INTRODUCTION
Cancer is the second leading cause of death worldwide with more than 8.7 million deaths in 2015 \(^1\). In the Netherlands alone, over 100,000 people are newly diagnosed with cancer each year, and this number is still growing \(^2\). Due to earlier diagnosis and better treatment options, the five-year overall survival rate for all tumors has increased from 46% for patients diagnosed in 1990 to 63% for patients diagnosed in 2011 \(^2\). The primary treatment modalities for cancer include surgery, chemotherapy, and radiotherapy. About half of all cancer patients will receive radiotherapy as (part of) their treatment, which makes it an important treatment modality \(^3\). This can be internally delivered radiotherapy, known as brachytherapy, but the most common form of radiotherapy is external beam radiotherapy, in which ionizing radiation is directed towards the tumor from outside the body \(^4\). The high-energy, megavoltage (MV), radiation damages the genetic material of cells, and if the damage cannot be repaired, this eventually leads to cell death. However, although healthy cells are generally less sensitive to radiation compared to cancer cells, it is inevitable that some healthy cells are also damaged as the radiotherapy beam passes through the body to reach the target area \(^4\). The goal of radiotherapy is, therefore, to kill the tumor cells while sparing surrounding healthy tissues as much as possible. Usually, radiotherapy is given as a fractionated treatment, meaning that the total radiation dose that will be delivered to the tumor is divided into smaller “fractions”. This allows healthy cells to recover in between fractions from the damage caused by the radiation, thereby reducing the toxic effect of radiotherapy, while tumor cells, which are known to be less efficient at recovering, accumulate damage \(^4\). High-dose radiotherapy is conventionally delivered in approximately 25 to 35 daily fractions of 1.8 to 2.0 Gy, treating 5 days a week, but due to technological advances, hypofractionation and stereotactic body radiation therapy (SBRT) are nowadays becoming more common. These techniques involve delivering high radiation doses to the tumor in only a few fractions, thereby decreasing the overall treatment time, and increasing the biologically effective dose. This can result in effective killing of tumor cells but is in general more damaging for healthy tissues. Therefore, it is even more important that the healthy surrounding tissues are spared as much as possible. This is achieved by accurately delivering conformal, high doses to the target, with a rapid fall-off of dose away from the target \(^5\).

Before the start of radiotherapy, a treatment plan is created. This treatment plan is created using a computed tomography (CT) scan, also referred to as the planning CT scan, on which the tumor itself, nearby volumes suspected of containing tumor cells, and nearby healthy tissues (organs-at-risk, OAR) are delineated. The tumor and the suspected areas comprise the target volume. This can be sub-divided into several conceptually different volumes to aid in the treatment planning process \(^6\):

1. The gross tumor volume (GTV), which is the visible tumor (e.g., on a CT, magnetic resonance imaging [MRI], or positron emission tomography [PET] scan).
2) The clinical target volume (CTV), which is the GTV expanded to include areas suspected of microscopic tumor involvement (not visible with currently available imaging techniques). In high-precision treatments like SBRT, the CTV expansion may be omitted (so that CTV = GTV).

3) The internal target volume (ITV), which takes into account physiologic movements and variations in size, shape, and position of the CTV within the patient. This volume is a concept used to ensure that the GTV and CTV receive the desired (prescribed) dose and is used primarily to account for influences of breathing motion. For targets that are not affected by breathing motion, the ITV is often omitted.

4) The planning target volume (PTV), which consists of the CTV/ITV and a margin to account for organ motion, variations in organ shape and size, patient movement, and day-to-day set up variations. The PTV is thus also a geometrical concept used to ensure that the GTV and CTV receive the prescribed dose. In high-precision treatments, smaller margins are used than in conventional radiotherapy. This helps to minimize OAR doses but can also increase the chance of missing the target, for example, if the GTV is inaccurately delineated or if the accuracy is sub-optimal.

Based on the delineated planning CT scan, a treatment plan is designed, the objective of which is to deliver a precisely calculated dose of radiation to the target with minimal damage to surrounding healthy tissues. This treatment plan specifies the settings of the treatment device to deliver the radiation dose, which include the direction, shape, and the intensity of the radiation beams. For stereotactic treatments, many medical centers routinely use volumetric modulated arc therapy (VMAT) to deliver the treatment. In VMAT, the gantry, i.e., the part of the treatment machine where the radiation beam comes out, is rotating around the target (and therefore the patient), enabling continuous radiation delivery over 360°. Highly conformal dose distributions are obtained by shaping the beam using a multileaf collimator (MLC), which consists of leaves that can move independently in and out of the treatment beam in order to block part of it, and by varying the gantry speed and dose rate.

In principle, this treatment plan is used for all treatment fractions. Since it is based on the patient’s anatomy at the time of the planning CT scan, it is essential that the patient is accurately positioned in the same way during each treatment fraction. This is especially important in SBRT plans since the steep dose gradients from the PTV to nearby organs-at-risk can result in a geographical miss of the tumor or an excessive dose to nearby OARs. Before the start of treatment delivery, patients are initially positioned on the treatment couch in the approximate treatment position using reference marks on the skin, and then the patient’s anatomy is imaged in order to obtain positional information on the target and OARs. This imaging is used for accurate positioning (“setup”). Patient setup for SBRT on a conventional linear accelerator (LINAC) is generally performed using cone-beam...
computed tomography (CBCT) scans. These scans are acquired using the gantry-mounted kilovoltage (kV) imager by continuous x-ray imaging of the patient while the imager rotates around the patient, and these images are then reconstructed into a 3D volume. This results in images that look similar to those of a CT scan, although the image quality may be lower. This CBCT scan is then rigidly registered to the planning CT scan, and the treatment couch is shifted by the amount necessary to achieve a good match. The total positional accuracy depends on several factors (e.g., the imaging system and couch shift capabilities), but can currently be within 1 mm. However, there may be a time gap of several minutes between CBCT acquisition and the start/end of treatment delivery, during which the position is not, or only approximately, monitored. If the patient moves, this may not be detected, especially if the displacement is small. In contrast to some specialized treatment systems, a conventional LINAC currently has limited options for positional verification during the actual irradiation, and so in general, there is no proof of the target position available during the most important time period: irradiation. Robust positional verification during irradiation itself is, therefore, desirable.

Although several techniques have been developed for real-time monitoring of internal targets, they rely either on additional treatment hardware or on implanted metal markers/transponders inside or near the tumor. These can then be monitored using kV or MV imaging/an electromagnetic array during irradiation. However, implantation of these markers/transponders is an invasive procedure with associated risks, and they can migrate and become unreliable. In addition, being able to monitor the position of internal targets without the need for additional hardware is desirable, to make the technology more cost-effective and more accessible.

The imaging capabilities available on most conventional LINACs include an on-board imager (OBI), a kV imager that is mounted perpendicular to the treatment beam, and an electronic portal imaging device (EPID) for MV imaging. Although the kV imager is generally only used for image acquisition for patient setup prior to the actual irradiation, some linear accelerators allow kV image acquisition during radiation (including VMAT) delivery. To determine the position of the target, it is desirable to use these two-dimensional kV images to calculate the position in three dimensions. In theory, the MV imager can also be used for positional monitoring during irradiation. However, the MV imager is mounted opposite to the gantry head and in VMAT treatments, the MLC leaves are frequently moving through the MV beam, blocking part of the target and making the MV images unsuitable for positional verification. For that reason, the focus of this thesis is on markerless kV-based positional verification techniques that are compatible with VMAT. This will be investigated for spine SBRT and hypofractionated/stereotactic lung treatments, for which the considerations are described in more detail below.
Spine SBRT

For patients with metastatic disease, spread to the vertebral column is common. In the Netherlands, it is estimated that ~25,000 patients are diagnosed with spine metastases each year. Radiotherapy is the guideline-recommended treatment for patients with spinal metastases that cause pain or neurological deficits. This is usually delivered with a dose high enough for pain relief, but often not high enough to achieve long-term local tumor control. In the VU University Medical Center, high-dose radiotherapy is used for metastases with intermediate to good prognosis (predominantly oligometastatic disease), re-irradiation, and complex palliation. Spine SBRT has been shown to be an effective treatment for spinal metastases, with high rates of local control and pain response. However, due to the close proximity of OARs, such as the spinal cord, careful radiotherapy planning and delivery is essential. To reduce the risk of radiation-induced myelopathy, which could result in long-lasting neurological deficits, a positional accuracy within 1 mm and 1° is often preferred to ensure that the delivered dose distribution closely reflects the one that has been planned. Some medical centers, therefore, use near-rigid immobilization devices for spine SBRT treatments. However, although the spine is usually considered to be stable, motion can occur with or without the use of immobilization devices. As it is hard to predict in advance which patients will move, and even short-duration positional offsets can cause substantial dosimetric deviations when high-dose-rate beams are delivered, frequent spine position monitoring during irradiation is desirable.

Hypofractionated/stereotactic lung treatments

In radiotherapy for lung cancer, respiratory motion is one of the factors that introduce positional uncertainty. As organ motion results in blurring/image artifacts on a regular 3D CT scan, a 4D CT scan is often acquired and used for lung cancer treatment planning. A 4D CT scan consists of multiple 3D CT scans, each of which represents a different part of the breathing phase. The simplest and most common method to account for respiratory motion is to use the ITV concept, in which the tumor is delineated on all phases of the 4D CT scan, and these delineations are combined to cover the full range of motion. However, when there is considerable respiratory motion, the size of the PTV can be substantial, resulting in a significant amount of, for example, healthy lung tissue being irradiated. Therefore, several methods have been investigated to account for breathing motion. These can roughly be divided into:

1) Methods that limit breathing motion, thereby reducing the size of the PTV, such as respiration-limiting techniques/devices (e.g., abdominal compression and active breathing control using a spirometer) and breath-hold techniques.
2) Methods that deliver the treatment based on the respiratory phase/observed motion, such as gating and tumor tracking.
With gating, the treatment beam can be automatically turned on and off at specific breathing amplitudes, while with tumor tracking the tumor can be automatically followed by the treatment beam. However, both techniques require accurate determination of the tumor position in order to be performed correctly. Currently, most gating and tumor tracking techniques rely on indirect information on the breathing phase obtained by monitoring the position of reflective markers on the thorax/abdomen or by directly monitoring the body surface, or on the position of implanted markers. However, (external) markers or the surface of the patient are only a surrogate for tumor position, and so monitoring of the tumor position itself is preferred.

In the VU University Medical Center, a breath-hold technique in combination with gating is used when there is considerable respiratory motion or if multiple lung tumors are being treated. The breath-hold is usually performed at end-inspiration or end-expiration. Although the reproducibility is higher at end-expiration, end-inspiration is often preferred as this increases the lung volume and reduces the relative amount of healthy tissue being irradiated. A voluntary breath-hold with visual feedback is performed by monitoring the position of reflective markers on the thorax/abdomen. When the patient establishes the breath-hold, the treatment beam is turned on, and when the breath-hold is released, the treatment beam automatically stops. However, for patients treated in breath-hold, inter- and intra-breath-hold variations in tumor position may occur, which makes it important to verify the lung tumor position during each breath-hold.
Chapter 1

OUTLINE OF THIS THESIS

The focus of this thesis is on markerless kV-based positional verification techniques that are compatible with VMAT, and compatible with the hardware configuration of most treatment platforms, i.e., a single kV imager mounted orthogonally to the treatment beam.

In Chapter 2, a markerless spine position monitoring technique based on template matching and triangulation using kV images acquired by a gantry-mounted imager during irradiation is evaluated. In addition, positional stability during spine SBRT is reported. This technique performs direct registration of prefiltered kV projection images and filtered digitally reconstructed radiographs generated from planning CT data to determine 2D spine position, and uses a form of sequential triangulation to determine 3D spine position for each image. This results in multiple 3D positions per second. Alternatively, these fluoroscopic kV projection images can be used to reconstruct CBCT scans, which is described in Chapter 3. In this chapter, CBCT scans are reconstructed from the kV images acquired during spine SBRT treatments, and the CBCT-CT match results are evaluated against the average spine position deviations found using template matching and triangulation. As standard CBCTs require ≥180° gantry rotation, there are additional considerations for patients treated in breath-hold. Firstly, multiple breath-holds are often needed before such a CBCT can be reconstructed, and inter-breath-hold variations may result in blurring of the tumor. Secondly, short, partial treatment arcs are frequently used during lung SBRT treatments. Therefore, limited-arc single breath-hold CBCTs (≥20°) are investigated for verification of tumor position during breath-hold lung SBRT. However, CBCT reconstructions are known to provide the dominant/average tumor position during treatment, and limited information on motion. To determine whether the patient is able to maintain a stable tumor position during breath-hold, near real-time verification is preferred. In Chapter 4, it is evaluated whether the combination of template matching and triangulation using kV projection images acquired during irradiation can be used to monitor lung tumor position during breath-hold stereotactic VMAT treatments. Because of the often low visibility of lung tumors on kV images due to low density and/or small size of the tumor, and overlapping structures, the influence of image pre-filtering and/or enhancement techniques prior to template matching was investigated.

Generally, the focus of (near) real-time positional verification is on the tumor itself. However, in some cases, the position of an OAR is just as important as, or even more so, than the tumor itself. For example, SBRT and hypofractionated radiotherapy for central lung tumors are associated with an increased risk of central airway toxicity, which in some patients may be life-threatening. Information on the position of the airways relative to the high-dose region could help to manage these risks and increase user-confidence. In Chapter 5, the feasibility
of markerless 3D airway position monitoring during gantry rotation is investigated using kV projection images acquired by a gantry-mounted imager.

Chapter 6 reports on our first experience with markerless online 3D spine position monitoring during VMAT SBRT delivery for 3 patients. This allows for immediate treatment interruption when excessive positional displacement is detected in order to reposition the patient. The treatments were performed on a standard LINAC using the gantry-mounted kV imager, with position monitoring based on the technique described in Chapter 2.

In medical imaging, phantoms (i.e., objects that to a greater or lesser extent resemble the human body or its parts) are widely used to provide a ground truth for testing and optimization of imaging devices and software, without needing to expose humans to radiation. However, although commercial phantoms often consist of materials with realistic tissue (radio)densities, they commonly have simple, generic forms and sizes that do not closely resemble real patients, which makes it difficult to extrapolate the performance of an imaging system in phantoms to humans. In Chapter 7, the manufacture of a thorax phantom with multiple tissue types/densities that closely resembles a real patient in terms of spatial accuracy for x-ray imaging purposes is described. This phantom is created with 3D printing techniques and is used for the phantom experiments described in Chapters 3, 4, 5, and 6.