increased in a step-wise fashion. The former represented a deforming tumour while the latter represented a deforming tumour system, e.g. the prostate and nearby lymph nodes moving independently of each other. Using DMLC tracking, the erroneously irradiated areas decreased by 82% and 86% for the two phantoms, compared to no tracking, respectively. However, the time needed to calculate deformation maps (several seconds) hindered real-time adaptation.

Another step towards a deepened understanding of the dynamics of DMLC tracking deliveries was the investigation of time-resolved dose distributions by Ravkilde et al. in 2013 [115]. Continuous dose readout from a dosimetric phantom was compared with time-resolved computation of the over- and underexposed areas. These were shown to be in a general agreement, and although the time-resolved gamma analysis showed only a threefold decrease in gamma failure rate with tracking than without (16.8% vs. 5.3%), gamma analysis of the cumulative dose showed a clear decrease from 17.9% without tracking to 1.0% with tracking. The results showed that although DMLC tracking was unable to instantaneously perfectly compensate for the observed motion, the errors were random and cancelled out when considering the accumulated dose.
3.4. Dose reconstruction

There will always be a difference between the planned dose to the patient and the dose that is delivered. Uncertainties in patient setup, patient anatomy, intrafractional changes and machine delivery are some of the factors that contribute to the difference. In 2010, Joffrey et al. envisioned the possibility of accurately accumulating the delivered dose to the patient on a fraction-by-fraction basis [116]. With an accurate assessment of the “true” dose, the outcome of the treatment could be modelled more accurately. On a patient-specific level, the treatment could be adapted based on the delivered dose up to that point in the treatment, accounting for geometric misses and changes in patient anatomy (e.g. weight loss). The authors recognized a number of technical issues that needed to be addressed, such as auto-segmentation, modelling of deforming anatomy and dose accumulation, as well as the need of accurately day-by-day information on patient anatomy and target motion.

In 2012, Poulsen et al. implemented a dose reconstruction method that used log files from the linac together with target motion data to reconstruct the delivered dose in TPS. The method allowed for synchronizing target motion with the actual MLC positions when using DMLC tracking, and shifted the entire patient volume to simulate target motion. Thus, deliveries both with and without DMLC tracking could be reconstructed in the TPS, allowing for an estimation of the dose delivered to the patient. The method was used in Study I and IV.

After the first patient treatments with DMLC tracking, the method was also used to assess the benefit of tracking by comparing the delivered dose with the dose should tracking not have been used [76]. Ravkilde et al. further developed the dose reconstruction method to divide the treatment into ten equal parts and calculate the delivered dose for each part separately [117]. The main limitation of the method is that target motion is simulated by shifts on the entire patient anatomy, meaning that rotations, deformations as well as changes in the relative position of organs are ignored. This approach emulates the motion of the phantom in Study I, Study II and Ravkilde et al. [117], but for real organ motion, this is obviously a simplification.
REAL-TIME MOTION MANAGEMENT

Dose reconstruction
4. Prostate motion in radiotherapy

4.1. Prostate motion

Organ motion during radiotherapy deteriorates the intended dose distribution. If the treatment margins are too small, there is a risk of geometrical miss when the tumour moves. Even if the margins are large enough, there is a risk of dosimetric errors when using intensity modulated delivery techniques as only a fraction of the tumour is irradiated at any given time (called the interplay effect) [118]. In prostate radiotherapy, a common approach is to treat the prostate with a margin to the intended dose, sometimes also including the proximal parts of the seminal vesicles in the target volume [12]. Motion of the prostate is thus of concern for conformal radiotherapy, for the abovementioned reasons, and is well studied in the literature [21, 50, 119, 120].

The prostate is located next to two organs whose size can change within the time-frame of a treatment (i.e. in minutes); the rectum and the bladder. Although this thesis focuses on prostate motion, it should be noted that the same issues are prevalent for essentially all treatments in the pelvic region, including cervical cancer which is the third most common cancer form among women worldwide. As for the prostate, the rectum and bladder cause motion of the cervix and uterus as well [121].

In 1990, Ten Haken et al. investigated prostate motion on 50 prostate cancer patients by taking lateral x-ray images before and after filling the rectum with 30 ml of contrast liquid. A balloon placed in the inferior part of the bladder gave an indirect measure of the prostate’s position. The change in rectal volume caused prostate displacement > 5 mm for 31 of the 50 patients, with a maximum displacement of 2 cm. In 1995, Balter et al. took weekly portal images during prostate radiotherapy [122]. Using implanted markers, the difference between the bony anatomy and the prostate was calculated, thus quantifying prostate motion at one specific time each week. They observed significantly larger motion in the superior/inferior (SI) and anterior/posterior (AP) directions than left-right (LR), with the maximum expected motion of 3.7 mm, 4.5 mm and 1.7 mm in the three directions, respectively. The same year, Crook et al. compared the position of the prostate for 55 patients after treatment to 40 Gy to the initial planning CT, using markers implanted in the prostate related to the bony anatomy [123]. Comparing the two observations, the prostate had moved minimally in the LR direction while 43% of the patients had prostate displacements > 5 mm inferiorly, and 11% had prostate displacements > 10 mm inferiorly. In the AP direction, the corresponding results were 63% and 30%, respectively.

In a study of 55 prostate cancer patients using magnetic resonance (MR) imaging by Padhani et al. in 1999, rectal movements were deemed the primary cause of prostate displacement [120]. The patients were imaged with 10 s intervals for approximately 7 min. Among the 55 patients, 16 had rectal movements that resulted in 33 prostate displacements in the AP direction, ranging from 1 – 5 movements per patient. The prostate movements lasted on average 25 s (range 10 – 80 s), and six were > 10 mm. A similar study was done by Ghilezan et al. in 2005, where six prostate cancer patients were MR-imaged for one hour three times during the course of radiotherapy [20]. There was a significant difference in prostate motion depending on the rectal filling, and for the midposterior part of the prostate, the probability of motion > 3 mm was 15% for patients with filled rectum, compared to 1% for patients with empty rectum.

In 2007, the introduction of electromagnetic localization allowed Kupelian et al. to report on real-time (10 Hz) localization of the prostate during 1157 radiotherapy fractions (typical length 9 – 11 min) of 35 prostate cancer patients [51]. In 75% of the fractions, the initial off-set between the skin marks (used for patient setup) and the prostate was > 5 mm (3D vector), clearly motivating prostate localization before each fraction, as opposed to setup...
based on skin marks only. Retrospective analysis of the intrafraction motion indicated that with a 3 mm, 30 s gating threshold, 41% of the fractions would have at least one gating event, while 15% of the fractions would have been gated with a 5 mm, 30 s gating threshold. In agreement with previous studies, LR motion was limited and the prostate moved predominantly in the SI and AP directions. The following year, Langen et al. provided a detailed analysis on a sub-set of the patients in Kupelian’s study; 550 fractions of 17 prostate cancer patients [50]. With the high temporal resolution, they could identify sudden movements of the prostate (mostly directed anteriorly and superiorly) as well as slow, drifting, motion (mostly directed posteriorly and inferiorly). The former generally resolved itself after a short time (similarly to the displacements reported by Padhani et al.), and was associated with rectum changes. The drifting motion was slow but could reach large magnitudes as the treatment progressed. The authors attributed the drifting motion to relaxation, rectal content moving away and bladder filling. For all patients, the prostate was on average displaced more than 3 mm 13.2% of the time, and more than 5 mm 3.1% of the time. However, for the worst fraction, the values were 98.7% and 98.6% of the time for 3 mm and 5 mm, respectively. For the worst patient, the prostate was displaced more than 3 mm 33.2% of the time, and more than 5 mm 10.9% of the time.

There have been some investigations into methods which aim to decrease the amount of prostate motion. As the motion is associated with changes in rectum volume and rectal distension, minimizing such occurrences would plausibly limit prostate motion as well. Lips et al. introduced dietary guidelines that aimed to minimize rectal gas among prostate cancer patients [124]. Among other interventions, the guidelines advised the patients to avoid hot and spicy food, to eat regularly and to avoid carbonated beverages. The intrafraction prostate motion among 105 patients treated with the dietary advice was compared against 739 previously treated patients, and the amount of motion did not decrease with the diet. Instead, the percentage of patients with motion > 3 mm for at least half of the fractions increased significantly from 19.1% to 42.9%. Shortly thereafter, Lips et al. performed a double-blind placebo-controlled randomized trial that investigated whether magnesium oxide would decrease the amount of intrafraction prostate motion. The magnesium oxide was hypothesized to decrease the amount of gas pockets in the rectum and thus prostate motion. Ninety-two patients were included in the study. No significant differences were found between the group given magnesium oxide and the group given placebo, neither with regards to prostate motion or quality of life.

One method that has been demonstrated to decrease intrafraction prostate motion is using an endorectal balloon; Smeenk et al. treated 30 prostate cancer patients with IMRT and monitored prostate motion with electromagnetic transponders [125]. Half of the patients were treated with an endorectal balloon, inserted prior to each fraction and filled with air. When inflated, the diameter and length of the balloon was 6 cm and 6.5 cm, respectively. Using a 3-mm threshold before repositioning the patient, 88 corrections were performed in the group treated with a balloon, compared to 207 corrections in the standard group. The percentage of 3D motion > 3 mm was also significantly smaller, 7.0% vs. 18.1% (after retrospective removal of the position corrections). Both the amount of drifting and transient motion was decreased with the use of an endorectal balloon, although it is unclear how the patient selection was performed.

In summary, prostate motion can be characterized as somewhat infrequent transient motion caused by rectal changes that move the prostate anteriorly/superiorly, sometimes as far as 2 cm, combined with drifting motion in the posterior/inferior direction. No indication of periodic components to the prostate motion has been reported and the motion seems to be unpredictable [50].

### 4.2. Modelling prostate motion

As with many other processes, there exists the possibility of modelling prostate motion. Current research attempting to model intrafractional prostate motion in the context of radiotherapy is limited. Instead, the primary focus has traditionally been mechanical modelling of the interactions between the prostate and surrounding organs. For example, in 1999, Yan et al. described a method for calculating the accumulated dose to an organ that is both deforming and moving between fractions, but did not include intrafraction motion. In 2009, Boubaker et al. modelled the mechanics of interaction between prostate, bladder and rectum, with the prostate modelled as an elastic tissue undergoing strains from the bladder and the rectum [126]. Reasonable agreement was found with measurements made on a deceased man. Söhn et al. specifically modelled the interfraction motion of the prostate, rectum and
Displacement (mm)

-10
-5
0
5
10

Time (s)

0 100 200 300 400 500 600

AP
SI
LR

Example of prostate motion from Langen et al. [50] with (left) and without (right) transient motion in the superior/anterior direction.

bladder using repeated CT datasets for four patients [127]. Principal component analysis, a method where independent and uncorrelated variables are extracted from a dataset, was applied to determine so called eigenmodes that with few parameters could describe the majority of the geometric variability.

In 2013, Lin et al. analyzed prostate motion during 1024 fractions for 31 patients and tested if the distribution of prostate positions in the AP, SI and LR directions, as well at oblique motion (the SI and AP directions combined) and 3D motion, could be described by a Gaussian distribution [128]. Any distribution of random displacements is expected to be Gaussian, but here, < 15% of the individual fractions were. For all fractions in a patient’s treatment, < 13% of the fractions were Gaussian, except motion in the LR direction, where the corresponding result was 33%. Thus, prostate motion, especially in the SI and AP directions, may not be sufficiently well described by a Gaussian approximation. Later the same year, Ballhausen et al. applied the random walk to prostate motion modelling [129]. The random walk is based on a simple idea: a particle moves in a random direction according to the external forces being applied to it. At each motion step, the probability of motion in a certain direction is independent of previous steps. The process is thus time-independent in the sense that the probability of motion steps in different directions remains the same – the random walk has no memory. However, the position of the simulated particle (or in this case, the prostate), is likely to be close to its recent position. If the external forces are evenly distributed, the average position for a large number of simulated particles will be equal to the origin. The random walk cannot reasonably be applied to organs experiencing periodic motion, such as the lung, but since the motion of the prostate seems to be random in general, applying the random walk model seems reasonable. Ballhausen et al. showed that treatment margins derived from a random walk distribution would be smaller than those derived from assuming Gaussian distribution. Using previously published prostate motion characteristics, the authors were able to fit random walk derived motion with excellent agreement to the observed motion.

The idea of using random walk for prostate motion modelling was independently investigated in Study III. The aim of the study was to simulate prostate motion using the motion characteristics of 17 patients treated for 548 radiotherapy fractions [50]. In contrast to Ballhausen et al., we had access to time-resolved prostate motion for a large number of fractions. These traces were categorized into two groups depending on whether any transient excursions occurred in the traces (figure 6). Transient excursions were rapid motion in the anterior/superior direction, followed by a return to the approximate starting position. The underlying hypothesis was that such rapid motion (which occurred in 42% of the motion traces) could not be modelled by the random walk alone. Instead, simulated transient motion was added to the random walk model. The simulated motion consisted of a motion step of random length (up to 5.5 mm), in the superior/an-
terior direction. After a random time, the opposite motion occurred, returning the simulated prostate to its previous position. Four sets of simulations were performed, each simulating 548 motion traces for 10 min. The first two aimed to recreate the motion for all 17 patients, the third aimed to recreate the motion of the excursion-free motion traces, and the fourth aimed to recreate the motion of traces with transient motion. Of the first two simulations, one used motion data for all traces and only a random walk to simulate prostate motion while the other used motion data from only excursion-free traces and added simulated transient excursions. The outcome showed that the latter was better able to describe the quick increase in variance in prostate position, while the overall agreement to the observed motion traces was good for both simulations. The best agreement was however seen for the third simulation which used the random walk to recreate motion for excursion-free traces. For the first five minutes, the agreement was excellent. Afterwards, the variance among the simulated traces increased linearly (in accordance to the random walk model), while the variance for the observed motion seemed to reach a threshold. These results, together with the article by Ballhausen et al., suggest that the random walk model is applicable for modelling intrafraction prostate motion.

4.3. Impact of uncompensated prostate motion

In this section, an overview is given on studies investigating the impact of uncompensated prostate motion.

Clinical outcome

Clinical outcome data with regard to prostate motion is sparse. The available outcome data is limited indirectly investigation of the effect of interfraction motion. In 2005, De Crevoisier et al. published a retrospective analysis of 127 prostate cancer patients treated with 3DCRT without daily image guidance [130]. It was the first report on clinical outcome (presumably) due to prostate motion, albeit interfractional. The hypothesis was that a patient with large rectal distension at the planning CT would be likely to have a smaller rectum at treatment, and thus the prostate would be displaced to a larger extent than patients with small rectum distension. Without prostate image guidance (i.e. patient setup was done according to skin marks and portal images of bony anatomy), the risk of geometric miss would consequently be higher. The results indicated that rectal distension was a more important predictive factor than risk group (hazard ratios 3.9 and 2.4 respectively) for risk of biochemical failure. Similarly, two years later, Heemsbergen et al. reported 549 prostate cancer patients, and found worsened tumour control for patients with large rectal volume at the planning CT and > 25% diarrhea during the treatment, but only for the sub-group of high-risk patients. Rectal distension was close to significance. However, Heemsbergen et al. used a portal imaging to keep the systematic error to < 5 mm, possibly limiting the impact of rectal distension. The year after, Kupelian reported no association between rectal distension and biochemical relapse-free survival when daily prostate image guidance was used for 488 prostate cancer patients (p = 0.8 in a multivariate analysis) [131]. Thus, the use of daily imaging seemingly eliminated the issue of rectal distension and any associated systematic errors.

Sandler et al. reported on clinical outcome for a prospective study of 64 patients treated with real-time motion monitoring (with 2 mm gating threshold) using a 3 mm CTV-to-PTV margin and compared their quality of life with 153 comparable patients, treated without motion monitoring and with 5 – 10 mm margins [132]. The 64 patients had significant decrease in bowel morbidity in relation to the group of comparable patients. The decrease in side-effects was attributed to the decreased treatment volume and specifically the smaller volume of the rectum receiving a high dose due to overlap with the PTV. However, the lack of randomization and short follow-up limits the usefulness of the study. As the study reported on short-term treatment outcome, it did not address tumour control for the small-margin treatments. With a smaller margin, decreased side-effects would be expected and the crucial parameter would be the risk of decreased tumour control. At the time of writing, no follow-up results have been released.

Engels et al. reported on the outcome for 238 prostate cancer patients treated with image-guided conformal arc therapy. For 213 patients, image guidance was done based on bone structures and CTV-PTV margins of 6 mm and 10 mm in the LR and AP/SI directions, respectively. The remaining 25 patients were positioned based on imaging of implanted markers and treated with 3 mm and 5 mm in the LR and AP/SI directions. Using a multi-variable statistical analysis, the association between patient parameters and freedom from biochemical failure (FFBF) was investigated. Beside risk group and dose level, the average rectal cross section area
(≥ 16 cm² vs. < 16 cm²) was found to be a significant predictor of biochemical failure. Also, the second patient group with smaller margin and prostate-based setup did significantly worse than the first group, with 5-years FFBF of 58% compared to 91% (p = 0.02). The worsened outcome was attributed to the smaller margins and the treatment regime was subsequently changed to isotropic 6 mm margins. The study highlights the risk associated with using too small margins and the remaining uncertainties due to contouring, rotations, deformations and intrafraction motion, a topic further discussed in the next section.

### Treatment margin calculations

Although no clinical outcome study has demonstrated impact of intrafraction motion specifically, the treatment margins needed to ensure complete dose coverage in the presence of prostate motion and for different interventions (such as gating) is well investigated.

In 2006, Litzenberg et al. used intrafraction motion data for 11 prostate cancer patients (combined with data for skin to prostate setup errors) to calculate the treatment margins required to ensure that 90% of the patients receive ≥ 95% of the prescribed dose [52]. The margin calculations were done for no motion correction, pre-treatment motion correction, pre-beam motion correction (simulating a four-field delivery), and gating with a 3 mm threshold. Neither rotations nor uncertainties in target (delineation) were taken into account in the margin calculation. For the different protocols, the calculated margins in the SI direction (the direction with the largest margin) were 12.5 mm (no intervention), 7.1 mm (pre-treatment), 1.8 mm (pre-beam) and 1.5 mm (3 mm gating threshold). Six years later, Litzenberg et al. published a study with a similar method but expanded by using the prostate motion data first published by Kupelian et al. in 2007 [51]; continuous motion data for 35 patients and 1157 fractions [132]. The calculated margins in the AP direction for the protocols used in the 2006 article were 15.9 mm (skin-based setup, no correction), 4.7 mm (pre-treatment setup), 0.7 mm (pre-beam) and 0.5 mm (pre-beam setup and 3 mm gating threshold). As in the 2006 paper, target delineation uncertainty and prostate rotations were not accounted for in the analysis, likely causing the small margins to be underestimated.

In 2009, Li et al. analyzed intrafraction prostate motion during 775 treatment fractions randomly chosen among 105 patients. The authors calculated the required margin necessary to ensure that, on average, 99% of the CTV (i.e. the prostate) is covered by at least 95% of the planned dose [133]. Aside from no intervention, gating with 5 mm and 3 mm threshold as well as real-time motion compensation either with or without rotational compensation was simulated. Prostate rotation was largest around the lateral axis, meaning that the prostate rotated in the SI and AP directions. The treatment times were 10 – 20 min. For the 775 fractions, the prostate was displaced > 3 mm and > 5 mm 13.4% and 1.8% of the time, respectively. The required margins in the posterior direction, were 7.7 mm, 7.5 mm, 7.2 mm, 6.4 mm and 4.6 mm for no intervention, 5 mm gating, 3 mm gating, real-time translation correction and real-time translation and rotation correction, respectively. The seven patients with the most motion were analyzed separately. For these patients, the required posterior margins were 9.5 mm (no intervention), 8.2 mm (5 mm gating), 7.6 mm (3 mm gating), 6.4 mm (translation correction) and 4.6 mm (translation and rotation correction).

### Dosimetric impact of prostate motion

In order to estimate the dosimetric impact of target motion, the motion-encompassing dose to the patient has to be calculated. One method of approximating the dose to the patient in presence of motion is to blur to planned dose distribution according to the observed motion, using a convolution operation. The convolution method cannot however take interplay between the motion and the MLC into account [134]. In order to do so, the dose for each part of the treatment has to be calculated, taking the motion at the relevant time interval into account.

One study that used the convolution approach was published by Li et al. in 2008, who calculated probability density functions (PDFs) for prostate motion based on 1267 tracking sessions among 35 patients [134]. The PDFs were calculated for all patients, for each patient and for each session, and convoluted with the planned dose for two prostate cancer IMRT plans. The minimum dose to the prostate for a standard fractionated treatment regime was found to be well maintained (> 95% of the planned dose) with a 2 mm margin. Even though single fractions had large dose errors, those tended to wash out when considering the cumulative dose.

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6 Note that the author is not the same as Li et al. 2009 [133].
One of the first articles that calculated the motion-encompassing dose was published by Langen et al. in 2009 [135]. The intrafraction motion for 16 patients was recorded during 515 fractions. For all patients, Tomotherapy plans were retrospectively created and the motion traces were used to simulate motion-inclusive Tomotherapy treatments. The CT data was moved rigidly for each projection (each gantry rotation in Tomotherapy treatments is divided into 51 projections), according to the prostate motion. The minimum dose, maximum dose and the dose delivered to 95% of the volume of interest (D95%) were calculated for the PTV and the prostate. For individual fractions, the PTV and prostate D95% was reduced up to 20%, but the reduction was on average < 1%. The cumulative change in D95% for the prostate and for all fractions was small, 1.1% on average (1.0% SD), with a range of -1.0% to 3.2%. The cumulative prostate D95% for a 5-fraction treatment was on average 0.8% (1.4% SD).

Three years later, in 2012, Langen et al. did a similar study for IMRT plans, using intrafraction prostate motion from 486 fractions and 15 patients [136]. Step and shoot IMRT plans were created retrospectively and the fluence for each segment was shifted according to the observed motion and imported for dose calculation in the TPS. Thus, the patient was assumed to move as a rigid body. For the CTV and PTV, 4% and 12% of the fractions caused a dosimetric change larger than 1%, respectively. There was poor correlation between dosimetric changes in the two volumes and between motion amplitudes and dosimetric changes in the CTV, indicating that dosimetric changes occurred due to the interplay effect. Cumulative dose calculations showed that, after 5 and 25 fractions, the average and standard deviation in CTV dose was 0.0% (±0.2%) and 0.1% (±0.2%), respectively.

In 2013, Azcona et al. described dose reconstruction of 32 prostate IMAT treatments using cine MV-imaging to localize the prostate. Monte Carlo dose calculation was performed for the dose at each control point with the isocenter shifted to simulate the observed motion [137]. The method assumed a rigid patient motion and did not take rotation and deformation into account (similarly to Poulsen et al.’s dose reconstruction method [109]). The authors observed some variability in dosimetric impact of the motion, with the minimum dose given to 0.03 cm³ of the prostate decreased to 94.1% of the planned dose. No correlation was seen between motion amplitude and dose degradation.

Earlier this year, van de Water et al. investigated the dosimetric impact of prostate translation and rotation during hypofractionated CyberKnife treatments [138]. The prostate motion data from Langen et al. [50] was used, and rotations derived along the LR axis by conversion of AP motion. Treatments were simulated for three prostate patients with either no correction, translation correction or translation and rotation correction (with corrections of either ± 5°, ± 10°, or full correction), and for different imaging intervals. The dose for each beam was convoluted with the corresponding prostate motion to simulate intrafraction motion during treatment of 4 fractions with 99% of the CTV receiving a total dose of 38 Gy. Without motion correction and using 0 mm CTV-to-PTV margin, the volume of the CTV that received the prescribed dose (V100%), decreased from 99.5% to 93.6% ±4.8% (1 SD). With 3 mm margin, the V100% decreased to 97.4% ±3.4%. Correspondingly, 11.2% and 61.0% of the treatments with 0 mm and 3 mm margins, respectively, had at least 98% of the CTV covered with the planned dose. With translation correction, the coverage increased to 56.6% and 90.3% for 0 mm and 3 mm margins respectively using a 15 s localization interval (the shortest investigated). The addition of ≤ 5° rotational correction increased the percentages to 84.8% and 96.9%. With ≤ 10° correction, the coverage increased further, to 94.9% and 99.1%. Finally, with complete rotational correction, the CTV coverage was > 98% in 100% of the treatments for either margin. The study did not account for delineation uncertainties, which would increase the necessary margins.

In Study IV we investigated the impact of intrafraction motion using the dose reconstruction method (previously used in Study I) to simulate hypofractionated prostate treatments with motion. Three hundred and forty-two prostate motion traces, previously described by Langen et al. [50], was used to simulate motion for a hypofractionated approach with 36.25 Gy delivered in 5 fractions. The CT-data for four prostate cancer patients scanned with a catheter was used with a 5 mm PTV-margin around the prostate (except 3 mm posteriorly, towards the rectum). The catheter made the urethra visible on the scan and a slightly lower dose of 5 × 6.25 Gy was prescribed to the prostatic urethra. Intensity-modulated arc treatments were optimized for one arc and two arc plans, using either a standard beam or a flattening-filter free (FFF) beam, the later allowing higher dose rates than standard (flattened) beams. The hypothesis was that the use of FFF-beams would decrease the treatment time and there-
fore decrease the impact of prostate motion, which is known to increase with time. Treatments were simulated by randomly selecting five traces from the motion data set and reconstructing the dose for five fractions. Then, the doses were summed and DVH parameters for targets and OARs were extracted. In general, the impact of motion was found to be small, with the median dose to the prostatic CTV (the prostate minus the urethra and a small margin) was 100% of the planned dose. For the worst five-fraction treatment, the CTV D99 decreased from 92.5% to 84.4%. Correspondingly, the D95 decreased from 94.8% to 92.8%. Even in the presence of motion, the longer two-arc treatments were found to give better dose coverage than one-arc treatments, while the use of FFF slightly improved the dose coverage than flattened beams. Although the PTV-margins enabled sufficient CTV coverage for the majority of the simulated treatments, the dose to the OARs, especially the rectum, varied from 70% to 120% of the planned values for traces with extensive motion.

### 4.4. Rotation and deformation

In this section, a brief overview is given of the frequency and dosimetric importance of rotation and deformation in prostate radiotherapy.

In 2005, Deurloo et al. investigated shape variation (i.e. deformation) of the prostate and seminal vesicles among 19 patients, each with 8 – 12 repeated CT scans [139]. The two volumes defined the GTV and were delineated on each scan by the same observer, and aligned by translation and rotation for each patient. Then, the average GTV was calculated, and the variation perpendicularly to the surface of the average GTVs was calculated. The deformation was the largest at the tip of the seminal vesicles (SD = 2 mm) and smallest at the left and right sides of the prostate (SD = 1 mm). The corresponding amount of organ motion (obtained in the alignment process, relative to the bony anatomy), was in the AP-direction 2.4 mm (SD) for the center of mass of the GTV, and 3.5 mm (SD) for the top of the seminal vesicles. Thus, the authors concluded that deformation was small in comparison to organ motion.

Using MRI before the start of radiotherapy and once at a random time point during radiotherapy, Nichol et al. investigated in 2007 prostate deformation and the relationship between the prostate and implanted markers [140]. Twenty-five patients were included in the study, each with three implanted fiducial markers. The prostate and markers were contoured, and the repeated scan aligned to the centre of the markers, either using only translations, or using translations and rotations. Significant association was found between fraction number and volume decrease (0.5% per fraction) as well as intermarker distance decrease (0.05 mm per fraction). Also, prostate deformation between the first and second MRIs was seen, with similar magnitude regardless of the aligning method. The mean deformation was < 0.5 mm, with standard deviations of 1.1 mm and 1.0 mm in the AP direction, for the two methods respectively. The maximum vector between 95% of the prostatic surfaces, for 95% of the patients, was 6.4 mm and 5.4 mm for the two approaches, respectively.

Liang et al. investigated interfraction motion and deformation for the prostate and seminal vesicles using repeated CT scans of 24 prostate cancer patients, with at least 16 scans per patient. For each patient, the scans were aligned based on bone anatomy, and the volumes delineated. Fifteen-fraction treatments were simulated for IMRT and 3DCRT, with pre-treatment patient setup according to either only the prostate or both prostate and seminal vesicles (the CTV). For the first approach, margins were either uniform around the CTV (margin A) or fixed at 3 mm for prostate and varying for the vesicles (margin B). For the latter approach, margins were uniform around the CTV (margin C). An isocenter shift method was used for dose reconstruction. Correlations between prostate and vesicles motion was seen but only in the AP direction (R² = 0.7 with relatively larger motion for the vesicles by a factor 1.25). Without considering accumulated doses, the required margins to ensure 95% coverage with 90% of the time were 4.0 mm, 4.0 mm and 2.5 mm, for margins A, B and C, respectively. When considering the simulated accumulated doses, in order to ensure D99 (i.e. minimum dose) of the CTV to be at least the prescribed dose to the PTV for 95% of the patients, margins of 4.5 mm, 4.5 mm and 3.0 mm for margins A, B and C respectively were required for the IMRT plans. Corresponding margins for 3DCRT were 2.5 mm, regardless of margin strategy.

In 2008, van der Wielen et al. performed three repeated CT scans (plus the original planning scan) for 21 prostate cancer patients [141]. On each scan, the prostate and the seminal vesicles were delineated. Using implanted markers, the scans were rigidly aligned and the resulting deformations and rotations were evaluated using deformable registration between the repeated and original structures. Little
deformation was seen for the prostate (SD ≤ 1 mm), while it was larger for the seminal vesicles (SD ≤ 3 mm). Studying the effect of rotation, the seminal vesicles co-rotated with the prostate “to a certain extent”. Deformation was nevertheless the major cause of displacements for the seminal vesicles.

Three years later, in 2011, Mutanga et al. followed up van der Wielen et al.’s study by developing a framework for margin evaluation based on the effect of population-based translation, deformation and rotation of the prostate and seminal vesicles [142]. Based on repeated CT scans of 21 patients, synthetic and clinical dose distributions, using 5 mm margins, led to 5.2% (±7.4%, 1 SD) risk of prostate underdosage (quantified as any point of the target receiving < 95% of the prescribed dose). Meanwhile, an 8 mm margin for the seminal vesicles still led to a 28.8% (±26.9%, 1 SD) risk of underdosage, primarily attributed to deformation, as correction of rotations only slightly improved CTV coverage.

In 2013, Thörnqvist et al. used deformable registrations to create deformation models for 19 patients, using repeated 7 – 10 repeated CT scans for each patient [143]. Prostate treatments that, besides the prostate included the seminal vesicles and pelvic lymph nodes, were simulated using different CTV-PTV margins for the three targets. The deformation models were used to create a new target shape for each fraction and the dose were accumulated, simulating an entire treatment regime. Using the criteria that 99% of the tumour should receive > 95% of the prescribed dose (D99 > 95%), with 5 mm margin around, 18/19 patients, 11/19 patients and 18/19 patients had D99 > 95% for the prostate, the seminal vesicles and the lymph nodes, respectively. For the seminal vesicles, a treatment margin of 11 mm, gave D99 > 95% for 17/19 patients, while 13 mm was required for the remaining two patients.

In summary, prostate rotation and deformation seems to be of relatively limited importance and should probably be considered a second-order correction, together with intra-fraction motion management (with pre-treatment alignment being a first-order correction). However, deformation and rotation of the seminal vesicles, commonly included in the target volume for high risk patients, have a higher dosimetric impact and should be considered in any motion/deformation management strategy. Although not specifically considered here, deformations are likely to be of higher importance for other treatment sites in the pelvis region, such as bladder and rectal cancer.
5. Plan complexity in advanced radiotherapy

With the introduction of advanced techniques in radiotherapy, such as IMRT, IMAT and DMLC tracking, the need for plan-specific quality assurance (QA) presented itself. An IMRT treatment is delivered in a dynamic fashion; different parts of the treatment machine move according to a pre-programmed sequence in order to deliver an integrated dose that is the summation of several small fields. Thus, the complexity in both delivery and dose calculation increased by an order of magnitude compared to the older 3DCRT technique which use open fields and a static gantry [144]. Plan specific QA procedures ensures that the delivered dose agree with the planned dose, i.e. the dose calculated in the treatment planning system (TPS).

There are several options for measuring the delivered dose with sufficient accuracy, including film [13], ionization chambers [7], arrays of diodes or ionization chambers placed in a phantom [14–16] and imaging with the portal imager [17]. In clinical practice, many institutions perform QA of all IMRT or IMAT treatment plans [144]. Thus, the time required for each measurement becomes an important factor when deciding which option to use.

5.1. Gamma index

A commonly used metric to compare the measured and the planned dose is the gamma index [145]. The gamma index allows for a combined analysis of deviations in dose and distance to agreement. Two gamma criteria, one for dose difference and one for the distance agreement, are used to define a sphere in a space that consists of both dose and spatial distance. Each point in the measured dose distribution is investigated to find the shortest distance to the planned dose distribution, and the calculated gamma value is \( \leq 1 \) if the result meets the criteria. The gamma index pass rate is the percentage of the measurement points that has a gamma value \( \leq 1 \) [145]. For plan-specific QA, criteria of 3% dose deviation and 3 mm distance to agreement are often used. A certain threshold is used above which the pass rate is considered high enough for the plan to be considered acceptable [144].

In recent years, the usefulness of the gamma index, at least at the 3%, 3 mm level, in predicting clinically relevant dosimetric errors has been questioned. Nelms et al. introduced four different intentional errors in 24 IMRT head & neck-plans and compared them with error-free plans [146]. Each field in the IMRT plans were analyzed separately. The gamma index pass rate, using either 3%, 3mm, 2%, 2mm or 1%, 1mm had at best a moderate correlation to clinically relevant dose errors (e.g. spinal cord overdosage, parotid dose error and target coverage), and in several cases caused false-negatives. In 2012, Fredh et al. investigated the ability of a range of dosimetric systems to detect intentional errors in IMAT plans [147]. The authors noted a lack of correlation between the 3%, 3 mm pass rate and dose-volume histogram deviations and variation in the different systems’ ability to detect the errors. In 2013, Nelms et al. reported seven cases for a variety of techniques, measurement systems and vendors where the 3%, 3 mm gamma index pass rate was above recommended thresholds and thus failed to detect important errors [148]. The errors originated in the TPS in all cases and resulted in local dose variations up to 31%. Despite the criticism in recent years as to the clinical relevance of the gamma index pass rate and its ability to detect errors, it is still widely used [14,147,149–154], presumably due to gamma index being intuitively sound and practical to use in the clinic. Further, the gamma index is derived directly from a comparison of measurements and calculations, and requires no additional data or assumptions. In order to derive DVH data from measurements, however, assumptions on radiation transport, plan and MLC properties may be needed. Therefore, though the clinical usefulness might be more obvious of DVH deviations than gamma index pass rate, it is likely that both metrics have a place in patient-specific QA.
5.2. Plan complexity

One of the cases presented by Nelms et al. in 2013 [148], was an example of a too complex IMAT plan. The pass rate was approximately 95%, but in the high dose region (i.e. the tumour), there was a dose loss of about 5.5%. The plan was characterized by narrow MLC openings, a situation known to be challenging for dose calculation algorithms to handle correctly [155,156]. As exemplified by Nelms et al., complex plans are expected to worsen the agreement between the measured and planned dose. Thus, overly complex plans, where the disagreement is large, should not be used for patient treatments as the planned dose cannot be trusted. Usually, this is ensured by patient-specific QA, but it would be preferable to discard a too complex plan already at the treatment planning stage. To do so, the plans complexity would need to be quantified.

Already in 2000, Mohan et al. introduced the concept of plan complexity, defining it as

“frequency and amplitude of fluctuations (‘complexity’) in intensity distributions on IMRT dose distributions” [157]

Approximative modelling of MLC characteristics, such as the rounded leaf tips, were identified as sources of uncertainty for IMRT dose calculations. By use of a schematic treatment, more complex IMRT fields were obtained by using more challenging optimization scenarios. More complex plans used smaller field openings and more monitor units (MUs) to deliver the same dose. This relationship is explained by the fact that as a smaller part of the target is irradiated (smaller field size), the irradiation must be prolonged for the entire target to be covered (more MUs).

Plan complexity metrics

In 2010, McNiven et al. introduced a qualitative metric of IMRT plan complexity with the modulation complexity score (MCS) [153]. The metric combined the variability in leaf positions along each MLC bank with the degree of irregularity in the field shape. The possible values ranged from zero to unity, where unity implied an open, rectangular field. Gamma index analysis using 3%, 3 mm criteria showed no relationship to MCS. However, when using stringent criteria (2%, 1 mm), the data could be separated into two groups, divided at MCS = 0.8. Still, the usefulness of the metric was not evident. In 2013, Masi et al. adapted the MCS metric for IMAT treatments [154]. The leaf position variability was calculated for each control point in the arc and the field size for each control point was related to with the field size defined by the outermost position for each leaf through the arc. Then, the average of the two metrics was calculated and weighted to the dose delivered in the different parts of the arc. There was a significant correlation between MCS and gamma index pass rate (using 3%, 3 mm and 2%, 2 mm). Other plan complexity metrics that have been used include the ratio between field circumference and field area [158], the amount of MLC leaf travel [154], and number of MUs per prescribed dose (MU/Gy) [159]. The circumference-to-area ratio was included in the treatment planning for arc plans by Younge et al. in 2012 [158]. By introducing a modest penalty on a high ratio (i.e. a complex plan) during optimization, the complexity could be lowered with a small reduction in plan quality. The agreement between calculated and delivered dose was quantified with film measurements using the gamma pass rate. For two measured plans (one with a penalty and one without), the gamma pass rate increased from 79.5% to 95.4 with 3%, 1 mm criteria, and from 97.5% to 98.9% with 3%, 3 mm criteria.

In Study V we investigated the usefulness of the dose weighted average adjacent leaf distance (ALDw) as a plan complexity metric for IMAT plans. The metric was previously used to quantify plan complexity in the context of DMLC tracking [107,108,111]. The usefulness of ALDw as well as MCS, leaf travel, MU/Gy and a novel metric termed the relative exposed area (REA) to predict QA failure was investigated for two dosimetric systems. The REA metric was defined as the average irradiated area divided by the area of the outermost position for each MLC leaf throughout the arc. One of the two dosimetric systems was a diode array based system while the other used the portal imager. Significant correlations were found between all six plan complexity metrics and gamma index pass rate, using 3% 3 mm. The 3%, 3 mm criteria were used despite the arguments noted above for using more stringent criteria. There were two reasons for this: (1), 3% 3 mm was used clinically, and (2), the portal imager based system had pass rates as low as 75%, far from the clinical acceptance level of 94%. Interestingly, the relationship between plan complexity and pass rate were opposite for the two systems; for the phantom based system, more complex plans led to worse agreement, but for the portal imager based system, the opposite was true. The phantom based system used a well established dose calculation algorithm called the anisotropic...
analytical algorithm (AAA), while the portal imager based system used a simpler dose convolution based algorithm, called the portal dose image prediction (PDIP). A different portal imager based system that used AAA also had worsened agreement with increased complexity, as demonstrated, although not explicitly investigated, by Fogliata et al. in 2011 [152]. Thus, the likely cause of the different relationships between plan complexity and gamma index pass rate was the simpler PDIP algorithm, although Study V was not designed to investigate the performance of the algorithm (the opposite relationships were an unexpected finding from the study). Still, the study was the first to demonstrate such a correlation for the specific system, and to use the ALDw metric in a context other than DMLC tracking. The fact that the metric could predict QA results as well as tracking performance, suggests that decreasing the plan complexity, e.g. by using the leaf position constraint, would be useful for ordinary treatment plans as well as DMLC tracking plans.
6. Summary and conclusions

Real-time motion management of prostate motion during radiotherapy with DMLC tracking is feasible using current technology. The prostate is relatively easy to locate with implanted markers; the options include x-ray imaging and implanted electromagnetic transponders. Since the prostate usually has small and uncomplicated motion, e.g. compared to lung tumours, the mechanical strain associated with DMLC tracking is manageable and the delivered dose will be very close to the intended dose, provided that the prostate is correctly located. Finally, by reconstructing the delivery, the delivered dose can be verified at a level beyond that which is currently used in clinically.

The question is rather whether or not it is necessary to correct for prostate motion in real-time. There are three arguments to be conveyed here. First, the motion can (almost) always be mitigated by using treatment margins that are wide enough. This will however lead to an increased radiation dose to the surrounding healthy tissue. Using motion management, the margins can potentially be reduced (or, if the same margins are used, the percentage of patients receiving the intended dose can be increased). Secondly, even if real-time motion management only will benefit a fraction of the patients, the number of prostate cancers patients is large and a substantial number of patients would potentially stand to benefit from this. Finally, the technology can be transferred to treatments sites other than prostate, and its usability expanded.

We showed that DMLC tracking is suitable for real-time prostate motion compensation. We demonstrated excellent agreement between the dose delivered with tracking in the presence of motion and the dose calculated in the treatment planning system, where a static delivery is assumed. We also validated a novel dose reconstruction method by finding agreement between the measured dose with motion, with and without DMLC tracking, and the reconstructed doses. These findings were essential when the technology was transferred from the experimental stage to the clinic. Firstly, it made it possible (for prostate treatments) to calculate the dose for a static tumour only and then applying tracking to ensure that the tumour is covered by the intended dose. Secondly, the dose reconstruction method would allow the physicist to estimate the actual dose delivered to the patient and thus ensure the quality of the treatment (Study I).

We investigated treatment plan complexity and showed that it was significantly less important for prostate motion compared to lung motion. The main cause of tracking errors during prostate tracking was the ability of the MLC to achieve the desired shape, limited by the width of the MLC leaves. The study was the first to investigate the impact of leaf width on the performance of DMLC tracking and it showed that the total error (quantified as the area incorrectly irradiated) could be approximately halved by halving the leaf width (Study II).

We attempted to describe prostate motion using a random walk model. The motion traces were categorized into two groups, based on whether any transient excursions (i.e. rapid motion following by a return to the approximate starting position) occurred. For the group without excursions, the random walk model well described the prostate motion. However, the excursions, occurring with an average probability of 0.1 per minute, made the model less accurate. Simulated transient excursions, on top of the random walk model, slightly improved the agreement between simulated and observed motion. The implications of describing prostate motion with a random walk may be a possibility to decrease the treatment margins, and, for real-time motion management, the method can be used to lower the position verification frequency with maintained localization accuracy. However, the latter is only true for excursion-free motion. The dynamics of the
rectum, which is the likely cause of the excursions, could potentially be modelled in a further effort to understand prostate motion (Study III).

We also investigated the dosimetric impact of prostate motion during hypofractionated radiotherapy. Hypofractionation is characterized by delivering the intended dose in a small number of fractions and it may be the treatment of choice for prostate radiotherapy in the future. The dose reconstruction method was used to simulate 10,000 treatments (each consisting of five fractions), in a Monte Carlo approach with each fraction assigned a random motion trace. The study showed that for selected treatment margins and investigated motion traces, the dose to the prostate is well maintained in the vast majority of the treatments. Still, prostate motion may cause relatively large dose deviations for occasional treatments. The study also investigated the impact of using one or two arcs in intensity-modulated arc therapy, as well as the impact of a decreased treatment time by using a treatment beam with a higher dose rate. Two arcs was found to be preferable to one, although the number of patients may have been too small to make that a general conclusion, while the shorter treatment time was found to slightly improve the agreement to the planned dose (Study IV).

Finally, we investigated the impact of plan complexity in standard (i.e. not tracked) treatments. Among other plan complexity metrics, the adjacent leaf distance used in Study I and II was found to be suitable for quantifying the complexity of a treatment plan. Overly complex treatment plans risk being incorrectly calculated in the treatment planning system. Plan complexity metrics has the potential to reduce the risk such plans being used for patient treatments by discarding the most complex plans. Additionally, in an effort to reduce the workload of medical physicists, plans that are simple can be identified and allowed to be used for patient treatments without customary plan-specific measurements (Study V).
7. Future perspectives

With the first patient recently treated with DMLC tracking, the technology is certainly in a very exciting phase at the moment [76]. This thesis showed that for prostate cancer, standard intensity-modulated arc therapy plans can be used successfully with DMLC tracking. It also demonstrated the ability of the dose reconstruction method to verify the tracked treatments. However, in order for DMLC tracking to find widespread use, it needs to be implemented by the main manufacturers of radiotherapy equipment. Such implementations are likely to be associated with legal issues since the use of DMLC tracking represents a paradigm shift in radiotherapy; no longer would a treatment plan be optimized and checked once and then used as-is for the duration of the patients treatment. Instead, the plan would be continuously changed and adapted. Indeed, with current quality control procedures, significant changes in both clinical practise and quality control philosophy would be necessary. The use of plan complexity metrics may be a first step in such a process. If these challenges could be overcome, there is no fundamental reason why DMLC tracking could not be applied for a large fraction of the treated patients. The only additional necessary part would be tumour localization. There are already several available options, and in the future, potentially by combining different methods, intrafraction tumour localization could be feasible for most treatment sites.

Besides rigid translation and rotation, correction of deformations has recently been demonstrated with DMLC tracking [114]. Intra-fractional deformation correction requires real-time volumetric imaging, a challenge for conventional linear accelerators. However, pre-treatment volumetric imaging is used routinely in the clinic. There is therefore a possibility of combining deformation correction based on pre-treatment imaging, with corrections of translations and rotations using intra-fraction motion. For such an approach, combined modelling of both interfraction deformation and intrafractional motion would be essential.

There are at least two major trials currently underway that will determine the usefulness of prostate hypofractionation [160]. Should the trials determine that hypofractionation is a viable alternative to standard treatments; the number of treatment fractions for prostate cancer patients would be reduced from approximately 40 to as few as 5. The smaller number of fractions would increase the impact of beam-prostate misalignment during single fractions. Flattening-filter free beams have the potential to allow such treatments to be delivered as quickly as standard treatments. Besides increasing the patients’ convenience, there would be time available to increase the workload during each fraction. Intra-fraction monitoring and possibly DMLC tracking could then be implemented without increasing the burden on already busy radiotherapy clinics.
References


REFERENCES


REFERENCES


REFERENCES


## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>3D</td>
<td>three dimensional</td>
</tr>
<tr>
<td>3DCRT</td>
<td>3D conformal radiation therapy</td>
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<tr>
<td>ALD</td>
<td>average adjacent leaf distance</td>
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<tr>
<td>AP</td>
<td>anterior-posterior</td>
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<tr>
<td>BEV</td>
<td>beam’s eye view</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CTV</td>
<td>clinical tumour volume</td>
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<tr>
<td>DMLC tracking</td>
<td>dynamic multileaf collimator tracking</td>
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<tr>
<td>EBRT</td>
<td>external beam radiotherapy</td>
</tr>
<tr>
<td>EPID</td>
<td>electron portal imager device</td>
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<tr>
<td>FFBF</td>
<td>freedom from biochemical failure</td>
</tr>
<tr>
<td>FFF</td>
<td>flattening-filter free</td>
</tr>
<tr>
<td>GTV</td>
<td>gross tumour volume</td>
</tr>
<tr>
<td>Gy</td>
<td>gray</td>
</tr>
<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units and Measurements</td>
</tr>
<tr>
<td>IMAT</td>
<td>intensity-modulated arc therapy</td>
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<tr>
<td>IMRT</td>
<td>intensity-modulated radiotherapy</td>
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<tr>
<td>IPL</td>
<td>intra-prostatic lesions</td>
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<tr>
<td>kV</td>
<td>kilovoltage</td>
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<tr>
<td>linac</td>
<td>linear accelerator</td>
</tr>
<tr>
<td>LPC</td>
<td>leaf position constraint</td>
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<tr>
<td>LR</td>
<td>left-right</td>
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<tr>
<td>MCS</td>
<td>modulation complexity score</td>
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<tr>
<td>MLC</td>
<td>multileaf collimator</td>
</tr>
<tr>
<td>MR</td>
<td>magnetic resonance</td>
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<tr>
<td>MU</td>
<td>monitor unit</td>
</tr>
<tr>
<td>MV</td>
<td>megavoltage</td>
</tr>
<tr>
<td>OAR</td>
<td>organs at risk</td>
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<tr>
<td>PTV</td>
<td>planning target volume</td>
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<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>REA</td>
<td>relative exposed area</td>
</tr>
<tr>
<td>RMS</td>
<td>root mean square</td>
</tr>
<tr>
<td>RTMM</td>
<td>real-time motion management</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SI</td>
<td>superior-inferior</td>
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<tr>
<td>TPS</td>
<td>treatment planning system</td>
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<tr>
<td>VMAT</td>
<td>volumetric modulated arc therapy</td>
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</table>
Dosimetric benefit of DMLC tracking for conventional and sub-volume boosted prostate intensity-modulated arc radiotherapy

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Abstract

This study investigated the dosimetric impact of uncompensated motion and motion compensation with dynamic multileaf collimator (DMLC) tracking for prostate intensity modulated arc therapy. Two treatment approaches were investigated; a conventional approach with a uniform radiation dose to the target volume and an intraprostatic lesion (IPL) boosted approach with an increased dose to a subvolume of the prostate. The impact on plan quality of optimizations with a leaf position constraint, which limited the distance between neighbouring adjacent MLC leaves, was also investigated. Deliveries were done with and without DMLC tracking on a linear accelerator with a high-resolution MLC. A cylindrical phantom containing two orthogonal diode arrays was used for dosimetry. A motion platform reproduced six patient-derived prostate motion traces, with the average displacement ranging from 1.0 to 8.9 mm during the first 75 s. A research DMLC tracking system was used for real-time motion compensation with optical monitoring for position input. The gamma index was used for evaluation, with measurements with a static phantom or the planned dose as reference, using 2% and 2 mm gamma criteria. The average pass rate with DMLC tracking was 99.9% (range 98.7–100%, measurement as reference), whereas the pass rate for untracked deliveries decreased distinctly as the average displacement increased, with an average pass rate of 61.3% (range 32.7–99.3%). Dose–volume histograms showed that DMLC tracking maintained the planned dose distributions in the presence of motion whereas traces with >3 mm average displacement caused clear plan degradation for untracked deliveries. The dose to the rectum and bladder had an evident dependence on the motion direction and amplitude for...
untracked deliveries, and the dose to the rectum was slightly increased for IPL boosted plans compared to conventional plans for anterior motion with large amplitude. In conclusion, optimization using a leaf position constraint had minimal dosimetric effect, DMLC tracking improved the target and normal tissue dose distributions compared to no tracking for target motion $>3$ mm, with the DMLC tracking distributions showing generally good agreement between the planned and delivered doses.

(Some figures may appear in colour only in the online journal)

1. Introduction

Dose escalation studies have shown improved biochemical control with increasing radiation doses to the prostate in patients with prostate cancer (Kuban et al 2008, Al-Mamgani et al 2008, Zelefsky et al 2008). Intraprostatic lesions (IPLs) can be identified by imaging modalities such as magnetic resonance imaging (MRI) (Cruz et al 2002, Puech et al 2009, Groenendaal et al 2010). Pathological studies have determined that IPLs are the sites of recurrences of prostate cancer. An increased dose to the IPLs may therefore increase disease control (Cellini et al 2002, Pucar et al 2007), an approach that has been investigated in planning and modelling studies (Pickett et al 1999, Kim and Tomé 2008, Ost et al 2011) as well as in small clinical studies (De Meerleer et al 2005, Singh et al 2007). Creating complex dose distributions in which small volumes within the prostate are boosted to a higher dose could therefore be beneficial to patients as compared to the conventional approach where the whole prostate is prescribed a uniform dose.


The aims of this study were: (1) to examine the possibility of boosting the IPL, while decreasing the complexity of the MLC configuration, without compromising the plan quality; (2) to investigate the potential benefit of DMLC tracking of IPL boosted and conventional prostate treatments for a range of target motion; and (3) to determine whether IPL boosted plans were more sensitive to uncompensated intrafraction motion than conventional treatment plans.

2. Materials and methods

2.1. Treatment planning

Four patients with prostate cancer were used in this study. For two patients, IPLs visible on T2W MRIs were delineated and for the two other patients, artificial spherical IPLs were drawn in the peripheral zone of the prostate with a volume of 2.1 cm$^3$ which was the median volume in 19 identified IPLs in Lips et al (2009). The patient data are shown in table 1.
Table 1. Patient data. For patients 1 and 2, IPLs were contoured based on MRI images, for patient 3 and 4, fictitious spherical IPLs were drawn in the peripheral zone.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>PTV volume (cm$^3$)</th>
<th>Prostate volume (cm$^3$)</th>
<th>IPL volume (cm$^3$)</th>
</tr>
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<tr>
<td>1</td>
<td>61.3</td>
<td>13.8</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>137.0</td>
<td>44.5</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>117.4</td>
<td>47.6</td>
<td>2.1</td>
</tr>
<tr>
<td>4</td>
<td>83.9</td>
<td>27.9</td>
<td>2.1</td>
</tr>
</tbody>
</table>

For the plan optimization, the Delta4 dosimetric phantom (Scandinos, Uppsala, Sweden) was used instead of the patient CT data. This allowed for comparison between the delivered dose to the phantom and the optimized dose distribution. To account for the different beam attenuation, the dose per fraction was adjusted according to the ratio in isocentre dose for a full arc for the phantom and for the patient CTs. Thus, the plans optimized to the phantom volume had approximately the same number of monitor units as the plans would have had if optimized to the patient volume. The following contours were propagated from the patient CT to the phantom: the prostate, the seminal vesicles, the PTV, the IPL, the rectum and the bladder. The femoral heads were excluded as they were only partially localized within the phantom volume. The PTV was created by expanding the prostate and the seminal vesicles with 5 mm margin in the AP and LR directions and with 7 mm margin in the SI direction. The PTV was reduced in overlap regions between the PTV and the rectum. For optimization in the IPL boosted cases, a PTV$_{\text{minus IPL}}$ structure was created by subtracting the PTV by the IPL volume with a 4 mm margin around the IPL. No planning margin was however used for the IPL, which allowed a high dose to the IPL without compromising the planning objectives for the maximum dose to the PTV$_{\text{minus IPL}}$.

IMAT treatment plans (RapidArc from Varian Medical Systems, Palo Alto, CA) were optimized in a research version of Eclipse version 10 either with or without an IPL boosted approach for delivery on a Novalis TX linear accelerator with a high-definition MLC (2.5 mm central leaf width). The conventional approach was planned for 2.3 Gy per fraction to the PTV, corresponding to 2 Gy per fraction to the patient volume. For the IPL boosted case, the dose to the IPL was increased to 2.79 Gy, or 121% of the PTV dose, corresponding to circa 94 Gy in a 39 fraction schedule. In order to make the plans robust to DMLC tracking, a leaf position constraint (LPC) was applied during the optimization (Falk et al 2012). The LPC limited the allowed distance between adjacent MLC to 0.83 cm, which was the maximum possible leaf travel between two MLC/gantry control points used in the IMAT delivery, and assured that the MLC aperture during tracking could be shifted by one leaf in case of target motion perpendicular to the MLC leaf direction. No LPC equated standard treatment planning, where no LPCs were imposed. Optimizations with and without a LPC were compared to evaluate the impact of the LPC on the plan quality. Only plans with LPC were used during the experimental part of this study. To facilitate DMLC tracking, the jaws were set approximately 2 cm wider than the largest PTV projection. Each plan was optimized with a single 358° arc with a 45° collimator, used 6 MV and a maximum dose rate of 600 MU min$^{-1}$. No monitor unit objective was used in the optimizations.

2.2. Prostate motion traces

The motion traces used in this study were extracted from a dataset of prostate motion obtained during 548 radiotherapy fractions (Langen et al 2008). In this study, the first 75 s (the delivery time for a single arc) after patient setup was used with the first position adjusted to origin.
Figure 1. The six prostate motion traces used in this study. The average 3D displacements relative to isocentre during 75 s are shown in brackets.

Of the 548 traces, within the first 75 s, 14 traces (2.6%) had a maximum 3D-displacement >10 mm and 5 traces (0.9%) had an average 3D-displacement >5 mm. Six of the motion traces were selected for use in the experimental part of this study, with average displacements ranging from 1.0 mm to 8.9 mm (figure 1). The used motion traces were selected to give a representation of the range of motion available in the dataset, including atypical but possible motion with large displacements.

2.3. Experimental setup

Target motion was performed with a motion platform (HexaMotion from Scandidos, Uppsala, Sweden), capable of accurately reproducing target motion in three dimensions (Falk et al. 2011). The Delta4 dosimetric phantom was integrated with the motion platform, which allowed the dose to be measured with the phantom moving according to the prostate motion traces. The phantom consisted of two orthogonal diode array placed in a cylindrical PMMA phantom. The diodes were separated by 5 mm in the central 6 cm × 6 cm of the arrays, and by 10 mm in the rest of a 20 cm × 20 cm area.

A research DMLC tracking system, described by Sawant et al. (2008), with a direct optimization leaf sequencing algorithm (Ruan et al. 2009), was used to compensate for target motion. The phantom location was obtained with infrared reflective markers placed on the phantom and monitored with the optical part of the ExacTrac system (Brainlab, Germany). The location was then sent to the DMLC tracking software which in real-time calculated new MLC positions that compensated for the observed motion. As prostate motion generally lack the periodicity of lung motion, no prediction algorithm was used for the measurements. To investigate the uncertainty of the measurements repeated measurements were performed for a single plan and motion trace.

When the DMLC tracking system controlled the MLC, the closed MLC leaves next to an open aperture were placed with their ends adjacent to the nearest leaf opening, ready to be used for compensation of motion perpendicular to the leaf direction. More peripheral closed leaves were placed beneath the jaws (Sawant et al. 2008). To investigate the impact that
connecting the DMLC tracking system had on the dosimetric faithfulness, measurements were made to a static phantom with the following configurations: (1) no tracking, i.e. conventional IMAT treatment with the tracking system disconnected; (2) standard tracking with the leaves adjusted as described above; and (3) the tracking system set to emulate the no tracking treatment, i.e. with all leaves placed according to the treatment plan. For these measurements, in order to eliminate uncertainty originating in monitoring system, a simulated input with zero displacement was used.

2.4. Evaluation

To evaluate the dosimetric effect of compensated and uncompensated motion, gamma evaluation and dose reconstruction were used. Gamma evaluation of the measured dose was performed in the Delta4 software and gamma evaluation of the reconstructed dose was done with in-house developed software. Either the dose to a static target (delivered with tracking for tracking measurements and without tracking otherwise) or the planned dose was used as reference. For the measured doses, gamma calculations were performed in 2D along the diode array planes when measurements were used as reference and in 3D around the diodes when the planned dose was used as reference. Gamma calculation was performed for diodes receiving >5% of the prescribed dose.

Dose reconstruction was done for each delivery (both tracking and non-tracking) by creating motion-encoded Dicom treatment plans that reflected the actual treatment delivery and modeled intra-treatment target motion by isocentre shifts (Poulsen et al 2012). The motion-encoded plans were generated by an in-house developed computer program based on the original treatment plan, log files of gantry and MLC motion during the treatment and the motion trace reproduced by the phantom. The method has been described previously (Poulsen et al 2012) but is briefly repeated here for completeness. The positions in the motion trace were assigned to bins with 1 mm³ size and the MLC and gantry positions were assigned to the bin that corresponded to the phantom position during the arc. Together with the dose data from the original plan, a treatment plan was then created with one isocentre for each bin. Each motion-encoded plan consisted of approximately 1500 control points, corresponding to 20 control points per second (20 Hz logging of the MLC positions) during approximately 75 s treatment delivery. The motion encoded treatment plans were imported into the treatment planning system where dose calculation resulted in reconstructed dose distributions that allowed 3D gamma analysis and DVH evaluation (Poulsen et al 2012). Gamma calculations were performed once every 1.0 mm³ for the reconstructed doses, throughout the volume that received >5% dose. The structures included in the DVH evaluation were the target volumes: the prostate, the PTV, the PTV_{\text{minusIPL}} , the IPL, and the organs at risk (OARs): the rectum and the bladder. The same rigid motion was assumed for all structures. The difference in the D98% to IPL and prostate and V70Gy to the rectum and bladder between untracked delivery with motion and without motion was calculated for the IPL boosted and the conventional approaches, and tested for any significant difference with the Wilcoxon signed rank test.

3. Results

Comparison of planned DVHs showed that the decreased plan modulation caused by the LPC led to a small decrease in plan quality, and the additional planning challenge associated with the IPL boosted approach caused a slight further decrease in PTV homogeneity (figure 2). The planned number of monitor units was lower with LPC (mean 640 MU, range 579–703)
Figure 2. Impact on plan quality of a LPC on plans with and without IPL boost. Compiled planned DVHs based on four plans for each planning strategy, showing the impact on plan quality caused by applying LPC and IPL boosting.

than without LPC (mean 675 MU, range 643–741), but did not depend systematically on the addition of the IPL boost.

A visualisation of the effect that motion had for the IPL boosted and the conventional approach is shown in figure 3 using reconstructed doses for patient 1: for the static case, trace ‘C’ and trace ‘F’ (with an average displacement of 3.3 and 8.9 mm respectively). While the dose distribution for trace ‘C’ without tracking resembled the static dose distribution reasonably, the larger motion for trace ‘F’ resulted in large dose redistributions. As seen in the right side of the figure, tracking was able to restore the planned dose even for the large motion of trace ‘F’. The gamma pass rates for these examples (with 2% 2 mm criteria) are indicated in figure 3 while figure 4 shows the gamma pass rates for all experiments. With the planned dose as reference, the gamma pass rate for the tracked deliveries was higher than for non-tracked deliveries when the average displacement exceeded 3 mm, while similar pass rates were seen for both tracked and non-tracked deliveries for smaller average displacements (figure 4, top, left). The lowest pass rate for a single tracked measurement was 93.4%, (98.0% with 3%
Figure 3. Example of reconstructed dose distributions in the axial plane at isocentre for patient 1, with and without IPL boost, without tracking (middle and left) and with tracking (right), for the static delivery, trace ‘C’ and trace ‘F’ (average displacements 3.3 and 8.9 mm, respectively). The delineated structures are the PTV (cyan), the prostate (dark red), the IPL (orange) and the rectum (brown). The patient CT is shown here for visual guide as the plans were optimized for a phantom volume.

Figure 4. The gamma index pass rate (using 2% and 2 mm criteria) for a static target and six prostate motion traces with and without DMLC tracking, with either planned dose (left) or static measurement as reference (right), for the measured doses (top) and reconstructed doses (bottom). Each value is an average of four plans, the error bars show standard deviation. The inserts highlights the area with similar pass rates.
3 mm criteria), and the average pass rate was 96.7% (99.7% with 3% 3 mm criteria). Using the planned dose as reference resulted in some dose discrepancies for tracking due to the different positions of closed leaves in the experiments and in the plan (figure 4, left graph inserts). This discrepancy was absent when the static measurements were used as reference as the static measurements had the same closed leaves positions as the tracking experiments (figure 4, right inserts). When measurements with a static target were used as reference, higher pass rates were seen with tracking for all investigated motion traces (figure 4, top, right). The same trend in gamma results was observed for measured and for reconstructed doses, indicating that the dose reconstruction method worked adequately (compare top and bottom panels in figure 4). The difference in the number of points used for gamma calculation was the probable cause of the difference in pass rates between evaluations of measured and reconstructed doses; the gamma calculation for the measured doses were based on the readings from at least 500 diodes, whereas > 2 000 000 calculation points were used for the reconstructed doses.

The DVHs showed that untracked motion had a large impact on both the target conformity and the doses to OARs, especially for the motion traces with an average displacement > 3 mm (figure 5). As seen in figure 5, the OAR doses depended considerably on the particular motion trace in the non-tracked deliveries. In general, traces leading to increased rectum doses resulted in decreased bladder doses, and vice versa (figure 5). This is a result of the typical prostate motion directionality where anterior prostate motion increases the rectum dose and inferior motion decreases the bladder dose. This is illustrated further in figure 6 which shows how the

Figure 5. Reconstructed DVHs with and without DMLC tracking for the investigated prostate motion traces and two treatment approaches; with IPL boost (top), no IPL boost (bottom). The DVHs are averaged for four treatment plans.
rectum and bladder volumes receiving 89.5% or more of the prescribed dose (corresponding to 70 Gy or more (V70Gy) for a prescribed dose of 39 × 2 Gy) depended systematically on the direction and magnitude of the traces. Larger inter-patient variability occurred for the larger displacements. A larger increase in rectum dose was seen for the motion in the anterior direction for the IPL boosted cases compared to the conventional cases. For the tracked deliveries, the V70Gy for the OARs varied only slightly for the different motion traces (figure 6). Statistical analysis with the Wilcoxon signed rank test showed that for the IPL boosted approach, untracked motion had a significantly larger impact on the D98 to the IPL and the V70Gy to the rectum (p < 0.001) than for the conventional approach (including all traces). When the analysis was limited to trace ‘A’ to trace ‘C’, the p-value was slightly increased but still <0.01. No significant difference was found for the prostate D98 and the bladder V70Gy.

Five repeated tracking measurements for a single plan and motion trace (trace ‘E’ in figure 1) showed excellent repeatability; with a static measurement as reference the gamma pass rate was 97.5 - 97.8% using 1% and 1 mm criteria and 100% using 2% and 2 mm criteria. With the planned dose as reference, the pass rate was 76.9–79.6% (1%, 1 mm) and 97.5–98.1% (2%, 2 mm). Measurements with the tracking software emulating a standard delivery showed an increased agreement with the no tracking delivery compared to the standard tracking. The effect was absent when the planned dose was used as reference (table 2). This indicated that some dose discrepancy was caused by connecting the tracking system.

4. Discussion

This study investigated the possibility of optimizing prostate IMAT treatment plans with a boost to a subvolume of the prostate with the added constraint on the distance to adjacent MLC leaves, the dosimetric effect of uncompensated motion and motion compensation with DMLC tracking and whether boosted plans were more sensitive to uncompensated motion. Treatment planning with increased dose to IPLs has previously been studied for different approaches of rotational therapy (Ost et al 2011, Jolly et al 2010). This study added the aspect of planning constraints to make the plans robust for DMLC tracking, as suggested in
Table 2. Gamma index pass rate for repeated static measurements with either a measurement with no tracking or the planned dose as reference. The average for three deliveries is shown with range in brackets, except for “no tracking versus no tracking”, for which two deliveries were compared with a third.

<table>
<thead>
<tr>
<th></th>
<th>Gamma pass rate 0.5% 0.5 mm</th>
<th>Gamma pass rate 1% 1 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracking standard versus no tracking</td>
<td>94.2 [93.8–94.6]</td>
<td>97.8 [97.8–97.8]</td>
</tr>
<tr>
<td>Tracking emulate versus no tracking</td>
<td>97.9 [97.3–98.7]</td>
<td>100 [100.0–100.0]</td>
</tr>
<tr>
<td>No tracking versus no tracking</td>
<td>100 [100.0–100.0]</td>
<td>100 [100.0–100.0]</td>
</tr>
<tr>
<td>Tracking standard versus planned dose</td>
<td>88.4 [86.5–90.1]</td>
<td>98.9 [98.9–99.0]</td>
</tr>
<tr>
<td>Tracking emulate versus planned dose</td>
<td>88.9 [88.3–89.9]</td>
<td>98.8 [98.6–99.0]</td>
</tr>
<tr>
<td>No tracking versus planned dose</td>
<td>93.1 [92.2–94.4]</td>
<td>99.6 [99.4–99.7]</td>
</tr>
</tbody>
</table>

(Keall et al 2011). In Falk et al (2012) the effect of the position constraint was studied for lung treatments, finding no significant difference in plan quality but significant improvement of DMLC tracking accuracy with more stringent leaf distance constraints. The improved DMLC tracking performance and thus the need of leaf constraints was expected to be lower for prostate motion when compared to lung motion. This study was limited to either no or a very stringent constraint and any trade-off between plan quality and DMLC tracking accuracy is subject to further study. This study used no additional planning margins around the IPLs. This could be motivated by the fact that the area surrounding the lesion is already a high dose area, i.e. the standard PTV, and the impact of setup errors and small motion would therefore, arguably, be limited. Obviously, adding a margin around the IPL would tend to increase the overall PTV dose and in particular the dose to the urethra.

For the deliveries with motion, DMLC tracking was superior to no tracking for all investigated prostate motion traces when the effect of motion was isolated, i.e. when measurements with a static target were used as reference in the gamma evaluation, and stringent (2% and 2 mm) gamma criteria were used. However, when the evaluations were performed versus the planned dose, a benefit of tracking was seen only for motion traces with average displacements larger than 3 mm. Comparison of the tracked deliveries with the planned dose was associated with certain challenges; the DMLC tracking software moved unused leaves from their planned position (to avoid leakage irradiation and keep the leaves ready for tracking). This made deliveries with tracking and no motion to deviate slightly from the planned dose. Optimizing treatments with this taken into account would likely improve the agreement with the planned dose. Measurements with the tracking software emulating a standard delivery showed increased agreement with the static delivery but no difference on the agreement with the planned dose.

The measurement and the dose reconstruction strategy used in this study assumed that the target moved rigidly along with the OARs and used external markers as substitute for actual target localization. There are several methods that could be used for real-time target localization of either the tumour or markers during treatments, including kV imaging (Poulsen et al 2010), electromagnetic localization (Keall et al 2011), MV-imaging with the treatment beam, MRI and ultrasound. However, as the purpose of this study was to investigate the planning and dosimetric aspect of DMLC tracking, the use of external markers was warranted. Although limited to translational motion in this study, DMLC tracking also has the potential to correct for rotation (Wu et al 2012) and deformation. It should finally be noted that the DMLC tracking software is a research system that is under development and its performance can be expected to be improved in future versions.
5. Conclusions

For the investigated cases, dose escalation to a subvolume of the prostate was achieved without any clear increase in risk organ doses. An added constraint on the distance between adjacent MLC leaves in the treatment plan introduced only a very minor reduction of the plan quality. The delivered dose with DMLC tracking was for the first time compared directly to the planned dose calculated with the treatment planning system for patient cases. The evaluation showed that DMLC tracking could accurately deliver the planned dose with or without dose escalation and regardless of target motion extent. For the patient-derived motion traces used in this study, the use of DMLC tracking improved the dose fidelity for traces with average motion larger than 3 mm when compared to the planned dose. Without tracking, and assuming that the OARs move with the target (i.e. no deformation), the risk of increasing the dose to the rectum was higher for the IPL boosted approach than the conventional approach, while it was unaffected for the bladder. Similarly, without tracking, the coverage of the prescribed dose to the intra-prostatic lesions was significantly more sensitive to motion for the IPL boosted plans.

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The impact of leaf width and plan complexity on DMLC tracking of prostate intensity modulated arc therapy

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Purpose: Intensity modulated arc therapy (IMAT) is commonly used to treat prostate cancer. The purpose of this study was to evaluate the impact of leaf width and plan complexity on dynamic multileaf collimator (DMLC) tracking for prostate motion management during IMAT treatments.

Methods: Prostate IMAT plans were delivered with either a high-definition MLC (HDMLC) or a Millennium MLC (M-MLC) (0.25 and 0.50 cm central leaf width, respectively), with and without DMLC tracking, to a dosimetric phantom that reproduced four prostate motion traces. The plan complexity was varied by applying leaf position constraints during plan optimization. A subset of the M-MLC plans was converted for delivery with the HDMLC, isolating the effect of the different leaf widths. The gamma index was used for evaluation. Tracking errors caused by target localization, leaf fitting, and leaf adjustment were analyzed.

Results: The gamma pass rate was significantly improved with DMLC tracking compared to no tracking (p < 0.001). With DMLC tracking, the average gamma index pass rate was 98.6% (range 94.8%-100%) with the HDMLC and 98.1% (range 95.4%-99.7%) with the M-MLC, using 3%, 3 mm criteria and the planned dose as reference. The corresponding pass rates without tracking were 87.6% (range 76.2%-94.7%) and 91.1% (range 81.4%-97.6%), respectively. Decreased plan complexity improved the pass rate when static target measurements were used as reference, but not with the planned dose as reference. The main cause of tracking errors was leaf fitting errors, which were decreased by 42% by halving the leaf width.

Conclusions: DMLC tracking successfully compensated for the prostate motion. The finer leaf width of the HDMLC improved the tracking accuracy compared to the M-MLC. The tracking improvement with limited plan complexity was small and not discernible when using the planned dose as reference.

Key words: intrafraction motion, motion management

1. INTRODUCTION

Intensity modulated arc therapy (IMAT) has been shown to facilitate a high degree of efficiency and conformity in radiation delivery. Patient or tumor motion during IMAT delivery may, however, degrade the delivered dose distribution and cause unwanted loss of tumor coverage and increased dose to organs at risk. Prostate motion and its impact on margins and delivered dose distributions in radiotherapy are well studied.

Dynamic multileaf collimator (DMLC) tracking is a method to compensate for intrafraction target motion by real-time adaption of the MLC aperture to the targets movement. Other methods of motion compensation, not covered in this study, include beam gating, moving the source, and couch tracking. The accuracy of DMLC tracking depends on the alignment between the leaves and the target motion, with motion perpendicular to the leaf travel being more challenging. There are two reasons for this; (1) the finite leaf width limits the leaf fit to the closest physically possible shape and (2) perpendicular motion can lead to large MLC aperture changes where leaves may be unable to reach the desired position in sufficient time to avoid dose errors. The leaf width is an inherent limiter of DMLC tracking accuracy, as it defines the smallest possible correction of perpendicular motion. A recent study by Falk et al. showed that optimal tracking performance for IMAT lung treatments with sinusoidal target...
Plans were created for two prostate cancer patients with Eclipse version 10, Varian Medical Systems, Palo Alto, CA). The plans were optimized for two prostate cancer patients with 2 Gy/fraction prescribed to the PTV. The PTV volumes were 63 and 140 cm³ for patient #1 and patient #2, respectively. To create plans with varying plan complexity, a leaf position constraint (LPC) limited the maximum allowed distance (AD) between adjacent MLC leaves. The AD was varied between 0.81, 1.44, 2.07, and 2.69 cm (the same for both MLCs). The most stringent constraint, AD = 0.81 cm, corresponded to the maximum distance a leaf could travel between two control points and the other constraints were multipliers of that distance. Additionally, plans were created with no LPC. With the distance between adjacent leaves restricted, the leaves would have a shorter distance to travel to compensate for motion perpendicular to the MLC leaves.

The plans were optimized for two MLCs; the high-definition MLC (HDMLC) and the Millennium 120 MLC (M-MLC) (Varian Medical Systems, Palo Alto, CA). The HDMLC has 32 2.5 mm central leaf pairs and 28 5.0 mm peripheral leaf pairs. The M-MLC has 40 5.0 mm central leaf pairs and 20 10.0 mm peripheral leaf pairs. Ten plans were made for each patient, five for each MLC with varying LPC. The same planning objectives were used for all plans for each patient, chosen to obtain a similar degree of intensity modulation regardless of the LPC. To isolate the effect of the different leaf widths, the M-MLC plans for patient #1 (with the smaller PTV) were converted for delivery with the HDMLC. The size of the PTV allowed the converted plans to only use the central part of the MLC with 2.5 mm leaves. The jaws were placed approximately 2 cm wider than the PTV projection in order to allow for DMLC tracking. The plans used a 358° arc, 6 MV, and 45° collimator angle.

2.2 B. Experimental setup
A motion platform with accurate 4D motion capability was used to reproduce four prostate motion traces (average 3D displacement 1.8–4.4 mm, maximal 3D displacement 7.2–13.2 mm), selected from a dataset of 548 motion traces. The traces represented characteristic types of prostate motion: continuous drift, high frequency excursions, persistent excursion, and transient excursion. The traces are the same as in Keall et al. The traces started at isocenter. A dosimetric phantom was mounted on the motion platform (Delta4 with Hexamotion, Scandidos, Uppsala, Sweden). The phantom consisted of two orthogonal diode arrays placed in a cylindrical PMMA phantom, diameter 21.8 cm. The diodes were separated by 0.5 cm in the central 6 x 6 cm of the arrays, and by 1 cm in the peripheral part.

A research DMLC tracking system was used to shape the MLC to the target motion in real-time, considering both longitudinal and lateral motion from the MLCs beams eye view, but also in-depth motion corrected by magnification. Infrared reflective markers were placed on the phantom and monitored with a stereoscopic optical system (Exactrac, from Brainlab, Germany) to provide positional input to the tracking system. Based on the planned MLC shape, the tracking program adapted the MLC to compensate for the observed motion. The system latency was 260 ms (approximately the same for the two MLCs). No prediction algorithm was used in the experiments as prostate motion cannot be expected to be periodic. Deliveries were made with and without DMLC tracking and with and without target motion. For a single trajectory-plan combination, five repeated measurements were performed with motion and DMLC tracking in order to investigate the reproducibility of the experiments.
fitting error, and (3) leaf adjustment error. Target localization error is caused by system latency and uncertainties in the monitoring system. Leaf fitting error occurs when the desired MLC shape is fitted unto the closest physically possible MLC shape and is caused by the finite leaf width. Leaf adjustment error is the difference between the actual and the requested leaf positions and is caused by the finite leaf speed.

To investigate the relative contribution of the abovementioned errors, log files from the DM LC tracking software and the linear accelerator, the treatment plan, and the motion trace were analyzed. The method is explained in detail by Poulsen et al. The analysis allowed for computing over- and underexposed areas, $A_\text{o}$ and $A_\text{u}$ (cm²), which were the areas from the beams eye view that were not shielded by a MLC leaf when they should have been, and vice versa. The dose weighted $A_\text{o}$ and $A_\text{u}$ were calculated for each error source and for the combined effect of all errors, which was not a linear sum of the three contributing terms as errors sometimes partially cancelled each other out.

2.E. Average leaf distance

To measure the impact of applying leaf position constraints and to quantify plan complexity, the dose weighted average adjacent leaf distance (ALDw) was calculated for each plan. The mean distance to the two adjacent leaves for all leaves used in an open MLC aperture was calculated for each control point, weighted to the dose delivered at the control point, and averaged for the entire plan. The metric has previously been shown to correlate with DMLC tracking performance for sinusoidal target motion. In order to offer a reasonable comparison between the MLCs, as twice as many leaves were available for the HDMLC compared to the M-MLC, the ALDw was normalized to the (central) leaf width.

3. RESULTS

The gamma pass rate for the two MLCs and range of ADs with static measurements as reference and gamma criteria of 1%, 1 mm is shown in Fig. 1 (top left). For both MLCs, the pass rate with $AD = 0.81$ cm and $AD = 1.45$ cm were significantly higher ($p < 0.05$) than the pass rate with no LPC, while no significance was found between $AD = 2.07$ cm and no LPC, and $AD = 2.69$ cm and no LPC. The pass rate with no LPC for the HDMLC (90.8% ± 3.0%) was the same as the pass rate with $AD = 0.81$ cm for the M-MLC (90.8% ± 3.2%). With gamma criteria of 2% 2 mm (Fig. 1, bottom left), $AD = 0.81$ cm gave significantly higher pass rate than

![Fig. 1. Gamma pass rate for the two MLCs and different allowed distances (ADs) to adjacent MLC leaves, using measurement with a static phantom as reference (left) or the planned dose as reference (right) with 1%, 1 mm gamma criteria (top) and 2%, 2 mm criteria (bottom). Each data point represents the average of eight measurements (two patients and four motion traces per patient). The error bars show standard deviation.](image-url)
TABLE I. Average gamma index pass rates (in per cent) with and without DMLC tracking with different gamma criteria. Each value represents the average of 40 measurements (all combinations of two plans, four traces, and five LPCs) with range shown in brackets. Also presented are p-values from HDMLC vs M-MLC t-tests.

<table>
<thead>
<tr>
<th></th>
<th>Motion vs static</th>
<th>Motion vs planned</th>
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<tr>
<td></td>
<td>1%, 1 mm</td>
<td>2%, 2 mm</td>
</tr>
<tr>
<td>HDMLC</td>
<td>92.6 [86.0–97.9]</td>
<td>98.7 [95.1–100]</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>M-MLC</td>
<td>87.6 [77.5–95.6]</td>
<td>97.0 [93.3–100]</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No tracking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDMLC</td>
<td>48.9 [37.9–68.8]</td>
<td>72.0 [61.0–85.6]</td>
</tr>
<tr>
<td>M-MLC</td>
<td>52.0 [38.8–70.9]</td>
<td>74.7 [61.0–88.8]</td>
</tr>
<tr>
<td>p-value</td>
<td>0.002</td>
<td>0.002</td>
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no LPC for both MLCs while AD = 1.45 cm vs no LPC was significant only for the M-MLC.

Changing reference from the static measured dose to the planned dose in the gamma evaluations added uncertainties associated with dose calculation and phantom setup. No trend of increased pass rate with more stringent LPC was observed, neither using 1%, 1 mm (Fig. 1, top right) nor 2%, 2 mm gamma criteria (Fig. 1, bottom right).

The gamma pass rates with both references and 1% 1 mm, 2% 2 mm, and 3% 3 mm criteria are presented in Table I. The pass rate for tracking with the HDMLC was significantly higher than the M-MLC for all used gamma criteria and using either reference. Without tracking, HDMLC plans had consistently lower pass rate than M-MLC plans. The pass rate was also significantly higher with tracking than without tracking (p < 0.001). Measurements without motion showed a slightly worse agreement to the planned dose with tracking than without tracking. The average pass rate with tracking a static target was 99.3% (3%, 3 mm) and 95.6% (2%, 2 mm) and the corresponding pass rates without tracking were 99.9% and 98.3% (p < 0.001).

An example of the leaf fitting step for the plans with AD = 0.81 cm for patient #1 is shown in Fig. 2 with the M-MLC plan (Fig. 2, left), the same plan converted to HDMLC (middle) and the plan optimized for the HDMLC (right). The figure illustrates the benefit of halving the leaf width, as well as examples of plan optimizations with the most stringent LPC. The primary tracking errors contribution was leaf fitting, which was decreased by 42% when the M-MLC plans were converted for delivery with the HDMLC (Fig. 3). More stringent ADs decreased all individual errors as well as the total error with tracking, which was approximately two times larger without tracking than with tracking.

The gamma pass rate with tracking using 1%, 1 mm and measurements as reference is plotted versus the normalized ALDw for patient #1 in Fig. 4. The impact of LPC on ALDw is visualized as more stringent LPC leads to decreased ALDw. The gamma pass rates for patient #1 was significantly higher for the HDMLC plans and the converted plans compared to the M-MLC plans (p < 0.001), while no difference was found between the HDMLC plans and the converted plans (p = 0.31).

Five repeated measurements were performed with DMLC tracking for the high frequency excursions motion trace and a HDMLC plan with AD = 1.44 cm. With a single static measurement as reference, the gamma pass rate was 92.4%–94.4% (1%, 1 mm), 98.8%–99.6% (2%, 2 mm), and 100% (3%, 3 mm).

![Fig. 2. Example of the leaf fitting step. The ideal shape based on target motion is shown as an outline. This shape is not achievable due to the finite MLC leaf width. The leaves are positioned to the optimal compromise position, leaving residual underexposed (A_u) and overexposed (A_o) areas. The converted plan delivered the M-MLC plan with the HDMLC, using two HDMLC leaves for each M-MLC leaf. The plans shown in the figure were optimized with a maximum distance to adjacent leaves of 0.81 cm.](image-url)
4. DISCUSSION

This study investigated the impact of leaf width and plan complexity on the delivery accuracy of DMLC tracking. The DMLC tracking accuracy was for the first time directly compared between MLCs with different leaf widths by using MLCs with either 0.25 cm (HDMLC) or 0.50 cm central leaf width (M-MLC). The HDMLC gave consistently higher DMLC tracking accuracy than the M-MLC. The plan complexity was varied by applying leaf position constraints (LPCs) in the plan optimization. Decreased plan complexity increased the DMLC tracking accuracy when using static measurements as reference, which isolated the effect of motion from uncertainties arising from dose calculation and phantom setup. However, no difference was seen when the reference was changed to the planned dose, i.e., any benefit from decreased plan complexity was overshadowed by calculation or phantom setup uncertainties, suggesting that the impact of LPC, although measurable, would be small for prostate DMLC tracking. These results are in clear contrast to the previous study of LPC and lung motion, and the characteristics of prostate motion likely reduced the need of a LPC. Thus, leaf width is a more crucial parameter than plan complexity for prostate DMLC tracking.

A deviation from the delivery without tracking was caused by the tracking software moving unused leaves from their planned position to either a position beneath the jaws or next to an open aperture. In Pommer et al., this effect was isolated (by keeping the planned positions for all MLC leaves) without any improved agreement to the planned dose, suggesting other causes for the deviation. The agreement with the planned dose can thus possibly be improved with future versions of the tracking software.

When tracking was not used, regardless of gamma criteria and reference, the HDMLC showed more deteriorated dose distributions than the M-MLC. This was likely caused by the finer leaf width allowing more complex delivery patterns and, therefore, an increased interplay effect.

This study investigated two of the approaches for improved DMLC tracking accuracy suggested by Keall et al. and Poulsen et al.: thinner leaves and robust planning. The abovementioned studies used clinically applicable target monitoring systems, whereas this study utilized external markers placed on the phantom. The performance of the optical system used in this study and the electromagnetic-guided system used in Keall et al. were comparable, and by
using external markers, the impact of target localization error was minimized. As this study investigated the impact of leaf width and plan complexity, patient-specific characteristics were not the focus. Therefore, plans were made for only two patients. A previous study with four patients showed very small difference in DMLC tracking performance among the different patients.\footnote{K. Otto, “Volumetric modulated arc therapy: IMRT in a single gantry arc,” Med. Phys. 35, 310–317 (2008).}

The decreased tracking error with more stringent LPC in Fig. 3 was expected: target localization errors result in a shift of the adapted MLC aperture relative to the ideal MLC aperture, which gives errors along the circumference of the aperture. This contribution increases with the length of the circumference and thus with less stringent LPC. Similarly, leaf fitting errors are approximately proportional to the part of the circumference relative to the ideal MLC aperture. This contribution increases with the length of the circumference and thus with less stringent LPC. Finally, leaf adjustment errors are proportional to the average distance that leaves have to travel to adapt to target shifts, which also increases with less stringent LPC. Since the M-MLC plans and the converted M-MLC plans in Fig. 3 have identical apertures, the target localization errors in Fig. 3 would be identical for the plans if they were delivered identically with the same absolute phantom position and synchronization between gantry and phantom position. This was, however, not the case as there was a small difference in delivery time between the two linear accelerators used. We ascribe the small differences in localization errors to this.

5. CONCLUSION

DMLC tracking successfully compensated for the studied prostate motion and was able to reproduce the planned dose for a static target. The tracking accuracy was significantly higher with the HD MLC than the M-MLC. Limiting the plan complexity increased the dosimetric accuracy only when the effect of motion was isolated by using static measurements as reference in the gamma evaluation, suggesting that the impact of plan complexity for prostate DMLC tracking is small. Tracking error analysis indicated that leaf fitting was the major cause of tracking error, and decreased almost by half when the leaf width was halved.

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Simulating intrafraction prostate motion with a random walk model

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keywords: intrafraction motion; random walk; motion management

Abstract

Prostate motion during radiotherapy, i.e. intra-fraction motion, is well-established and can cause unwanted loss of radiation dose to the prostate and increased dose to surrounding organs at risk. A compact, but general, statistical description of this motion would potentially be useful for more accurate treatment planning and patient positioning. We therefore investigated whether prostate motion could be modelled with a random walk model. Prostate motion recorded during 548 radiotherapy fractions delivered to 17 patients was analyzed using a random walk model that aimed at describing the observed motion. The recorded motion traces were divided into two groups based on whether any transient excursions, i.e. rapid prostate motion in the anterior and superior direction followed by a return to approximately the original position, occurred in the trace. This allowed for a separated analysis and use of either groups motion characteristics as input for the model. Large transient motion probably related to bowel gas was separately modelled as a large step in the anterior/superior direction, followed by a returning large step. Simulations were done with and without the simulated transient motion, using either motion data from all observed traces or only traces without transient excursions as input, respectively. The simulations showed that agreement to the observed traces could be achieved with <0.2 mm difference in average position for a 0 – 600 seconds time span. The standard deviation of difference in variance between observed and simulated traces was <0.6 mm. Simulated and observed diffusion coefficients agreed within 0.03, 0.2 and 0.3 mm² min⁻¹ in the LR, SI and AP directions respectively. A rapid increase in variance at the start of observed traces was difficult to reproduce despite using simulated transient motion. The best agreement to observed traces was achieved when excursion-free motion was simulated and compared to excursion-free observed traces. In conclusion, the random walk modelling of prostate motion is feasible and useful, although motion in the first 30 seconds is not statistically regular and could not be modelled. Simulations with excursion-free traces as input showed excellent agreement to the observed excursion-free traces, indicating that the random walk model can be a suitable approach for prostate motion modelling.

1 Introduction

External radiotherapy targets the tumour while attempting to spare surrounding healthy tissue. Tumour motion during radiotherapy delivery, so called intra-fraction motion, requires additional margins and associated...
irradiation of healthy tissue. Prostate cancer is commonly treated with radiotherapy, and prostate motion has
been investigated in several studies using a wide range of localization modalities, including x-ray imaging
(Kitamura et al. 2002), magnetic resonance imaging (MRI) (Ghilezan et al. 2005), ultrasound (Huang et al.
2002) and electromagnetic monitoring (Langen et al. 2008a, Bittner et al. 2010, Kupelian et al. 2007). The
impact of motion in radiotherapy has been studied from treatment margin and dosimetric perspectives (Zhang
proposed methods for motion compensation in various stages of clinical implementation (Shirato et al. 2000,

There have been several investigations in recent years into biomechanical modelling of the pelvic organs
and their interaction, with some focusing specifically on radiotherapy implementations and implications. A
finite element method is commonly used (Alterovitz et al. 2006, Bharata et al. 2001, Hensel et al. 2007,
Yan et al. 1999), as is particle modelling (Jaillet et al. 1998). Söhn et al. (2005) modelled prostate motion
based on principal component analysis to determine eigenmodes for interfractional motion and deformation
of the prostate, rectum and bladder. However, none of the abovementioned studies considered intrafraction
motion. A recent study proposed a random walk model to describe intrafraction prostate motion (Ballhausen
et al. 2013), using population-based drift vectors, diffusion constants and Monte Carlo simulations. A random
walk is a model where the object of interest is subject to external forces, and moves stochastically according
to their probability distributions. It is characterized by each step being independent of previous steps, while
the summed displacement at a certain time is dependent of the displacement at an earlier time. The variance
in position for many samples increases linearly with time. The main argument from the authors for using
the random walk model was that they considered intrafraction motion as a time-dependent process, with dis-
placements accumulating over time, and that the model would be suitable as it does not require knowledge
of the external forces affecting the prostate. The authors achieved good agreement between simulations and
previously published prostate displacements.

Using real-time electromagnetic guided prostate positioning during radiotherapy, Langen et al. (2008a)
noted two main types of prostate motion; sudden, transient motion and slow, drifting motion. The former was
mostly directed anteriorly and superiorly, and the latter inferiorly and posteriorly, cf. figure 1 in Langen et al.
(2008a). It was suggested that the transient motion was caused by sudden changes in rectum volume and the
drift by bladder filling, pushing the prostate anteriorly/superiorly and posteriorly/inferiorly, respectively. In
this study, we aim to simulate prostate motion using a random walk model with simulation parameters based
on observed motion, with special attention to modelling the transient motion that occurred in the observed data.
Whereas Ballhausen et al. (2013) primarily recreated the motion characteristics of time averages, this study
will analyze each observed prostate motion trace to use as input for the model and compare the simulations
with the observed data at the time resolution of seconds. Furthermore, we intend to differentiate between the
slow and rapid motion components (i.e. the transient motion and the prostate drift). The purpose of this study
is to test whether it is possible to recreate the properties of the patient data using a random walk model, if
necessary with simulated transient motion.

2 Methods and materials

A dataset of prostate motion traces recorded with electromagnetic tracking at 10 Hz during 548 radiotherapy
fractions (mean length 607 seconds (s)) for 17 patients was used in this study (Langen et al. 2008a). The traces
that contained only translational information and prostate rotation were thus not considered in this study. The
motion traces were set to start at origin at the beginning of the trace and filtered with an averaging filter with a
filter length of 10 data points (an average time scale of 1 s) in order to remove high-frequency noise. A single
observer categorized the traces based on whether any transient motion was present (figure 1). Transient motion
was considered as rapid motion in the anterior/superior direction, followed by a return to approximately the
original position. The returning motion could be as fast as, or sometimes comparably slower than, the initial
transient motion. The categorization was repeated three times and the most common choice was used. The
categorization allowed for using a subgroup of the traces as input for the random walk and for comparing the
simulated traces with a subgroup of the observed traces.
2.1 Random walk model

The random walk model was essentially a Monte Carlo model that repeatedly selected a step size and direction based on a set of fixed probabilities. The probabilities were obtained by analysis of the observed traces (either all traces, only excursion-free traces or only traces with excursions). Two matrices were calculated from the observed traces used as input for the model: (1) a matrix describing the probability of prostate motion in all combinations of the cardinal directions, as well as no motion, and (2) continuous step size distributions (one for each direction) with the observed sizes of prostate motion steps from sampling point to sampling point. The actual matrix values are given in the online supplement. The motion traces were simulated one at the time by step-wise motion, with direction sampled based on a random number from the direction matrix and the step size randomly sampled from the step size distributions. The simulations were done with the same time steps as the observed traces, 0.1 s, during 600 s and for 548 traces.

The transient motion in the observed traces occurred over several consecutive sampling points. Using a random walk model, with small steps only, a simulation of the observed traces was found to be ineffective given that the same direction with several relatively large and improbable consecutive steps was required to reproduce them (cf. figure 1). Therefore, as mentioned, the possibility of simulating transient motion was added to the model (figure 2). A random number was generated to decide whether a transient motion step would occur instead of the random walk, directed superiorly and anteriorly. The size of the large step was randomly chosen between 0 mm and a maximum step length of 5.5 mm, selected to maximize the agreement to the observed traces (figure 3). The same step was used for the two directions, while the left/right direction was unaffected (to agree with the observation that transient excursions had a very small impact on the left/right position of the prostate). The probability of transient motion was set to give the approximately same number
Figure 3. Illustration of how the maximum length of the simulated transient motion was selected (left) and the change in probability after the initial transient motion occurred (right). The average of LR, SI and AP is shown for the difference in average position and standard deviation of difference in variance between simulated and observed traces in simulation #2. A maximum step length of 5.5 mm and a probability change of 10 were chosen for use throughout this study.

Table 1. The performed simulations, either using motion data from all observed traces or only traces without transient excursions as input. Simulated transient excursions were added to emulate the transient excursions in the observed data.

<table>
<thead>
<tr>
<th>Simulation #</th>
<th>Input parameters</th>
<th>Simulated transient excursions</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All traces</td>
<td>No</td>
<td>All traces</td>
</tr>
<tr>
<td>2</td>
<td>No excursion traces</td>
<td>Yes</td>
<td>All traces</td>
</tr>
<tr>
<td>3</td>
<td>No excursion traces</td>
<td>No</td>
<td>No excursion traces</td>
</tr>
<tr>
<td>4</td>
<td>All traces</td>
<td>Yes</td>
<td>With excursion traces</td>
</tr>
</tbody>
</table>

of excursions as the observed traces (0.12 min\(^{-1}\) for simulations, compared with 0.11 min\(^{-1}\) for the observed traces, motivated by the choice of not having a minimum value for the size of the simulated transient motion). The method is illustrated in figure 4. After the transient motion occurred within the model, the likelihood of a new (second) transient step was increased by a factor of 10 (figure 3). When the second transient step would occur, it would be assigned the exact opposite direction and the same magnitude as the initial first transient motion thus effectively returning the prostate to its approximate starting position.

2.2 Simulations

Four combinations of input parameters and choice of evaluation were used in simulations and are presented in table 1. The purpose of each simulation was as follows:

- Simulation #1: to reproduce the motion of all observed traces without simulated transient excursions
- Simulation #2: to reproduce the motion of all observed traces using simulated transient excursions
- Simulation #3: to reproduce the motion of excursion-free observed traces without simulated transient excursions
- Simulation #4: to reproduce the motion of observed traces with excursions using simulated transient excursions

2.3 Evaluation

To quantify the difference between the simulated and the observed traces, the difference in average position and the difference in variance were evaluated. Specifically, two metrics were calculated; the average difference in average position in three dimensions, \( \text{diff}_{\text{position}} \), and the standard deviation of the difference of the variance, \( \text{diff}_{\text{variance}} \).
Figure 4. Overview of the steps in the random walk simulation. Transient motion was simulated by a large step, alternatingly directed anteriorly/superiorly and then posteriorly/inferiorly. For simulations #1 and #3, the probability of transient motion was set to zero.

The average and the variance of all trace positions were also calculated for each motion trace set. This allowed for qualitative comparison of the agreement between the simulated and observed traces on a finer time scale than the course time scale used above.

For both simulated and observed traces, the diffusion coefficient was calculated in each dimension according to:

\[ D = \frac{1}{2t} \langle x^2 \rangle \quad (2.4) \]

where \( D \) is the diffusion coefficient, \( \langle x^2 \rangle \) is the average of the squared displacement at time \( t \) for all traces. The diffusion coefficient was calculated at \( t = 4 \) min and 8 min, chosen to reflect an intermediate and a long elapsed time since patient setup (with assumed zero prostate displacement).

To investigate the repeatability of and impact of randomness on the simulations, it was found to be adequate to repeat each simulation five additional times. The evaluation described above, previously applied to the simulated vs. observed traces, was then applied for each repeated simulation vs. the original simulation. The average \( diff_{position} \) and \( diff_{variance} \) for the repeated simulations was used as a measure of the variation in the simulations.
3 Results

Of the 548 prostate motion traces in the dataset, lasting an average of 10.1 minutes, 228 had one or several excursions (the maximum number for a single trace was 13), while 320 had no transient excursions (cf. figure 1). The overall probability of transient motion was 0.11 min⁻¹. There was in general a good agreement between simulated and observed traces, quantified as the average difference in position and standard deviation of the difference in variance (figure 5 and table 2). In figure 5, the calculations were done separately in time intervals of 100 s while table 2 contains the results for the entire time span of 0 - 600 s. Simulations #1 and #2, which attempted to recreate the behaviour of all the observed traces, showed similar agreement of the average position (0.06 mm and 0.07 mm respectively), while simulation #2 better reproduced the rapid increase in variance at the start of the observed traces (figure 6).

Simulation #3 used only the random walk without the simulation of transient excursions and was compared to traces without any transient excursions. Excellent agreement to the observed traces was observed with a 0.08 mm average difference in position, especially for the 0 - 300 s time interval (figure 7, left). At longer time spans, the variance of the observed traces seemed to reach a threshold while the variance of the simulated traces, in accordance to the random walk model, increased linearly. Lastly, for simulation #4, where simulated transient excursions were added, all traces were used as input and the results were compared to only traces with excursions, but the average position of the observed traces could not be reproduced (average difference 0.19 mm). However, some qualitative agreement to the observed variance could be seen (figure 7, right).

The calculated diffusion coefficients for the simulations, and corresponding dataset of observed traces, agreed well (table 3), especially for simulation #3 at 4 min and simulation #4 at 8 min. The difference between simulated and observed diffusion coefficients was less than 0.03, 0.2 and 0.3 mm² min⁻¹ in the LR, SI and AP directions respectively, and even though the difference was smallest for simulation #3 at 4 min, it was also largest at 8 min for simulation #3 (cf. figure 7 left).

The difference between five repeated simulations and the original simulations was small (table 2). As randomness in an integral part of the random walk model, any two repeated simulations can never be expected to be equal.
Figure 6. Time-resolved results from simulation #1 (left) and simulation #2 (right), compared to the observed traces (including all observed motion), drawn as solid lines. Simulation #1 used a random walk model with input from all traces, while simulation #2 used the same model with only traces without excursions as input and added simulated transient excursions.

Table 2. Agreement between simulated and observed traces, as well as agreement between five repeated simulations and the original simulation for the four simulations setups. The metrics were calculated for the entire time span of the simulations, 0 - 600 s, whereas the results in figure 5 were calculated for each 100 s time interval separately.

<table>
<thead>
<tr>
<th></th>
<th>original sim. vs. observed traces</th>
<th>repeated sims. vs. original sim.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>diff position (mm)</td>
<td>diff variance (mm)</td>
</tr>
<tr>
<td>Simulation #1</td>
<td>0.06</td>
<td>0.37</td>
</tr>
<tr>
<td>Simulation #2</td>
<td>0.07</td>
<td>0.26</td>
</tr>
<tr>
<td>Simulation #3</td>
<td>0.08</td>
<td>0.28</td>
</tr>
<tr>
<td>Simulation #4</td>
<td>0.19</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Figure 7. Results from simulation #3 (left) and simulation #4 (right), compared to the observed traces (solid lines). Simulation #3 used a random walk model with input from traces without transient excursions, which also were used for comparison. Simulation #4 used the random walk model with input from all traces with added simulated excursions, and was compared to motion traces containing one or several excursions. Note the different scales on the Y axes.

Table 3. Diffusion coefficients, D [mm$^2$ min$^{-1}$], for observed and simulated traces, calculated using equation (2.4).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Simulated D</th>
<th>Observed D</th>
</tr>
</thead>
<tbody>
<tr>
<td>t = 4 min</td>
<td>LR SI AP</td>
<td>LR SI AP</td>
</tr>
<tr>
<td>Simulation #1</td>
<td>0.01 0.33 0.36</td>
<td>0.01 0.38 0.57</td>
</tr>
<tr>
<td>Simulation #2</td>
<td>0.01 0.39 0.45</td>
<td>0.01 0.38 0.57</td>
</tr>
<tr>
<td>Simulation #3</td>
<td>0.01 0.19 0.22</td>
<td>0.02 0.19 0.26</td>
</tr>
<tr>
<td>Simulation #4</td>
<td>0.01 0.59 0.99</td>
<td>0.01 0.74 1.22</td>
</tr>
<tr>
<td>t = 8 min</td>
<td>LR SI AP</td>
<td>LR SI AP</td>
</tr>
<tr>
<td>Simulation #1</td>
<td>0.03 0.65 0.86</td>
<td>0.01 0.54 0.81</td>
</tr>
<tr>
<td>Simulation #2</td>
<td>0.03 0.62 0.76</td>
<td>0.01 0.54 0.81</td>
</tr>
<tr>
<td>Simulation #3</td>
<td>0.03 0.53 0.65</td>
<td>0.02 0.37 0.40</td>
</tr>
<tr>
<td>Simulation #4</td>
<td>0.03 0.79 1.56</td>
<td>0.01 0.81 1.56</td>
</tr>
</tbody>
</table>

4 Discussion

The aim of this study was to model observed prostate motion using a random walk model, either with or without simulated transient excursions. The observed motion consisted of motion data from complete radiotherapy regimens for 17 patients. Two simulations in this study aimed to evaluate the accuracy of the model of motion in the entire dataset; using a random walk model with parameters from all observed traces, and using a random walk model with input from only excursion-free traces while adding simulated transient excursions.
Both approaches resulted in reasonable agreement, hinting at the applicability of a random walk approach to prostate motion modelling. The simulation with added transient motion better reproduced the quick increase in variance in position among the observed traces, with similar agreement between simulated and observed average position. A characteristic of the random walk is that the variance of the position increases linearly with time, which contrasts clearly to the variance in position among the observed traces, especially those which had one or several transient excursions. An attempt to recreate the motion in the excursion-free traces produced excellent results, especially during the first half of the simulation. This gives further reason to consider the random walk a viable alternative for prostate motion simulation. The difference between the observed traces in figure 6 (right) and figure 7 (right) is that excursion-free traces have been removed in the latter. Comparing the two figures, it is clear that the large variation in variance was due to observed transient excursions. When analysing only excursion-free traces (figure 7, left), the variance increased almost linearly with time, at least for the first 300 seconds, as expected from a random walk. However, the observed variance seemed to then reach a maximum value causing the agreement with the simulation to decrease.

Using a random walk model to simulate prostate motion was recently proposed by Ballhausen et al. (2013). The authors showed that treatment margins calculated assuming a random walk are smaller than those calculated based on a Gaussian approximation. This study compliments those results by isolating the effect of transient excursions on the applicability of the random walk model. Clearly, any random walk model will find it difficult to recreate the rapid motion shown in figure 1A, and a fit to prostate motion including such motion will overestimate the effect of the drifting component of prostate motion. The excellent agreement shown in this study between the simulations without transient motion that used excursion-free traces as input suggests that the random walk model is suited for modelling the prostate drift. Approximately half of the traces had one or several transient excursions, with an average of 0.11 excursions per minute. As long as the prostate returns to its original position quickly, it should have a marginal impact on the treatment, and required margins. If, however, the timing of pre-treatment imaging happens to coincide during an excursion, or the prostate does not quickly return to the original position, the prostate will be systematically misplaced during that treatment fraction.

Intrafraction prostate motion is arguably becoming more relevant with the increased prevalence of daily pre-treatment prostate imaging. Inter-fraction correction, i.e. correcting the target position before treatment, or inter-beam correction can be considered a first-order correction and intra-fraction a second order correction. Intra-fraction corrections should ideally include not only translations but also rotations and deformations. Studies that model deformation are, to the authors knowledge, limited to inter-fractional motion (Söhn et al. 2005). Modelling intra-fraction motion with rotations and deformations as well as translations, is a potential future research topic. Potential areas of improvement include a more sophisticated model of long-term trends (e.g., where variance may ‘calm down’ with time as observed for the excursion-free traces); a more sophisticated model of short-term noise (e.g., the patient is ‘getting comfortable’); and patient-specific modelling (e.g., do bowel gas events have Boson-like statistics?).

5 Conclusions

The random walk model could successfully recreate the characteristics of the observed prostate motion from seventeen patients, while instances of transient excursions were difficult to recreate without use of simulated excursions. However, simulations without transient motion were able to achieve reasonable agreement to patient motion where no excursions occurred, indicating that the random walk model is applicable for prostate motion modelling.

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The dosimetric impact of prostate motion during urethra-sparing hypofractionated prostate radiotherapy

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keywords: prostate SBRT; intrafraction motion; motion management

Abstract

Purpose: Flattening-filter free (FFF) beams have the potential to reduce delivery times during intensity-modulated arc therapy (IMAT). The purpose of this study was to investigate the dosimetric impact of intrafractional prostate motion during hypofractionated prostate radiotherapy with standard and FFF beams.

Methods: Urethra-sparing prostate IMAT plans were optimized for four patients with one and two arc IMAT using 6 MV flattened beams (STD) and 10 MV FFF beams. The plans were normalized to deliver 5 × 7.25 Gy to the prostate + margin (PTVp) and 5 × 6.5 Gy to the prostatic urethra + margin (PTVu). 342 prostate motion traces obtained during radiotherapy and a dose reconstruction method were used to simulate intrafraction motion and determine its dosimetric impact. A Monte Carlo-approach was used to randomly select five traces to simulate one treatment regime, and the accumulated dose was calculated for each patient and each treatment modality. Ten thousand treatments were simulated. The dosimetric effect was investigated by calculating D95 and D99 for the PTVs and the prostate excluding PTVu (CTVp), and V60% and V80% for the bladder and the rectum.

Results: The use of FFF beams reduced the treatment time from 3.4 min and 4.0 min to 1.0 min and 2.4 min for one arc and two arc plans, respectively. With motion, the CTVp D99 was at worst reduced from 92.5% to 84.4%, and CTVp D95 was reduced from 94.8% to 82.8%. The median CTVp D99 was 100% of the planned value. A larger variability was seen in the dose to organs at risk. The STD beams were slightly more sensitive to prostate motion than FFF beams.

Conclusions: Urethra-sparing prostate hypofractionation is feasible with IMAT using either FFF or flattened beams. The reduced treatment time of FFF slightly decreased the limited dosimetric impact of prostate motion.
1 Introduction

Radiotherapy is a useful treatment option for prostate cancer that increases the chance of survival [1]. Several studies have suggested a low alpha/beta ratio for prostate cancer [2]. Radiobiologically, using a higher dose per fraction will give a higher biologically effect dose if the alpha/beta ratio is low, and there are several randomized trials being conducted to compare standard and hypofractionated prostate radiotherapy [2].

State of the art radiotherapy includes intensity-modulated arc therapy (IMAT). During IMAT, the gantry rotates around the patient, continuously irradiating the tumour while achieving intensity-modulation through MLC-shaping and varying the dose per control point [3]. The dose per control point determines the gantry speed and dose rate, with the gantry speed kept as high as possible. The introduction of flattening-filter free (FFF) beam energies in clinical practise allows for increased dose rate compared to flattened (standard) beams [4]. The inhomogeneous fluence across the field makes FFF beams unsuitable for conformal treatments but with IMAT, the intensity-modulation enables dose distributions similar to conventional beams. One advantage compared to standard beams is that the higher dose rate can allow for decreased treatment time.

For prostate treatments, prostate motion during the treatment (i.e. intrafraction motion) has been shown to increase with increased treatment time [5]. Shorter treatment time would therefore be expected to decrease the impact of intrafraction prostate motion. For conventionally fractionated treatments, dose deviations caused by prostate motion may average out due to the large number of fractions [6–8]. However, for prostate hypofractionation, dosimetric coverage of the prostate gland may be more severely affected. The purpose of this study was (1) to determine if the use of FFF during hypofractionated prostate IMAT decreases the impact of prostate motion compared to flattened beams and (2) to quantify the risk of prostate motion causing underdosage of the tumour and overdosage of organs at risk (OARs) for both standard and FFF beams.

2 Methods and materials

2.1 Treatment planning

The CT-data from four prostate cancer patients who had urinary retention at the time of simulation were used in this study. The patients were CT-scanned with catheter allowing contouring of the urethra, and retrospectively planned for hypofractionated urethra-sparing prostate treatments. Single and double-arc IMAT plans were optimized in the Eclipse treatment planning system version 10 (Varian Medical Systems). The arcs used 358° gantry span and a 45° collimator angle (315° for a second arc). Two beam models were used; one standard beam and one FFF beam, deliverable on a Varian Truebeam STx linear accelerator. For the standard beams, 6 megavoltage (MV) was used, while for the FFF beams, 10 MV was used. The maximum dose rate for the two beam models were 600 MU/min and 2400 MU/min, respectively. Ten MV was chosen for FFF (as opposed to 6 MV) to provide a best-case scenario with regards to treatment time, as the dose rate is higher than for 6 MV FFF. The two beam models are hereafter referred to as STD and FFF, referring to 6 MV standard and 10 MV FFF.

Treatment plans were optimized to deliver $5 \times 7.25$ Gy to a prostate-PTV (PTVp) and $5 \times 6.5$ Gy to a urethra-PTV (PTVu). The prostate (delineated on MR scans) was considered the CTV in this study. The PTVp was created by addition of 5 mm margin extension around the prostate, except in the posterior direction (towards rectum), where a 3 mm margin was used. The PTVu was created by a 3 mm margin extension around the urethra. Subsequently, the PTVu was subtracted from the PTVp, and any part of the PTVu that was outside the PTVp was removed (to avoid prescribing dose to the urethra outside of the PTV). A CTVp structure was created by removing the PTVu from the CTV. Included OARs were the bladder and the rectum. For planning purposes, a planning-PTV structure was used by removal the innermost 2 mm of the PTVp, closest to the PTVu. Planning OAR structures were created by removal of the PTVs from the OARs. A ring structure, extending from 0.5 cm to 3 cm from the PTVp, was used to limit the risk of hotspots outside of the PTVs. No restriction on the number of monitor units (MUs) was used. The treatment plans were initially optimized for single-arc STD with interactive balancing between target coverage and dose to OARs. The same optimizing parameters were then used for dual-arc STD and single- and dual arc FFF treatments. The plans were normalized so that the prescribed dose was equal to the mean dose to PTVp. Dose calculations were done with AAA version 10.0.28 using a 2.5 mm grid size.
Table 1. Prostate and PTV volumes for the four patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prostate volume (cm³)</th>
<th>PTVp volume (cm³)</th>
<th>PTVu volume (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75.5</td>
<td>133.7</td>
<td>3.7</td>
</tr>
<tr>
<td>2</td>
<td>38.8</td>
<td>77.7</td>
<td>3.8</td>
</tr>
<tr>
<td>3</td>
<td>38.8</td>
<td>72.2</td>
<td>3.4</td>
</tr>
<tr>
<td>4</td>
<td>42.0</td>
<td>79.50</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Figure 1. Distribution of average 3D displacement for the motion traces used in this study, calculated during the time required for the plan with the longest delivery time.

2.2 Motion traces

To simulate intrafraction prostate motion, motion traces from a set of prostate motion obtained during 548 radiotherapy fractions for 17 patients were used [5]. Of the 548 traces, 342 (62%) were longer than 9.5 minutes and included in this study, as initially sliding window IMRT (with longer treatment time) were to be included as well. The traces were set to start at isocenter, thus assuming perfect pre-treatment alignment to the prostate at treatment onset. Among the 342 traces and during the time required for the longest delivery (4.26 min), the mean of the average 3D displacement was 1.25 mm (range 0.24 - 9.38 mm). The average 3D displacement distribution is shown in Figure 1. The maximum displacement during a single trace was 20.7 mm, and 58 of the traces had a maximum displacement > 5 mm. Among the 34 traces (i.e. 10%) with the largest 3D displacement, the mean of the average displacement was 3.80 mm (range 2.15 - 9.38 mm). Among the two patients with the largest average 3D displacement, the mean 3D displacement was 2.15 mm (range 0.43 - 7.38 mm).

2.3 Treatment simulation

In order to investigate the effect of intrafraction motion, treatments were simulated using a dose reconstruction approach [9]. The dose reconstruction method used the recorded MLC and gantry motion during delivery (obtained by delivering each plan once and analysing the treatment log files), the original treatment plans and the motion traces to create motion-inclusive Dicom treatment plans that simulated target motion by isocenter shifting (thus assuming rigid motion). Briefly, each motion trace was divided into 1 mm³ target positions bins. For each position bin, the corresponding MLC and gantry positions during delivery were identified using the time-resolved log file from the treatment. The dose data in the original treatment plans were then used to create a motion-encoded plan with one isocenter for each position bin. One motion-encoded treatment plan was created for each plan-trace combination, 5472 in total. The plans were imported in an automated fashion to the TPS, where dose calculations were performed using the same dose calculation algorithm and grid size as for the original plan. Finally, the resulting motion including dose was exported. For more detailed description on the dose reconstruction method, the reader is referred to Poulsen et al. 2012 [9]. As the method has been experimentally verified, no comparisons between simulated and actual dose with target motion were performed in this study [9,10].
Table 2. Number of MUs and delivery time (in minutes) for the different patient and treatment modalities.

<table>
<thead>
<tr>
<th>Patient</th>
<th>STD 1 arc</th>
<th>FFF 1 arc</th>
<th>STD 2 arcs</th>
<th>FFF 2 arcs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1868 (3.1)</td>
<td>1997 (1.0)</td>
<td>1973 (3.7)</td>
<td>1962 (2.4)</td>
</tr>
<tr>
<td>2</td>
<td>2053 (3.4)</td>
<td>1992 (1.0)</td>
<td>2105 (3.9)</td>
<td>2043 (2.4)</td>
</tr>
<tr>
<td>3</td>
<td>1994 (3.3)</td>
<td>1960 (1.0)</td>
<td>2072 (3.9)</td>
<td>1947 (2.4)</td>
</tr>
<tr>
<td>4</td>
<td>2255 (3.8)</td>
<td>2066 (1.0)</td>
<td>2295 (4.3)</td>
<td>2205 (2.4)</td>
</tr>
</tbody>
</table>

2.4 Dosimetric evaluation

After dose calculation, the dose matrices were exported and analyzed using parts of the CERR code [11] in order to obtain dose-volume histograms (DVHs). From the DVHs, the following dosimetric parameters of interest were extracted: D99 and D95 (the dose in per cent of prescribed dose, 36.25 Gy, given to 99% and 95% of the structure volume, respectively), D2 (the dose given to 2% of the volume, essentially the maximum dose), V80% and V60% (the volume (in per cent) receiving at least 80% and 60% of the prescribed dose, respectively). To simulate five-fraction treatments, a Monte Carlo-approach was used where five traces were chosen at random and the doses for the corresponding dose reconstructions were summed. For each five-trace combination, dose summation was done for all patient and treatment modalities, allowing for comparison between patients and modalities. In total, 10 000 five-trace combinations were analyzed. The motion traces were thus considered independent of each other. Additionally, 1000 five-trace combinations were randomly chosen among the two patients in the motion dataset with the largest amount of motion. Prostate motion has previously been shown to be unpredictable, rationalizing the approach [5]. The mean prostate 3D displacement during delivery (including the necessary pause between the first and second arc, when applicable) for the corresponding motion traces was calculated in order to investigate any correlation between dosimetric effect and amount of motion.

Statistical analysis of difference in dosimetric results between treatment modalities was done using Kruskal-Wallis one-way analysis of variance, utilizing that the same motion traces were simulated for each modality. A multiple comparisons test was used in order to determine if differences between groups was significant at the 0.05 level. All dosimetric and statistical analysis was performed in Matlab version R2009b.

3 Results

The number of MUs and required treatment time is for all plans are shown in table 2. For the two arc treatments, the pause necessary to rotate the collimator and mode up the second beam was 24 s, measured with a stopwatch. The linear accelerator had a maximum gantry rotation speed of 6 degrees/s and for dual-arc treatments, the delivery times included the 24 s pause.

The largest motion induced CTVp coverage reduction observed for any combination of five motion traces and four patients was a D99 decrease from 92.5% to 84.4% and a D95 decrease from 94.8% to 92.8%. The dose distribution in the sagittal plane for the particular treatment is shown in Figure 2. For the majority of the simulated treatments, D99 and D95 were very close to their planned values (Figure 3, tables 3-4). Also shown in Figure 3 is the higher D99 for double arc treatments than for single arc treatments, as the use of a second arc gave additional degrees of freedom to the optimizer. This finding also holds true when comparing CTVp D95, PTVu D95, and PTVu D2 where two arcs are favourable to one arc for all but PTVu D2 for one patient. In table 3, the median, 2nd and 98th percentiles are shown for the four treatment modalities and for target coverage and doses to risk organs. Each metric was averaged for the four patients. In table 4, the values are shown in percentage of the planned values. Although the coverage of the PTVs was compromised, the margins were sufficient to ensure the planned CTV coverage. Very little overdosage of the prostatic urethra was observed (quantified as PTVu D2), despite the surrounding high dose regions. Some variation in doses given to the rectum and bladder was seen, with the rectum V80% for the worst cases being 119% of the planned value. The planned rectum V80% was however small, causing the absolute increase to be relatively modest (Table 3). The modest differences in dosimetric results (listed in Table 3 and Table 4) between the treatment modalities were significant (p < 0.05) for all parameters except the relative change compared to planned dose for bladder V80%, where the difference between STD 1 arc and FFF 1 arc was not significant.

In Figure 4, the relationship between CTVp D99 and PTVu D99 is shown, with each data point corre-
Figure 2. Example of 95% dose coverage for the planned (left) and simulated treatment with five motion traces with extensive motion (corresponding to the data point in the bottom left corner in Figure 5) for a two arc, FFF plan. The CTV (red contour) is the entire prostate, while the CTVp excludes the urethra and a 3 mm margin (i.e. the PTVu, pink contour). The PTVp (cyan contour) was created by extending the CTVp with a 5 mm margin (3 mm posteriorly), causing some overlap with the rectum (brown contour).

Table 3. Dosimetric results shown as median, 2nd and 98th percentile for 10,000 simulated treatments, averaged for the four patient CT datasets used in this study. The PTVu corresponds to the prostatic urethra and a 3 mm margin, the CTVp is the prostate minus PTVu, while the PTVp is a 5 mm margin extension outside the CTVp (3 mm posteriorly).

<table>
<thead>
<tr>
<th>Modality</th>
<th>STD 1 arc CTVp D99 (%)</th>
<th>STD 1 arc CTVp D95 (%)</th>
<th>STD 2 arcs FFF 1 arc CTVp D99 (%)</th>
<th>STD 2 arcs FFF 1 arc CTVp D95 (%)</th>
<th>STD 2 arcs FFF 2 arcs CTVp D99 (%)</th>
<th>STD 2 arcs FFF 2 arcs CTVp D95 (%)</th>
<th>STD 1 arc PTVp D99 (%)</th>
<th>STD 1 arc PTVp D95 (%)</th>
<th>STD 2 arcs FFF 1 arc PTVp D99 (%)</th>
<th>STD 2 arcs FFF 1 arc PTVp D95 (%)</th>
<th>STD 2 arcs FFF 2 arcs PTVp D99 (%)</th>
<th>STD 2 arcs FFF 2 arcs PTVp D95 (%)</th>
<th>STD 1 arc CTV D99 (%)</th>
<th>STD 1 arc CTV D95 (%)</th>
<th>STD 2 arcs FFF 1 arc CTV D99 (%)</th>
<th>STD 2 arcs FFF 1 arc CTV D95 (%)</th>
<th>STD 2 arcs FFF 2 arcs CTV D99 (%)</th>
<th>STD 2 arcs FFF 2 arcs CTV D95 (%)</th>
<th>STD 1 arc Rectum V80%</th>
<th>STD 1 arc Rectum V60%</th>
<th>STD 2 arcs FFF 1 arc Rectum V80%</th>
<th>STD 2 arcs FFF 1 arc Rectum V60%</th>
<th>STD 2 arcs FFF 2 arcs Rectum V80%</th>
<th>STD 2 arcs FFF 2 arcs Rectum V60%</th>
<th>STD 1 arc Bladder V80%</th>
<th>STD 1 arc Bladder V60%</th>
<th>STD 2 arcs FFF 1 arc Bladder V80%</th>
<th>STD 2 arcs FFF 1 arc Bladder V60%</th>
<th>STD 2 arcs FFF 2 arcs Bladder V80%</th>
<th>STD 2 arcs FFF 2 arcs Bladder V60%</th>
</tr>
</thead>
</table>

Corresponding to one of the 10,000 simulated treatments, and the value averaged for the four patients. As long as the CTV–PTV margins are sufficient, increased motion will cause decreased PTV D99 but not CTV D99. This is the case for most of the simulated treatments. In Figure 5, the same relationship is shown for 1000 histories using only motion traces from the two patients in the motion dataset with the largest motion. Although the 2nd percentile for PTVp D99 was < 78% for all modalities but STD 2 arcs, the 2nd percentile for CTVp D99 was > 91.0, corresponding to a decrease by < 1 percent point relative to the plan. In Figure 6, the relationship between CTVp D99 and average 3D prostate displacement during delivery is shown. For most simulated treatments, the decrease was limited as long as the average motion was < 2 mm. The figure also illustrates the lower average 3D displacement for the shorter treatments. The average 3D displacement for all simulations was 1.14 mm, 0.77 mm, 1.21 mm and 1.01 mm for STD 1 arc, FFF 1 arc, STD 2 arcs and FFF 2 arcs, respectively. The corresponding maximum average displacements were 5.0 mm, 4.4 mm, 5.1 mm and 5.0 mm, respectively. In Figure 7, the relationship between PTVp D99 and average 3D displacement is shown. As expected, compared with CTVp D99, increased displacement has a direct impact on PTV coverage, with a small shoulder seen for all modalities but FFF 1 arc. In Figure 8, the relationship between rectum V80% and average displacement is shown, illustrating the impact on motion on rectum dose. Depending on the direction of motion, the rectum can either move away or towards the high dose region, as seen in the triangular-shaped relationship.
Table 4. Dosimetric results relative to the planned values, shown as median, 2nd and 98th percentile for 10 000 simulated treatments, averaged for the four patients.

<table>
<thead>
<tr>
<th></th>
<th>STD 1 arc</th>
<th>FFF 1 arc</th>
<th>STD 2 arcs</th>
<th>FFF 2 arcs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTVp D99 (%)</td>
<td>100.0 [99.7 - 100.6]</td>
<td>100.1 [99.6 - 100.5]</td>
<td>100.0 [99.6 - 100.5]</td>
<td>100.0 [99.5 - 100.5]</td>
</tr>
<tr>
<td>CTVp D95 (%)</td>
<td>100.1 [99.8 - 100.5]</td>
<td>100.0 [99.7 - 100.5]</td>
<td>100.0 [99.7 - 100.5]</td>
<td>100.0 [99.7 - 100.4]</td>
</tr>
<tr>
<td>PTVp D99 (%)</td>
<td>99.7 [91.7 - 100.1]</td>
<td>99.8 [92.2 - 100.1]</td>
<td>99.9 [91.9 - 100.0]</td>
<td>99.8 [92.6 - 100.1]</td>
</tr>
<tr>
<td>PTVp D95 (%)</td>
<td>99.7 [96.7 - 100.0]</td>
<td>99.6 [96.4 - 100.0]</td>
<td>99.9 [96.3 - 100.1]</td>
<td>99.7 [96.6 - 100.0]</td>
</tr>
<tr>
<td>CTV D95 (%)</td>
<td>100.1 [99.9 - 101.0]</td>
<td>100.3 [100.0 - 101.3]</td>
<td>100.0 [99.9 - 100.9]</td>
<td>100.2 [100.0 - 101.2]</td>
</tr>
<tr>
<td>PTVu D2 (%)</td>
<td>100.1 [99.7 - 101.4]</td>
<td>100.2 [99.7 - 101.7]</td>
<td>100.1 [99.8 - 101.4]</td>
<td>100.3 [99.9 - 101.9]</td>
</tr>
<tr>
<td>Rectum V80%</td>
<td>96.9 [75.3 - 118.9]</td>
<td>95.7 [72.7 - 116.2]</td>
<td>99.8 [80.7 - 115.5]</td>
<td>97.7 [75.2 - 116.0]</td>
</tr>
<tr>
<td>Rectum V60%</td>
<td>99.5 [90.1 - 112.4]</td>
<td>98.8 [87.6 - 113.9]</td>
<td>100.2 [92.0 - 113.1]</td>
<td>99.3 [88.1 - 115.1]</td>
</tr>
<tr>
<td>Bladder V80%</td>
<td>100.8 [93.0 - 105.7]</td>
<td>100.8 [92.5 - 105.7]</td>
<td>100.0 [91.4 - 103.6]</td>
<td>100.3 [92.8 - 104.6]</td>
</tr>
<tr>
<td>Bladder V60%</td>
<td>100.8 [95.0 - 106.2]</td>
<td>100.6 [94.4 - 106.5]</td>
<td>100.1 [93.7 - 104.3]</td>
<td>100.4 [94.6 - 106.2]</td>
</tr>
</tbody>
</table>

Figure 3. Histogram over PTVp D99 (%) (dark blue) and CTVp D99 (%) (red) for the four treatment modalities; one or two arc VMAT with 6X flattened beam (STD) or 10X flattening-filter free beam (FFF). The values without motion are shown as diamonds. The D99 values are averaged for four patients.
4 Discussion

This study investigated the dosimetric impact of prostate motion during profoundly hypofractionated IMAT treatments using one or two arcs and using either a flattened beam or an FFF beam. Despite the rather high fraction dose of 7.25 Gy, each plan in this study could be delivered within 4.25 min. The use of a second arc only slightly prolonged the treatment for flattened beams but improved the plan quality compared with a single arc. For FFF beams, owing to the high maximum dose rate, the gantry could rotate at the maximum speed throughout the treatment, and the fraction dose could be delivered in 1 min. The increased treatment time led to a higher average prostate displacement, as prostate motion have been shown to increase with treatment time [5]. Zwahlen et al. compared flattened and flattening-filter free beams with both 6 MV and 10 MV for prostate IMAT hypofractionation with $19 \times 3$ Gy, using either one or two arcs depending on planning complexity [4]. The authors found similar target coverage for all energies, and some additional rectum sparing when using 10 MV FFF compared to the other energies. The use of 10 MV FFF in this study therefore seems reasonable.

The motion-including dose to the PTV was studied as the structure basically represented a zero margin target volume that moved together with the CTV. The seminal vesicles were not included in the target volumes in this study, since the available motion data were exclusive to the prostate. The seminal vesicles have been shown to move independently of the prostate and deform to a larger extent than the prostate [12,13]. Thus, the conclusions drawn from this study may not be applicable for treatments of high risk prostate cancer, where the seminal vesicles are included in the target volume.

Azcona et al. performed dose reconstruction by using a Monte Carlo-based dose calculation and simulating motion by shifts the dose distribution for each control point according to the motion [8]. In contrast to the method used here, they used the planned MLC positions in the dose calculation. In our experience, the MLC error as recorded by log files is small and is not likely to impact the findings. Similar to this study, they found the impact of motion to be limited, with a minimum value in dose given to 0.03 cm$^3$ of the GTV to decrease to 94.1% of the planned value for a single fraction.
Figure 5. Relationship between CTVp and PTVp coverage for 1000 simulations using only motion traces from the two patients in the dataset with the highest average 3D displacement. The D99 values without motion are shown as diamonds. All values are the average of four patients.

Figure 6. CTVp coverage visualized as D99 (%) vs. average prostate displacement during delivery for the five motion traces that made up the treatment, averaged for four patients. The planned D99 is shown as a dotted line.
Figure 7. PTVp coverage plotted vs. average prostate displacement during delivery for 10 000 simulated treatments, averaged for four patients. The planned D99 is shown as a dotted line.

Figure 8. Dose to rectum, quantified as the volume (in per cent) receiving at least 80% of the prescribed dose vs. average prostate displacement. The planned V80% is shown as a dotted line.
There are several limitations to this study besides the definition of the target mentioned above. The DVH metrics were averaged for the four patients. The results thus better represented the general population, but it may hide deviations caused by the interplay effect. Assuming no interplay effect, there would be no trend towards reduced CTV coverage in Figure 4 and 5. Some of the treatments seemed to follow such a trend, indicating that the interplay effect besides geometrical misses may have caused some dose deviation. In this study, an ideal pre-treatment setup was assumed, as each motion trace was set to start at isocenter at the start of treatment. Preferably, the starting position would have been displaced according to a Gaussian distribution. However, such an approach would have increased the already high number of dose reconstructions. This study therefore underestimates the impact of motion if the prostate would have moved between setup imaging and treatment start. A further point to note is that the dose for each fraction was added linearly, ignoring the radiobiological implications of varying dose per fraction. Given the generally small variations in dose per fraction, the linear summation is likely to be reasonable for most of the treatment courses simulated. Finally, this study only investigated the effect of prostate translations, while rotations and deformations were ignored. Although prostate deformation seems to be limited, the rectum and bladder are deformable organs and a complete investigation of the effect of intrafraction organ motion should include both these effects together with translational motion. While prostate rotations are likely to have only small effects on the prostate dose coverage, they may result in misalignment of the urethra with the urethra-sparing low-dose volume.

5 Conclusions

The impact of intrafraction prostate motion was in general small, and the median prostate dose was equal to the planned dose. For motion traces with significant motion, the target coverage decreased somewhat and caused rather large variations in dose to organs at risk. Although significant differences were found between one and two arcs, and flattened and flattening-filter free beams, the magnitude of the differences was small. The target coverage was better for two double plans and the impact of motion due to an increased treatment time was arguably not large enough to motivate single arc treatments. Flattening-filter free beams gave comparable plans to flattened beams, and seem a feasible option for prostate hypofractionation radiotherapy due to the shorter treatment time.

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References


Opposite relationship between intensity-modulated arc therapy plan complexity and gamma pass rate for two patient-specific QA systems

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fax: +45 3545 3990

keywords: intensity-modulated arc therapy; quality assurance; plan complexity

Abstract

Background and Purpose: Intensity-modulated arc therapy (IMAT) allows for quick delivery of conformal dose distributions. Quality assurance (QA) of IMAT is important for safe radiotherapy but is a time-consuming procedure. We wished to use plan complexity (PC) metrics to identify IMAT plans at high risk of failing QA to reduce QA effort.

Material and Methods: IMAT plans were analysed for 841 fields measured with an electronic portal imager device-based system (EPID) and 161 fields measured with a phantom based system (PBS). Six MLC-related PC metrics and a number of plan parameters were tested for correlation with gamma pass rate using Spearman rank correlation.

Results: For the PBS gamma pass rates correlated with increased PC (p < 0.05), while the correlation for EPID was reversed (p < 0.05) for all six PC metrics. Field size-related parameters showed similar behaviour, with smaller magnitude. The number of monitor units (MU) and MU per degree was not significantly correlated with gamma pass rate for either system.

Conclusions: Plan complexity was significantly correlated to gamma pass rate for both systems. However, the relationships were opposite and care should be taken when transferring experiences drawn from one system to another.

1 Introduction

Intensity-modulated arc therapy (IMAT), as introduced by Otto [1] allow for quick delivery of conformal dose distributions. The technique has been in clinical use at our institution for several years [2,3], and we routinely treat brain, head and neck, lymphoma, lung, oesophageal and pelvic tumours with IMAT. The concept of patient-specific quality assurance (QA) for IMAT is well investigated [4-12]. One approach to the topic is to measure all IMAT plans before the start of treatment, while another approach is to use independent dose calculation systems, such as Monte Carlo-based methods [13,14]. The time consumption may be substantial if all IMAT plans are to be verified by using measurements in clinical practise. Therefore, the ideal dosimetry system for that approach should be both accurate and fast to use.
Current practise at our clinic includes measuring all IMAT plans using the electronic portal imaging device (EPID) which requires small workload during both preparation and measurement. In addition to the EPID based dosimetry system, we have the option to use a phantom based system. As large amount of QA data accumulate, we are able to investigate the dependence of QA results on IMAT plan parameters. This could save time by identifying plans that are likely to fail QA prior to discussion at plan conference and QA measurements.

Both the dose downstream of a single MLC leaf [15] and very small field openings [16] have been shown to be challenging to calculate accurately. We hypothesise that a plan complexity metric describes either the difficulty in accurately delivering a treatment plan on the treatment machine or the difficulty in accurately calculating the planned dose in the patient (or a combination of both). To our knowledge, four well-defined plan complexity metrics have been published; the field circumference to area ratio [17], the average distance to adjacent leaves [18], the amount of leaf travel and the modulation complexity score (MCS) [19,20]. MCS combines the variability in leaf positions with the variability in field aperture. It was first suggested for IMRT by McNiven et al. [19] and adapted for volumetric modulated arc therapy (VMAT) by Masi et al. [20].

To reduce the QA effort it would be useful to identify IMAT plans that are likely to fail QA. We have recently shown that errors in a treatment plan introduce gamma pass rate failures [8]. The purpose of this study was to determine whether complexity metrics correlate with the agreement between the planned and delivery dose for two QA systems and thus predict QA failure.

2 Methods and materials

2.1 Dosimetry systems

The Portal Dosimetry (PD) (Varian Medical Systems, Palo Alto, CA) software uses the integrated EPID to record an integrated dose image, which is compared to the expected dose image to assure accurate delivery of the treatment plan. As the EPID is fixed opposite of the gantry, the setup inaccuracy is small. When commissioned, a measurement using the device yields a calibrated unit (CU) that is used to associate image response with absorbed dose. The expected dose image is calculated with the Portal Dose Image Prediction (PDIP) algorithm. PD has previously been demonstrated to be a suitable option for IMAT patient QA [7].

The Delta4 dosimetry system (Scandidos, Uppsala, Sweden) is a phantom-based system and consists of two diode arrays, placed orthogonally in a cylindrical PMMA phantom, 21.8 cm in diameter. The diodes are separated by 5 mm in the 6 cm × 6 cm central part of the arrays and by 10 mm in the remaining 20 cm × 20 cm. The measurement unit is placed on the couch with its centre aligned to the isocenter, and connected to a computer where the measurement is recorded and analysed. The Delta4 is an established option for patient-specific QA for IMAT treatments [4,21].

2.2 Patient QA measurements

Routine PD measurements carried out between September and December 2013 were recorded for 518 patient IMAT plans, resulting in 841 separately analysed IMAT fields, measured on ten different linacs (four with the high-definition MLC (HDMLC) and six with the Millennium 120 MLC (M-MLC)). The EPID imagers were calibrated with dark field, flood field and dosimetric calibration on a monthly basis, with additional calibrations when necessary. The dosimetric calibration was performed with 10 cm × 10 cm open fields delivering 100 monitor units (MUs) at a source to detector distance (SDD) of 100 cm. The IMAT plans were measured with SDD = 100 cm. Diagonal profile correction was performed in accordance with the manufacturers recommendation. The patient QA measurements were reviewed immediately after they were performed, and this resulted in recalibration and additional measurements of the same plan if deemed necessary by the clinical physicist. If this was the case, the measurement with the highest pass rate was included in this study. All plans were optimized and measured in version 11 of the Aria software with PDIP version 11.0.31 and PD software version 11.0. Gamma evaluations were done with 3% 3 mm gamma criteria, using global gamma evaluation and performed for all pixels within the MLC irradiated area (MLC CIAO). The auto align software feature was used to align the measured and planned dose images before gamma calculation.

As customary patient QA measurements are no longer done with the Delta4 at our institution, results were collected from research (122 fields) and acceptance measurements (39 fields), resulting in 114 IMAT treatments and 161 fields (analysed separately). The measurements were carried out on six different linacs, two
Table 1. Summary of measured IMAT fields included in this study for the two dosimetric systems sorted by MLC type and treatment site.

<table>
<thead>
<tr>
<th></th>
<th>Delta4 HDMLC</th>
<th>Delta4 Millennium MLC</th>
<th>Portal Dosimetry HDMLC</th>
<th>Portal Dosimetry Millennium MLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>1</td>
<td>19</td>
<td>108</td>
<td>81</td>
</tr>
<tr>
<td>Prostate</td>
<td>9</td>
<td>21</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
<td>60</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>H&amp;N</td>
<td>4</td>
<td>4</td>
<td>98</td>
<td>58</td>
</tr>
<tr>
<td>Brain</td>
<td>4</td>
<td>-</td>
<td>107</td>
<td>10</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>63</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>-</td>
<td>13</td>
<td>5</td>
<td>74</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>-</td>
<td>-</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>55</td>
</tr>
<tr>
<td>Sum</td>
<td>38</td>
<td>123</td>
<td>365</td>
<td>476</td>
</tr>
</tbody>
</table>

with the HDMLC and four with the M-MLC. The planned doses were calculated with AAA version 11.0.31 (73 fields), AAA version 10.0.28 (48 fields) and AAA version 8.6.15 (40 fields). Before each measurement session, the Delta4 was normalized to the daily output of the treatment machine and corrected for setup errors with the help of static fields. All evaluations were performed in the Delta4 software (version 2012 February), with 3% 3 mm gamma criteria, limited to diodes receiving 5-500% of the planned dose to the isocenter.

The number of included fields and the distribution of treatment sites for the two systems are shown in Table 1, specified for the two MLC types used at our institution.

2.3 Plan complexity metrics

A number of MLC-related plan complexity metrics were calculated for each field as follows:

1. Number of MUs per prescribed dose (MU/Gy). For plans using more than one arc the contribution to the prescribed dose from each arc was calculated as the ratio of MU per field to the total MU.

2. The average MLC leaf travel distance between control points, averaged for all control points and all involved leaves (a leaf was considered involved if it defined an opening > 0.08 cm).

3. The average distance to adjacent leaves, averaged for all involved leaves and control points and weighted towards the relative dose contribution for each control point (ALDw) [18].

4. The MLC aperture area divided by its circumference, averaged for all control points (AoC). A simple aperture (e.g. a circle) will have high AoC, while a complex shape (e.g. a comb) will have low AoC.

5. The relative exposed area (REA). This metric was calculated as the average open MLC area for each control points, divided by the area of the MLC outline, i.e. the area defined by the outermost position for each leaf during the arc. To avoid influence on the MLC outline definition from closed leaf pairs moving beneath the jaws, each leaf had to define an opening > 0.3 cm to be considered. A highly modulated field would have small REA, while an arc field with a static MLC will have a REA of 100%. The REA was weighted towards the relative number of MU for each control point.

6. The modulation complexity score (MCS). The MCS combines the leaf position variability for each MLC bank with the aperture area variability resulting in a score between 0 and 1 with a lower value for more complex plans [20]. The aperture area variability is the same as the REA with the exception that no threshold is used for whether closed leaves moving to the side should be included in the maximum aperture calculation.

In addition to the plan complexity surrogates listed above, the following metrics were also extracted:

1. The number of MU per degree during the arc (average and standard deviation).

2. Number of MUs.
3. Average dose rate.

4. Average and maximum MLC opening in the X direction (parallel to the leaf travel).

5. Average and maximum MLC opening in the Y direction (perpendicular to the leaf travel).

6. The area of the MLC outline (used to calculate REA), which, as long as the isocenter is placed in the middle of the target, is a surrogate for target volume.

2.4 Statistics

The correlation between the plan metrics and gamma pass rate was quantified using Spearman’s rank correlation. The confidence interval (CI) was calculated using a bootstrap technique, drawing 10,000 random samples with replacement. The 95% CI was then taken as the range from the 2.5 to 97.5 percentile of the distribution of the resulting 10,000 rhos. The correlation between each metric and the gamma pass rate for the two systems was investigated separately with this technique. Correlations were considered significant if the 95% CI did not overlap zero.

3 Results

The relationship between the MLC-related plan complexity metrics and gamma index pass rate is shown for the two QA systems in Fig. 1. The top three metrics in Fig. 1; MU/Gy, leaf travel and ALDw, increase with increased plan complexity, while the bottom three metrics; AoC, REA and MCS, decrease with increased complexity. Both the PD and Delta4 QA systems showed significant correlation between the six plan complexity parameters and gamma index pass rate (Fig. 2, Table 2). However, the behaviour was opposite for the two systems. For the Delta4, increased plan complexity correlated with worsened agreement with the planned dose, while for PD, increased complexity correlated with improved agreement with the predicted dose image. The MU/degree metric did not correlate with gamma index pass rate, neither when considering average nor standard deviation of MU/degree. The dose rate did not correlate for the Delta4 and was only borderline significant for the PD. The number of MU, in contrast to MU/Gy, did not correlate with the gamma pass rate. For either system, the outline area (Fig. 3), the maximum MLC opening in X and Y directions, as well as the average opening in Y direction, correlated significantly with gamma pass rate. As for the complexity metrics, the correlation had opposite signs for the two systems. The magnitude of, and separation between, Spearman’s rho was however smaller than for five out of six plan complexity metrics. The choice of MLC did not impact the correlation between pass rate and MU/Gy (Fig. 4), justifying a combined analysis.
Fig. 1. Gamma index pass rate (using 3%, 3 mm criteria) vs. plan complexity metrics for the two dosimetry systems. The first three plan complexity metrics increase with increased complexity (monitor units per prescribed dose (MU/Gy), leaf travel and, average adjacent leaf distance (ALDw)). The last three metrics decrease with increased complexity (area over circumference (AoC), relative exposed area (REA) and modulation complexity score (MCS)). Note the different scale on the Y axes.
Fig. 2. Spearman’s rho (mean and 95% confidence intervals) for the correlation between selected metrics and gamma index pass rate for the two dosimetry systems. Significant different at the 95% level was achieved when 95% confidence interval of the estimated Spearman’s rho did not overlap zero. The metrics are arranged as plan complexity metrics and other metrics. The first three plan complexity metrics increase with increased complexity (MU/Gy, leaf travel and average adjacent leaf distance (ALDw) and the remaining three decrease with increased complexity (area over circumference (AoC), relative exposed area (REA) and modulation complexity score (MCS)).

Table 2. Median and range of each plan metric and estimated Spearman’s rho with 95% confidence interval (CI). Significant difference from zero was noted if the 95% CIs did not overlap zero and are emphasized in bold.

<table>
<thead>
<tr>
<th>Metric (median and range)</th>
<th>Delta4</th>
<th>Portal Dosimetry</th>
<th>Spearman’s rho (point estimate and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delta4</td>
</tr>
<tr>
<td>MU per Gy</td>
<td>244 (142 – 461)</td>
<td>231 (112 – 495)</td>
<td>-0.42 (-0.55 – -0.28)</td>
</tr>
<tr>
<td>Leaf travel</td>
<td>0.29 (0.08 – 0.43)</td>
<td>0.31 (0.09 – 0.48)</td>
<td>-0.44 (-0.57 – -0.30)</td>
</tr>
<tr>
<td>Adjacent leaf distance</td>
<td>1.02 (0.29 – 2.12)</td>
<td>1.10 (0.35 – 2.51)</td>
<td>-0.50 (-0.62 – -0.37)</td>
</tr>
<tr>
<td>Area over circumference</td>
<td>0.60 (0.26 – 2.82)</td>
<td>0.62 (0.25 – 1.94)</td>
<td>0.18 (0.03 – 0.33)</td>
</tr>
<tr>
<td>Relative exposed area</td>
<td>42.3 (18.8 – 75.3)</td>
<td>38.7 (10.1 – 73.6)</td>
<td>0.58 (0.47 – 0.68)</td>
</tr>
<tr>
<td>MCS</td>
<td>0.27 (0.12 – 0.58)</td>
<td>0.27 (0.07 – 0.58)</td>
<td>0.40 (0.27 – 0.52)</td>
</tr>
<tr>
<td>Average MU per degree</td>
<td>1.21 (0.39 – 4.01)</td>
<td>1.02 (0.23 – 4.09)</td>
<td>0.01 (-0.15 – 0.16)</td>
</tr>
<tr>
<td>Stdv of MU per degree</td>
<td>0.16 (0 – 1.54)</td>
<td>0.20 (0.02 – 3.51)</td>
<td>-0.19 (-0.33 – -0.04)</td>
</tr>
<tr>
<td>Average dose rate</td>
<td>349 (113 – 600)</td>
<td>294 (67 – 600)</td>
<td>0.02 (-0.13 – 0.18)</td>
</tr>
<tr>
<td>Average opening X</td>
<td>3.2 (1.1 – 10.1)</td>
<td>4.0 (1.2 – 9.0)</td>
<td>0.08 (-0.08 – 0.22)</td>
</tr>
<tr>
<td>Max opening X</td>
<td>10.8 (3.1 – 17.6)</td>
<td>11.9 (2.9 – 23)</td>
<td>-0.25 (-0.39 – -0.10)</td>
</tr>
<tr>
<td>Average opening Y</td>
<td>12.0 (4.7 – 25.7)</td>
<td>14.3 (3.1 – 37.1)</td>
<td>-0.35 (-0.48 – -0.21)</td>
</tr>
<tr>
<td>Max opening Y</td>
<td>14 (5.5 – 29)</td>
<td>16 (3.3 – 38)</td>
<td>-0.36 (-0.49 – -0.21)</td>
</tr>
<tr>
<td>Outline area</td>
<td>120.7 (17.3 – 440)</td>
<td>160.8 (6.8 – 537)</td>
<td>-0.34 (-0.47 – -0.19)</td>
</tr>
<tr>
<td>Gamma</td>
<td>99.5 (87.3 – 100)</td>
<td>97.4 (75.9 – 100)</td>
<td></td>
</tr>
</tbody>
</table>
4 Discussion

An unacceptable patient QA result causes increased workload and avoiding such plans in the first place is therefore desirable. This study investigated the relationship between IMAT treatment plan complexity and QA success rate, quantified with the gamma index pass rate, for one phantom-based and one EPID-based patient QA system. The gamma index pass rate is the metric primarily used clinically to make decisions whether to use a plan for treatment or not. Significant correlations were found for both systems for six MLC-related plan complexity metrics, suggesting that they have potential for clinical use to predict and/or to avoid plans that are less likely to pass QA. Curiously, we found that the correlation of plan complexity metrics and gamma pass rate had opposite signs for the two QA systems investigated. The two systems utilize completely different geometries and different calculation algorithms to compare the planned delivery of the IMAT plan and the actual delivery, but the fact that opposite correlation was observed for the two systems is nonetheless unexpected. Ideally a QA system should be able to detect clinically relevant dose deviations and let clinically irrelevant dose deviations pass. However, defining a ‘clinically relevant deviation’ is very challenging. By performing measurements with both systems on the same treatment plans as well as using Monte Carlo calculations or e.g. film dosimetry, we might be able to find which of the systems that is more true to the actual delivered dose distribution. However, this is beyond the scope of the present analysis.

The average MU/degree and the standard deviation of MU/degree are not related to MLC-complexity but possibly delivery complexity. These metrics showed no correlation with gamma pass rate. We also investigated any correlation with field size, quantified as average and maximum openings in the X and Y directions, as well as the area of the MLC outline. Significant correlation was found for all five metrics for the two patient QA systems. However, the correlation was less evident than the plan complexity metrics when qualitatively inspecting the relationship and comparing the magnitude of the correlation, estimated with Spearman’s rho. This suggests that the area may be a property of interest alongside plan complexity for the two systems.
In 2008, Gagne et al. [15] identified several problematic situations with the AAA algorithm, which is the dose calculation algorithm used for measurements with the Delta4. Inaccurate calculations occurred with fields including e.g. a single open leaf, or downstream of a single blocking leaf. More complex plan geometries would therefore be expected to correlate with worsened agreement to the planned dose, as observed in this study for the Delta4. Using the EPID for IMRT dosimetry has been investigated since early 2000s [22,23]. Besides Varian PD there are other options for using the EPID for IMAT verification, including EPIQA (EPIdos s.r.o), EPIDose (Sun Nuclear Cooperation), and the GLAaS method [9]. Bailey et al. [24] compared PD with EPIDose for IMRT deliveries and noted that although PD did not correctly model the off-axis response of the EPID, the performance of the two systems was comparable for most clinical IMRT fields.

There are a few investigations of correlation between plan parameters and QA success rate, although none of them investigated the PD system. Fogliata et al. [10] reported on 321 plans (comprising 395 arcs) measured with the GLAaS method, and noted that the group with a small ratio between control point and field area (similarly to the relative exposed area metric proposed here) had the lowest gamma index pass rate. The GLAaS method is considerably different than the PD approach [11], even though a similar device is used for measuring. Lang et al. [12] analysed the QA success rate for 224 FFF-plans, measured with a variety of dosimetric systems, with respect to MU/Gy (slight decrease), average and maximum dose rate (no effect), and target volume (slight decrease). The observed correlations between gamma pass rate and MU/Gy and field outline (surrogate for target volume) for the Delta4 in this study is in agreement with the conclusions presented by Lang et al. Recently, Masi et al. [20] adapted the MCS for VMAT and investigated any correlation between leaf travel, MCS and gamma pass rate (measured with the Delta4). They specifically investigated the importance of angle spacing in the plan, a quantity not relevant for the treatment technique used here, but also found correlation between increased plan complexity and decreased gamma pass rate.

For treatment plans with two or more arcs fields, each arc was in this study considered an independent measurement. Even though the patient characteristics were identical, as the collimator and sometimes couch angles were different, the arcs did not necessarily correlate to each other allowing for a separate analysis. For the Delta4, different versions of the dose calculation algorithm were used. This may add to the variance to the results. Also, the PD system was not calibrated before each measurement session as the Delta4 was which might have increased the variability in the gamma pass rate results. However, neither of these two causes of uncertainty would be expected to invalidate the findings. Owing to the large number of included plans in this study, no plans were measured on both systems.
5 Conclusions

All six MLC-related plan complexity metrics investigated in this study significantly correlated to gamma index pass rate for both patient QA systems. Curiously, the relationships were opposite for the two systems. Significant correlation was also found between field size and gamma index pass rate, although the correlation was not as strong as the correlation between plan complexity and pass rate. Plan complexity metrics are promising tools for predicting patient QA gamma pass rate. However, the metrics may vary between QA systems and care should be taken when transferring experiences drawn from one system to another.

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Conflict of Interest Statement


References


