Improving radiation dose delivery for moving targets using image guidance

Rooijen, D.C. van

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General introduction and thesis outline

1.1 Radiotherapy

In the Netherlands 91.400 new cases of cancer were diagnosed in 2009 and 41.500 persons died of this disease (www.ikcnet.nl). Radiotherapy is an important treatment modality in the management of cancer, either as a single therapy, or in combination with chemotherapy, surgery or hyperthermia.

The probability of achieving a successful treatment with radiotherapy is related to the dose received by the tumor, as described by the linear-quadratic model [1]. However, the dose that can be delivered to the tumor is limited by the surrounding healthy tissue, in which a higher dose results in a higher risk of complications.

The most common machine for external beam radiotherapy is the linear accelerator (linac). The development of the linac occurred parallel on both sides of the Atlantic Ocean. Henry Kaplan en Edward Ginzton are considered to be the inventors of the linear accelerator [2]. They developed their accelerator at the Stanford University in California. The first actual treatment with a linac took place in the Hammersmith Hospital in London [3]. Figure 1.1a shows a model of this first linac in the Hammersmith Hospital, whereas figure 1.1b shows a modern linac, as currently installed in the Academic Medical Center in Amsterdam.

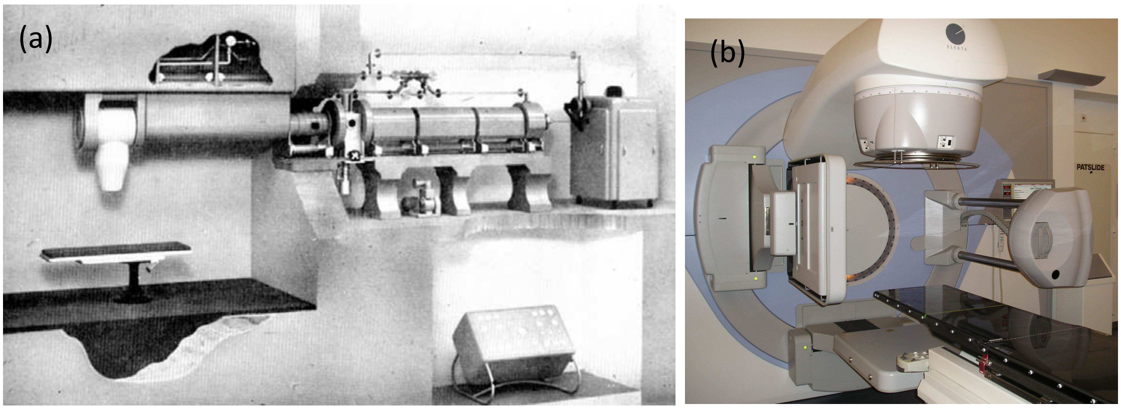

Figure 1.1 a: A model of the first linear accelerator at Hammersmith Hospital in London [3]. b: A modern linac.

The techniques of radiotherapy have greatly improved since the introduction of the first linac. An important development in radiotherapy was the development of the multi-leaf collimator (MLC), a device that was first described by Takahashi, who called it a sectional diaphragm in 1965[4]. The device consisted of tungsten plates in nine pairs opposite to each other. By moving these plates, which are now called leaves, the desired field shape can be created (figure 1.2a). Nowadays the MLCs consist of more leaf pairs and the leaves are smaller, but the principle is still the same (figure 1.2b).

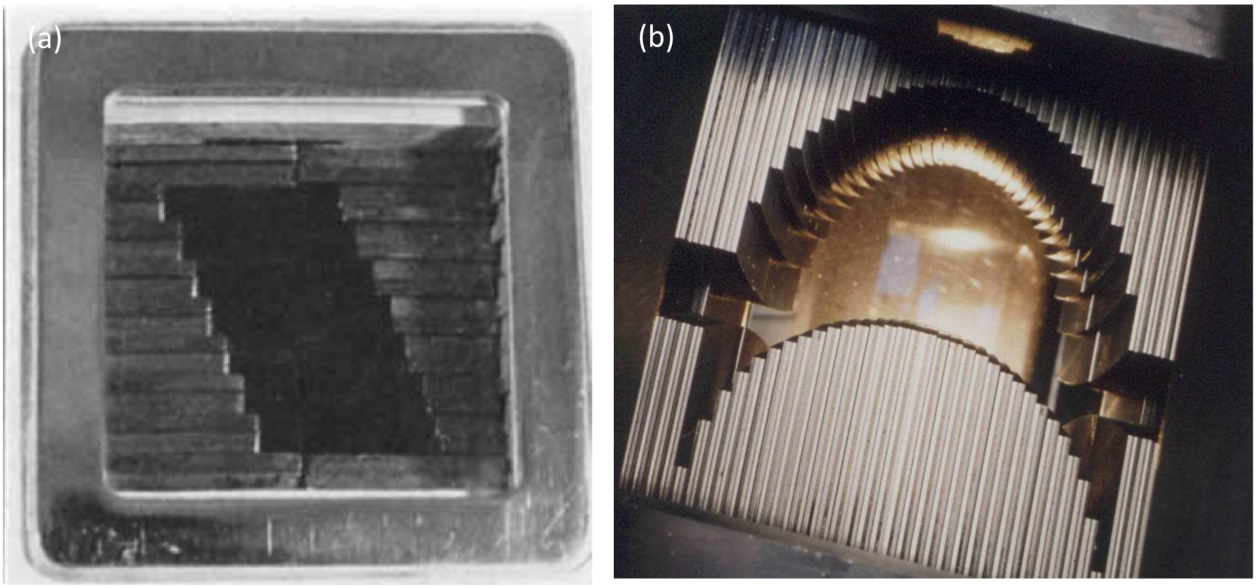

Figure 1.2 a: The first MLC as described by Takahashi [4]. b: A modern MLC as currently produced by Elekta.

The introduction of the MLC was a great improvement compared to the use of square shaped fields, or handmade blocks, which was common practice before. The treatment with field shapes that are adapted to the shape of the target is called three dimensional conformal radiotherapy (3D-CRT).

The introduction of the computed tomography (CT) scanner in the field of radiotherapy led to more accurate treatment planning options. The CT-scan renders a 3D image of the patient, which shows an accurate view of the shape of the tumor and the anatomy of the patient. The grey values of the CT-scan (Hounsfield units, HUs) are directly related to the relative electron density of the tissue. Using this, the given dose to the tumor and the healthy tissue can be accurately calculated.

Alongside the ‘regular’ linac, some new concepts were developed: Tomotherapy and Cyberknife. The Tomotherapy treatment machine was developed for dynamic conformal radiotherapy [5]. A linear accelerator is mounted on a CT-like ring. The radiation is delivered using a rotating fan beam, which is modulated by an MLC, while the patient moves through the ring. Cyberknife is developed for radiosurgery [6]. Cyberknife consists of a lightweight linear accelerator, which is mounted on a highly maneuverable industrial robot. The system also acquires radiographs during treatment. When the target moves, the coordinates are sent to the robot, which corrects the beam direction.

The radiotherapy department in the AMC Amsterdam has currently no access to dedicated machines like Tomotherapy and Cyberknife and therefore all the work in this thesis is based on a conventional linac.

1.2 The radiotherapy treatment chain

The radiotherapy treatment chain consists of several steps. As a first step the patient is scanned to determine the target area. Usually this is done with a CT scan, but nowadays it is more often combined with positron emission tomography (PET) or magnetic resonance imaging (MRI). The radiation oncologist determines the target area and the organs at risk (OARs) using these images.

The next step is the creation of a treatment plan. In this step the optimal beam angles, field shapes and weight per beam are determined in order to irradiate the tumor sufficiently, while avoiding the OARs. In the next paragraph treatment planning will be discussed in more detail.

The final step before the actual irradiation is the positioning of the patient on the treatment couch. The patient is positioned based on the laser system in the treatment room and marks that are applied on the skin. However, the internal anatomy of the patient can change with respect to the skin marks. The introduction of portal imaging and the cone beam CT (CBCT) presented the possibility to determine the actual location of the tumor and to correct the position of the patient, if necessary.

1.2.1 Treatment planning

The advances in treatment planning in the last few decades have been largely driven by developments in computer hardware and software. The first paper about the use of computers for the calculation of the treatment plan was published in 1955 [7]. The first 3D treatment planning system for clinical use was developed in 1988 [8].

The standard approach of treatment planning is what is called forward treatment planning. The CT scan of the patient is used to determine how many beams should be used and from which angles. Then, the shape of each beam is created, using the MLC and blocks. Next, the weights of all beams are varied in order to create the optimal dose distribution. If the produced dose distribution is not satisfactory, one should go back to a previous step.

The beams used for radiotherapy treatment have a uniform intensity. A gradient in the intensity of the beam can be created by placing a wedge in the beam, for example to compensate for missing tissue or to spare healthy tissue. In 1959 the first compensator that creates a patient-specific non-uniform intensity was described [9]. This compensator was handmade based on the patient’s anatomy. An example of such a compensator is shown in figure 1.3. However, because this compensator had to be constructed by hand for each beam for each patient, this technique could not be used on a large scale.

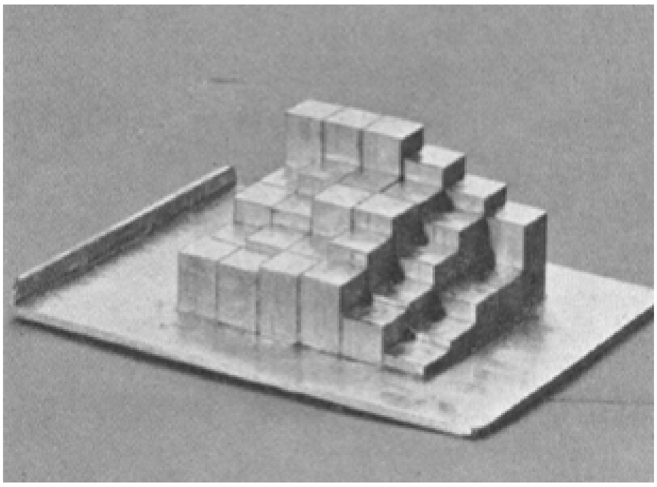

Figure 1.3: Compensator for creating non-uniform intensities [7].

In 1982 Brahme *et al.* published the first paper about the inverse planning problem [10]. This was a mathematical paper that described the calculation of the ideal intensity profile of the beam in order to create a dose distribution of a certain shape. He showed that a highly non-uniform intensity profile was needed to create a dose distribution for a doughnut-shaped target with an organ at risk in the center. This paper is now recognized as the first paper about intensity modulated radiotherapy (IMRT), although that term had not been invented yet. Figure 1.4 shows the principle of IMRT as proposed by Brahme[11].

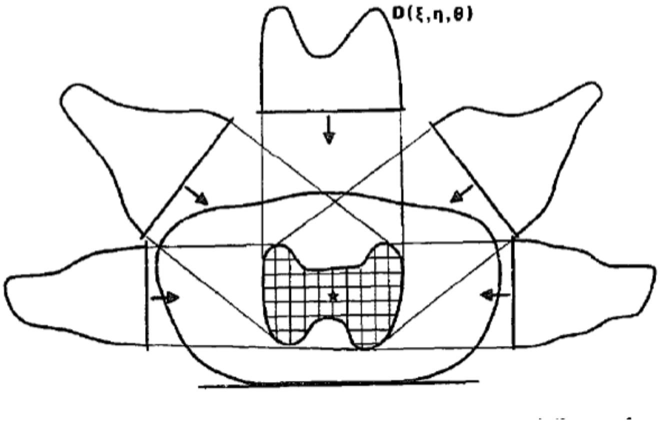

Figure 1.4: The principle of IMRT [11].

In 1989 Webb formulated the inverse planning as an objective function, or cost function, that can be optimized by minimizing the equation [12]. Nowadays, this approach is still used for planning IMRT in many commercial treatment planning systems. However, at that time non-uniform beam intensities only existed in theory and there was no practical way to actually execute them. In 1992 Convery and Rosenbloom published a procedure to create non-uniform beam intensities, which is by moving the leaves of the MLC during the irradiation of each static beam [13]. In 1994 the first IMRT plan was irradiated on a phantom [14]. This treatment took three hours, which made it unsuitable for treating patients at that time.

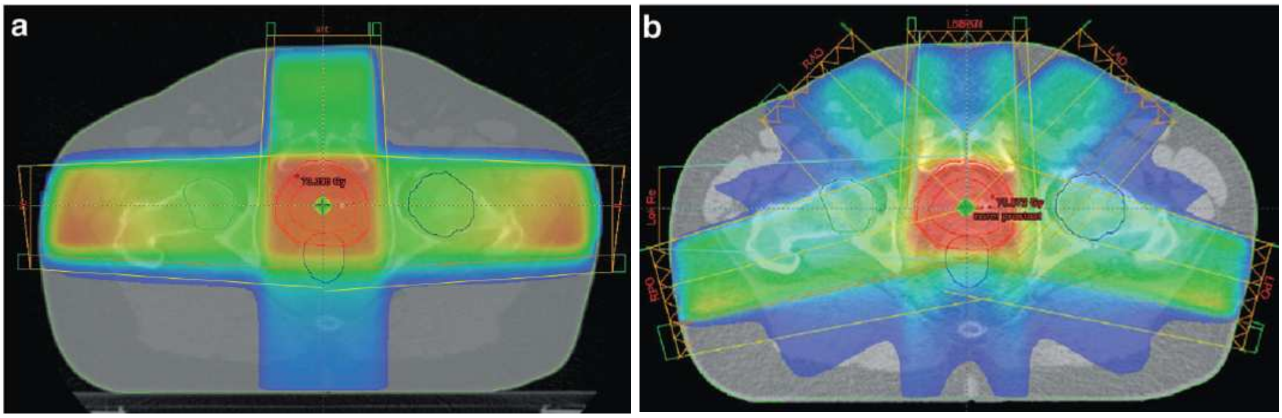

Figure 1.5: Comparison of a dose distribution using 3D-CRT (a) and IMRT (b) [15].

Nowadays, the treatment time of IMRT has greatly improved compared to the three hours in 1994 and it is now widely used in the radiotherapy clinics worldwide. Because concave dose distributions can be created, the organs at risk (OARs) can be spared better with IMRT. Many studies have compared dose distributions using IMRT with those using conventional treatment plans or 3D-CRT. Because of the better sparing of healthy tissue, IMRT is either used to decrease the risk of complications, or to increase the dose to the tumor while maintaining the same risk of complications. Examples of dose distributions using 3D-CRT and IMRT are shown in figure 1.5 [15].

1.2.2 Position verification

Before the irradiation starts, the patient is positioned on the treatment table. It is important that the patient’s position is exactly the same during treatment as during the planning CT, on which the treatment plan is based. In order to do this, laser systems are used. Laser systems are installed in the room of the CT scanner and in the treatment rooms. When the patient is scanned on the CT, marks are applied on the skin at the position where the laser coincides with the skin. Before each treatment, those marks are used to position the patient based on the laser system in the treatment room.

The marks on the skin are a reasonable indication of the location of the tumor. However, the skin is not fixed rigidly to other structures. When the patient’s position changes slightly, either due to being more relaxed or tenser than during the planning CT, or if the patient has lost weight, the position of the skin marks might not represent the location of the tumor anymore. The position of the tumor itself might also vary from day to day, depending on the region of the tumor. Tumors in organs that are rigid or experience no movement, like the bones or the brain, will show little movement. On the other hand, tumors in flexible structures, like the bladder wall or the cervix, can move up to a few centimeters. In order to be sure to capture the complete tumor, a large area around the tumor should be included in the treatment field in such cases. Increasing the amount of surrounding healthy tissue in the field of irradiation leads to a higher number of complications. This demands a solution for determining the position of the tumor at the moment of treatment more accurately. Immobilization devices counter only a part of the problem, because even if the patient is in exactly the same position as during the planning, most internal organs cannot be fixed.

The first study in which the position of the target area during treatment was determined used a radiographic film behind the patient [16]. Radiographic films were mainly used for comparison of immobilization devices. Because of the time it took to develop the films, this could not be used to determine the position of the patient instantly before treatment. This changed when electronic portal imaging was developed [17]. It was not until eight years later that the first results appeared of the use of an on-line portal imager for on-line evaluation and immediate adjustments on a daily basis [18].

A major drawback of portal imaging, for which the high energetic treatment beam was used, was the lack of soft tissue contrast. By 2002 the cone-beam CT had been developed [19]. Instead of using the treatment beam to make a radiograph of the patient, an x-ray tube is mounted on the gantry, with an accompanying detector. By rotating the gantry while the x-ray beam is on, a 3D image comparable to a CT image can be reconstructed. Because of the increased image quality and the increased availability of software for automatic registration, the use of image-guided radiotherapy (IGRT), has greatly increased in the last decade.

Because it is not effective to use a high precision technique like IMRT when the position of the target is unsure, the use of IMRT increased when IGRT became available on a large scale. The use of IGRT decreases the positional uncertainties and therefore the margin around the target can be decreased. This reduces the risk of complications and enables dose escalation.

Despite the improved soft tissue contrast of CBCT compared to other IGRT modalities, such as electronic portal imaging, some structures are still hard to discriminate. For an efficient workflow you need some clear landmarks to base the registration on, preferably clear enough to do the registration automatically. When such landmarks are not present in the human anatomy markers are inserted, if possible, to function as a surrogate for the tumor position. The use of markers to determine the position of the prostate on either CBCT or portal images is widely implemented in the radiotherapy clinics [20].

1.3 Applications

In principle the techniques described in the previous paragraphs can be applied for every target. However, every target has its own difficulties and therefore specific solutions have to be found for each target. The next paragraphs will describe two targets into more detail: the bladder tumor and the lung tumor.

1.3.1 Bladder cancer

In the year 2008, 2839 cases of bladder cancer were diagnosed in the Netherlands and 1169 persons died from this type of cancer (www.ikcnet.nl). In about 40% of the cases the disease is still in an early stage at diagnosis. When the tumor is muscle-invasive, radical cystectomy is the treatment of choice. During this type of surgery, the whole bladder is removed. This prodedure is associated with a high morbidity (15-40%) and mortality (1-4%) [21]. If the patient is unfit or unwilling to undergo this treatment, he or she is referred for radiotherapy.

Until recently it was common practice to irradiate the whole bladder when the patient was referred for radiotherapy. In order to keep the irradiated volume as small as possible, the patients were asked to empty their bladder before treatment. However, large day-to-day differences in bladder volume occurred, so large margins were required to irradiate the bladder adequately [22]. However, the survival rates were still low (14-45%) at 5 years [23].

Radiotherapy for bladder cancer was always the second choice after surgery, because of the poorer treatment outcome. However, a randomized trial has never been performed. It is hard to make an appropriate comparison between surgery and radiotherapy, because the patients selected for radiotherapy usually had more advanced tumors at diagnosis, were older and in worse condition than the patients selected for surgery. Besides, until recently, hardly any studies have been done on implementation of more advanced treatment techniques for bladder cancer. This might have been caused by the poor reputation of radiotherapy for bladder cancer, or by the small patient population.

In 2003 the first study describing a concomitant boost technique for bladder cancer was published [24]. Instead of irradiating the whole bladder to a dose of 60 Gy in fractions of 2 Gy, the small pelvis was irradiated with a dose of 40 Gy in 20 fractions and the tumor received a concomitant boost of 15 Gy. In this case the patient was asked to have a full bladder during treatment, in order to keep the healthy part of the bladder out of the high-dose area. Because of the large day-to-day variation of the bladder volume, the position of the tumor could be displaced with respect to the planning situation, so a margin of 1.5 – 2 cm had to be used around the tumor.

In order to decrease the high-dose area, an adaptive margin strategy was studied [25]. During the first five treatment days a CT was made right before or after treatment. A new summated gross tumor volume (GTV_{SUM}) was constructed that encompassed the GTVs of all five repeat CTs and the planning CT. The margin from the GTV to the planning target volume (PTV) was 1 cm. This resulted in a PTV that was on average 40% smaller than when a margin of 2 cm was used around the GTV of the planning CT and it resulted in less target misses.

In theory, the use of IGRT can be very beneficial for bladder cancer patients, because the tumor is very mobile and the margins are large. By determining the position of the tumor and adapting the position of the patient to it, the tumor can be irradiated more accurately. This means that the margins can be reduced and the amount of irradiated healthy tissue can be decreased. However, bladder tumors are hardly visible on CT and CBCT, because the bulk of the tumor is already removed with transurethral resection. Previous studies show that markers can be inserted around the tumor during cystoscopy, in order to determine the position of the tumor more accurately on CT [26,27]. These markers are also visible on CBCT. A major drawback of these markers is that most of them are lost in the first weeks after placement. A more recent development is the injection of small amounts of a contrast fluid, lipiodol, around the tumor [28]. There is some washout, but all spots remain visible throughout the whole radiotherapy treatment course. Lipiodol is visible on CBCT, which makes it suitable for on-line position verification and correction.

1.3.2 Lung cancer

In the year 2008, 10776 cases of lung cancer were diagnosed in the Netherlands (www.ikcnet.nl). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung tumors. Less than 20% of the patients present with stage I disease (www.ikcnet.nl).

Surgery is the standard treatment for stage I NSCLC tumors, with a 5-year overall survival of approximately 70%. The surgical treatment causes a high morbidity and mortality. In a recent clinical trial 1.4% of the patients died during surgery and 38% of the patients presented with one or more complications [29].

For patients who are unfit or unwilling to undergo surgery, radiotherapy is the alternative treatment. With conventional radiotherapy, the 3-year and 5-year overall survival are only 34% and 21%, respectively [30]. However, the technical developments of the last years have led to the introduction of stereotactic body radiotherapy (SBRT) for stage I NSCLC tumors. Stereotactic radiotherapy was developed in the 1950's for intracranial tumors [31]. It is a high precision technique that is characterized by a high biological dose in a small number of fractions. To prevent healthy tissue from receiving this high dose, a very tight dose distribution is planned. Good reproducible patient set-up and position verification techniques are essential for preventing target miss. For intracranial tumors the reproducibility of the patient set-up was guaranteed by fixing the skull in a stereotactic frame. This frame was fixed to the treatment table.

The introduction of SBRT for stage I NSCLC tumors was driven by the development of the CBCT. Because lung tumors are very well visible on CBCT, they are suitable for on-line position verification and correction (figure 1.5). Therefore, they can be irradiated very precisely. The first studies that used SBRT for lung tumors yielded a local control as high as 85-90% [32,33]. Most of the patients selected for these studies were patients who were unfit for surgery, which causes a selection bias. A sub-analysis of 100 patients who had declined surgery yielded a 5-year overall survival of 70.8% [33]. This is comparable to surgery.

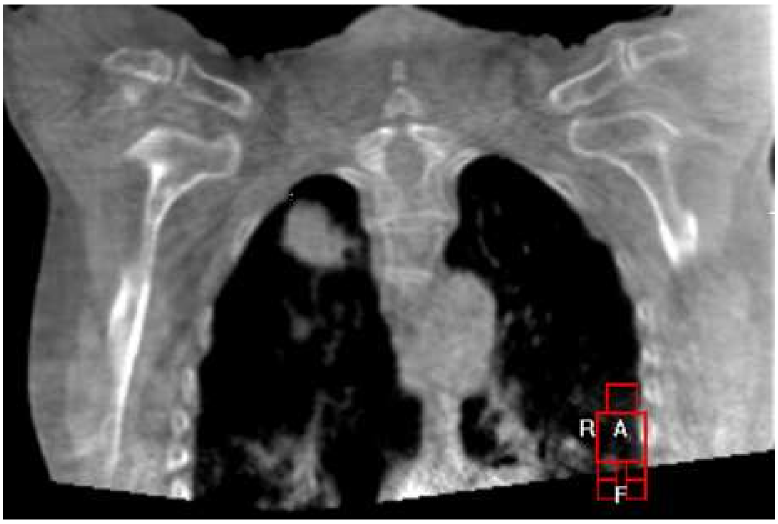

Figure 1.5: A coronal view of the CBCT of a lung cancer patient.

A problem of SBRT for NSCLC patients is the day-to-day variation of the time-averaged position of the tumor with respect to the bony anatomy. This is called the baseline shift [34,35]. CBCT is used to correct the position of the patient in order to position the tumor in the center of the beams. A consequence of the baseline shift may be that the tumor has moved towards an organ at risk, which can cause a higher dose in the OAR than planned. Because of the high fraction dose, this might lead to serious complications, even if it happens only in a single fraction. Underberg has shown that an isocenter shift of more than 5 mm occurs in around 25% of the patients in the first two treatment weeks [36]. An isocenter shift of more than 1 cm occurred in 2 out of 36 patients in this study.

1.4 Outline of this thesis

The goal of this thesis is to apply the newly developed IMRT and IGRT techniques described in paragraph 1.2 to improve radiotherapy. This thesis will describe multiple studies. The first part is dedicated to the application of advanced techniques for bladder cancer patients who receive radiotherapy. The first aim of this part was to use IMRT to decrease the dose in the OARs, while maintaining the dose in the target. The second aim of this part was to find the effect of on-line position correction on the dose distribution for bladder cancer patients. The aim of the second part of this thesis is to make on-line dose recalculation possible and to determine the potential benefits.

In chapter 2 the difference between IMRT and the standard planning technique at the time of this study, a concomitant boost technique, was investigated. At that time IMRT was already in use for several target areas, but for bladder irradiation the conventional approach was still used. The goal of this study was to reduce the dose to the organs at risk while maintaining the target dose.

As described earlier, the day-to-day variation of the position of bladder tumors is up to several centimeters. Chapter 3 describes a study that determines the effect of on-line position correction on the dose distribution. This study investigates how this effect can be predicted and handled.

In the Academic Medical Center, bladder cancer patients are treated with a dose of 40 Gy to the pelvic lymph nodes and the whole bladder, while an additional boost is given to the tumor. The movement of the lymph nodes is not related to the displacement of the tumor, so position correction based on the tumor position might result in missing a part of the lymph nodes. In chapter 4 the effects of separate position correction for the elective plan and the boost plan are studied.

In image-guided radiotherapy the set-up errors of the patient are determined and corrected, but this gives no information about changes in the dose distribution due to a change in the patient's geometry. In principle, this could be calculated on the CBCT. Because of the poor image quality of CBCT, the grey values cannot be directly related to relative electron density. In chapter 5 we perform a validation study on the use of CBCT for dose calculation for lung tumors.

In order to perform a dose calculation on CBCT a body contour is necessary. The standard algorithms for segmentation of body contours on CT fail for the CBCT, while manual delineation is too time consuming. In chapter 6 we present a method for automatic segmentation of body contours on CBCT.

An extensive position verification protocol using CBCT is performed for patients with NSCLC who are treated with a stereotactic treatment. In chapter 7 the potential benefit of on-line dose calculation on CBCT was investigated by retrospectively analyzing the dose distribution before and after position correction on the CBCT scans of the first ten patients that were treated with stereotactic irradiation.

In chapter 8 the results are discussed and some directions for future research are given. Chapter 9 is a summary of this thesis.