SUMMARY

Radiotherapy is one of the primary treatment modalities for cancer. The most common form of radiotherapy is external beam radiotherapy, in which ionizing radiation is directed towards the tumor from outside the body. However, as the radiotherapy beam passes through the body to reach the target, it comes into contact with healthy tissues, some of which may be damaged by the radiation. By irradiating from multiple directions, the dose received by the healthy tissues is minimized as much as possible. The goal of radiotherapy is to kill the tumor cells while causing as little damage as possible to the surrounding healthy tissues. Stereotactic body radiation therapy (SBRT) is different from standard (conventional) radiotherapy because it delivers high radiation doses to the tumor in only a few treatment sessions (fractions). This can result in effective killing of tumor cells. To deliver the radiation with high precision, volumetric modulated arc therapy (VMAT) is often used. In VMAT, the gantry, the part of the treatment machine where the radiation beam comes out of, is rotating around the patient, enabling continuous radiation delivery over a 360° arc. In addition, the intensity and shape of the beam can be adjusted (modulated). These features allow for accurate delivery of a conformal, high dose to the target, with a rapid fall-off of dose away from it. In radiotherapy, the treatment is planned based on a CT scan, also referred to as the planning CT scan. On this CT scan, the target area (tumor) and nearby healthy tissues that need to be spared as much as possible are delineated. Based on the delineated planning CT scan, a treatment plan is designed, which specifies the settings of the treatment device to deliver the radiation dose. To account for uncertainties in the radiation treatment process, for example, delineation inaccuracies, positional inaccuracies, and mechanical inaccuracies, margins are added to the target to make it a little larger than necessary. The high dose radiation is delivered to the expanded target so that if the position of the tumor changes slightly, then it will still receive the intended high dose of radiation. In SBRT these margins are small, which helps to spare healthy tissue. However, this can also increase the chances of a geographical miss of the tumor/target or of delivering excessive dose to healthy tissues if the patient is not accurately positioned. Since the treatment plan is based on the planning CT, and this plan is used for all treatment fractions, it is essential that the patient is accurately positioned in the same way during each treatment fraction. Accurate patient positioning for SBRT on a conventional linear accelerator (LINAC) is generally performed prior to irradiation using a cone-beam computed tomography (CBCT) scan. This is a scan that looks similar to a CT scan and is made using a kilovoltage (kV) x-ray device mounted on the gantry. It is used to place the patient in the position that they were in when the planning CT scan was made. However, there may be a time gap of several minutes between the CBCT acquisition and the start/end of treatment delivery, during which the position is not, or only approximately, monitored, and it is possible that the patient moves during this period. Because a conventional LINAC currently has limited options for continuous
positional verification during the actual irradiation, there is, in general, no proof of the target position available during the most important time period: irradiation. The use of fiducial markers/transponders in or near the target may be considered, but this requires an invasive procedure to insert them, which can cause side effects. Robust, markerless positional verification during irradiation itself is, therefore, desirable.

The aim of this thesis was to evaluate markerless kV-based positional verification techniques that could: 1) be used during SBRT delivery, 2) would be compatible with VMAT, and 3) would not require hardware modifications to conventional LINACs. This was investigated for spine and lung treatments. Three to fifteen kilovoltage images a second were continuously acquired during irradiation using the gantry-mounted imager while it rotated around the patient, resulting in images from different directions (360°). In this thesis, methods were evaluated to use these two-dimensional kV images to calculate the position of the target in three dimensions.

In Chapter 2, a markerless spine position monitoring technique based on template matching and triangulation was evaluated. Template matching takes reference images derived from the planning CT scan and matches them to the kV images made during irradiation to work out in 2D how far away the target is from the intended position. Triangulation is then used to determine target position in the 3rd dimension. This results in an automatically determined 3D target position for each individual kV image. To verify the accuracy and precision of the technique, a phantom was used. This is an object which is used to mimic a patient and can be x-rayed, moved, and irradiated, to enable testing and investigation on a LINAC. Testing template matching and triangulation with a phantom, we found that this technique could determine 3D position with an accuracy of better than 0.5 mm. This technique was also used to analyze images from patients treated with spine SBRT, and these showed that the patients were stable to within 1 mm of the intended position in 92% of the arcs. It was concluded that using kV images acquired during irradiation allows spine position detection with submillimeter accuracy at subsecond intervals.

In Chapter 3, it was investigated if CBCT scans can be reconstructed from the kV images acquired during irradiation. For CBCT reconstruction (i.e., reconstruction of the 2D images into a 3D volume), all kV images obtained during one (partial) arc are used. This would allow the “dominant” tumor position during treatment to be seen. This could be useful, for example, if the target position cannot be determined using template matching and triangulation. Full-arc CBCT scans were reconstructed from 38 kV imaging datasets (16 patients) acquired during spine SBRT. These CBCT scans were matched to the planning CT scan, and the results were compared to the average spine offset found using template matching and triangulation of the individual kV images. There was a mean difference of
0.1 mm between them. Standard CBCT scans require imaging over ≥180°. However, some patients are treated while holding their breath, and multiple breath-holds are often needed before enough kV images can be acquired to create such a CBCT scan. If the breath-holds vary in their depth, this may result in blurring of the tumor. In addition, short, partial treatment arcs (<180°) are frequently used during lung SBRT treatments. Therefore, limited-arc single breath-hold CBCT scans (20–180°) were investigated for verification of tumor position during breath-hold lung SBRT. For submillimeter accuracy, automatic 3D CBCT–CT matching, an arc length of ≥80° was found to be desirable. Although (limited-arc) CBCT reconstructions of kV images acquired during irradiation can identify the dominant position of the tumor during treatment delivery, they provide limited information on motion. They are therefore complementary to near real-time verification (e.g., using template matching and triangulation).

In Chapter 4, it was evaluated whether template matching and triangulation can be used to monitor lung tumor position during breath-hold treatments. Compared to free-breathing treatments, breath-hold treatments allow for a reduction in healthy lung tissue being irradiated by minimizing breathing motion. However, for patients treated in breath-hold, variations in tumor position may occur between different breath-holds (inter-breath-hold variations) and/or during a breath-hold (intra-breath-hold variations), which makes it important to verify the lung tumor position during each breath-hold. Lung tumors are often difficult to detect on kV images due to low density and/or small size and overlapping structures. To try and improve the detection of these tumors, image pre-filtering (band-pass filtering) and/or enhancement (digital tomosynthesis, DTS) prior to template matching was investigated. It was found that both 2D and 3D tumor position could be better determined in most images after using DTS + bandpass filtering. Although template matching and triangulation using DTS + band-pass filtered images could accurately identify the 3D position of stationary lung tumors, triangulation was less accurate/reliable for targets with continuous, gradual displacement in the left-right and forward-backward directions. This technique is therefore currently most suited to detect a change in position occurring between CBCT acquisition prior to irradiation and the start of treatment, differences in position between breath-holds, and tumors with predominantly up-down motion.

Generally, the focus of (near) real-time positional verification is on the tumor itself. However, in some cases, the position of an organ-at-risk (healthy tissue) is just as important as, or even more so, than the tumor itself. For example, SBRT for central lung tumors near the big airways and blood vessels is associated with an increased risk of central airway toxicity, which in some patients may be life-threatening. Information on the position of the airways could help to manage these risks. In Chapter 5, the feasibility of markerless 3D airway position monitoring was investigated. kV images of a moving phantom and ten patients
undergoing free-breathing lung SBRT were analyzed. For the phantom, the central airway position could be determined with an accuracy of <1 mm for all 3 directions. For each patient, 2D airway position could be identified, on average, in 90% of the images per dataset, and 3D position (excluding the first 20° due to the triangulation angle) in 85%. It was concluded that high-frequency 3D airway position verification during free-breathing is technically feasible using markerless template matching and triangulation of kV images acquired during gantry rotation.

Chapter 6 reports on our first experience with markerless real-time 3D spine position monitoring during VMAT spine SBRT delivery on a standard LINAC using the gantry-mounted kV imager. Kilovoltage images were acquired at 7 frames per second and streamed to a stand-alone computer. If the offset in any direction was more than a certain threshold, the treatment was manually stopped, and a CBCT scan was acquired to reposition the patient. During irradiation of 10 fractions in 3 patients, we interrupted the treatment beam 2 times based on the position results, for different patients. We conclude that online position monitoring has the potential to increase confidence in the treatment and reduce the risk of target miss and excessive organ-at-risk dose.

In medical imaging, phantoms are used for testing and optimization of imaging devices and software. However, commercial phantoms 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 size, shapes, and structures for x-ray imaging purposes is described. This life-size phantom was created using 3D printing techniques and is based on a clinical CT scan of the thorax from a patient with lung cancer. It was assembled from bony structures printed in gypsum, lung structures consisting of airways, blood vessels >1 mm, and outer lung surface, three lung tumors printed in nylon, and soft tissues represented by silicone (poured into a 3D-printed mold). This phantom was used for most of the phantom experiments described in this thesis.

Accurate position monitoring during irradiation reduces the risk of target miss and excessive organ-at-risk dose and is a necessary step towards real-time tumor tracking, in which the target is followed by shifting the treatment source, shifting the beam, or adjusting the patient position. In this thesis, it was shown that position monitoring on a standard LINAC using the gantry-mounted kV imager is possible for bony spine structures, the central airways, and some lung tumors treated in breath-hold. The prototype real-time online positional verification software has been used to monitor target position during treatments at the VU University Medical Center. Currently, when a target offset is detected, beam interruption
has to be performed manually, and a CBCT has to be acquired for patient repositioning. The next steps would be to automate these steps, which might eventually be replaceable by strategies to adjust the position of the treatment beam or re-position the target (e.g., shifting the couch position) when the target position changes.