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Improving radiation dose delivery for moving targets using image guidance

Rooijen, D.C. van

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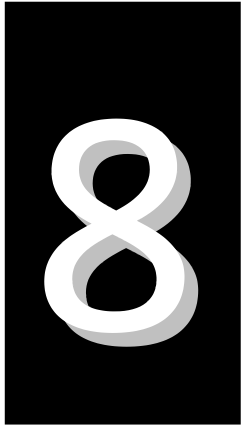
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Discussion and future directions

The general aim of this thesis was to apply intensity modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) techniques in order to improve the treatment of specific tumors. The first part of this thesis was dedicated to using IMRT to decrease the dose in the organs at risk while maintaining the dose in the target areas for bladder cancer patients and to finding the effect of on-line position correction on the dose distribution. The second part was dedicated to enabling dose calculation on cone-beam CT (CBCT) for early-stage non-small cell lung cancer (NSCLC) patients who were treated with a stereotactic treatment and evaluation of the results. In this chapter the results and the recent developments that may lead to future improvements will be discussed.

8.1 IMRT for bladder cancer

The organs at risk for radiotherapy treatment of bladder cancer are the small bowel, the rectum and the healthy part of the bladder. We succeeded in reducing the dose in the small bowel and the rectum by using IMRT (chapter 2). The largest benefit was seen in the small bowel, which is the organ in the pelvis that is most sensitive to radiation damage. Another result was that the pelvic lymph nodes had a statistically significant better coverage with IMRT than with the field-in-field (FiF) technique. The lymph nodes were underdosed in all patients when planned with FiF technique. However, the improved coverage of the lymph nodes is not directly a result of IMRT, but of the necessity to delineate the structure for the inverse planning procedure. With the FiF technique the pelvic lymph nodes were irradiated with a four-field box technique. The sizes of those fields were determined by landmarks of the bony anatomy. Apparently, this induces target miss.

The use of elective fields for pelvic lymph nodes is still a matter of debate. There are no reports on randomised trials that have studied the effect of irradiating the lymph nodes of bladder cancer patients. However, several cystectomy studies have shown that the treatment outcome is positively correlated with the number of lymph nodes removed during surgery [51-53]. A reason not to include the pelvic lymph nodes in the radiation field is the increased field size and with that an increased risk of complications, mainly for the small bowel. The target miss when the radiation field is based on the bony landmarks might explain why a benefit of the pelvic lymph nodes has never been proven. This statement would be very hard to prove, because the population of patients with bladder cancer treated with radiotherapy is rather small for a randomized trial. However, we would recommend following the patients who are treated with IMRT for the pelvic lymph nodes carefully. For the prostate was shown that irradiation of the pelvic lymph nodes

improves progression free survival [97]. Analysis of a subgroup has shown that larger field sizes yield a higher survival rate, but also increased toxicity [98].

Many studies about the clinical effects of IMRT have been published, both randomized trials as well as retrospective analyses. In 2010 Staffurth has published a review that provides an overview of these studies [99]. The studies included in this review showed, without exception, that the risk of complications after radiotherapy reduces when patients are treated with IMRT. For irradiation of bladder tumors the clinical benefit of IMRT has not been shown so far. However, for prostate treatment that included the pelvic lymph nodes it was proven that IMRT led to a reduced risk of complications [100]. In this study a correlation was shown between the volume of the small intestines that received 20-50 Gy and the risk of complications. Other studies, all concerning prostate cancer patients, have also shown that the risk on complications of the small intestines decreased when IMRT was used to irradiate the pelvic lymph nodes [50,101-103]. Because our dosimetrical comparison shows that the dose in the small intestines decreases when IMRT is used, it is reasonable to assume that the risk of complications will also decrease. In this case it might be unethical to perform a clinical randomized trial, which involves patients being treated with the old technique instead of treating all patients with IMRT. A retrospective analysis would still be interesting.

Instead of using IMRT to reduce the risk of complications, IMRT can also be used for increasing the dose in the target, without increasing the risk on complications. For the prostate this has already been applied [104,105]. Both studies show that a high dose, above 80 Gy, is very well tolerated when IMRT is used. Alicikus *et al.* show excellent long-term tumor control, with a 10 year cause-specific mortality rate of 0%, 3% and 14% for the low-, intermediate- and high-risk group, respectively [104]. Dolezel *et al.* do not report survival rates, probably because their follow-up is not long enough [105]. For bladder cancer it has not yet been shown that a higher dose would lead to better treatment outcome in terms of a higher survival rate. The current survival rate of 14-45% at 5 years suggests that there is room for improvement [23].

8.2 *Position variation of bladder tumors and dose*

The day-to-day variation of the position of a bladder tumor can be as large as 2 cm. When the tumor is repositioned in the center of the beams, by applying on-line position correction, some beams pass more tissue and experience more attenuation than planned and others less. The effect on the dose distribution of this changed attenuation was

studied in this thesis. When only the boost was considered, the dose in the target would still be 91.9% in the worst case scenario. However, this was with a treatment plan without a margin and based on the population statistics the probability that this scenario would actually occur is very small (chapter 3). When a CTV-PTV margin of 2 mm was added, the probability of an underdosage was reduced to $< 0.001\%$. Tomé and Fowler found in a modelling study that an underdosage in a subvolume as small as 1% of the volume of the tumor can already decrease the tumor control probability (TCP) [63]. However, this TCP decrease was apparent only if the dose in that subvolume was more than 10% lower than the prescribed dose. With a minimal $D_{99\%}$ of 91.9% a decrease in TCP is not likely in our study and therefore we do not recommend increase of the margin because of this effect.

When the pelvic lymph nodes are irradiated as well, two target volumes have to be considered, each with its own prescription dose: the tumor and the elective volume. The position of the tumor can move with respect to the elective volume. To cope with this one should either increase the CTV-PTV margins or one should apply position correction for each target individually. The latter solution requires that separate treatment plans are created for both target areas. The effect of independently shifting the two plans on the cumulative dose distribution was studied in this thesis. An advantage of making two plans and applying both position corrections separately is that the margin for each target can be minimized individually. A disadvantage is that the treatment time increases when two separate registrations and two table corrections have to be executed. However, when automatic registration algorithms and a robotic couch are used, this increase in treatment time will be minimal. When such technologies are not available one has to keep in mind that during the position verification procedure the bladder keeps filling, causing internal displacements. This additional uncertainty, however, might be compensated by the increase in accuracy of the treatment.

Based on the target coverages that are shown in the simulations in the chapters 3 and 4 of this thesis, the margin could be greatly reduced when on-line position correction is applied. However, the margins are not only meant for covering set-up errors and interfraction movement, but also for all other uncertainties that occur in the radiotherapy treatment chain that were not included in the simulation, for example the delineation uncertainty and intrafraction motion. Engels *et al.* have already shown an increased biochemical failure in patients treated for prostate cancer who had a distended rectum, even with on-line position verification and correction [66]. They state that the use of IGRT gave them a false confidence. Afterwards they calculated that the margin, based on the intrafraction motion of the prostate, should have been larger. Before the IGRT era, set-up errors and interfraction motion were the dominant sources of uncertainties. Now that

they are reduced by the implementation of IGRT, it is important to pay attention to the remaining uncertainties.

8.3 Dose recalculation on CBCT for lung tumors

The CBCT is very suitable for position verification during stereotactic body radiotherapy (SBRT) for stage I/II lung cancer patients, because of the good target visibility. A major problem in SBRT for lung tumors is the potential interfraction variation in the time-averaged tumor position relative to the bony anatomy: the baseline shift [34,35]. When a baseline shift of the tumor occurs in the direction of the organs at risk, it is hard to determine whether the tolerance dose of that organ is exceeded. Therefore, it would be convenient to be able to perform an on-line recalculation of the dose using CBCT. In this thesis we have shown how the grey values of the CBCT can be correlated to the relative electron density (chapter 5). We also developed a method for automatic segmentation of the body contour on CBCT, by combining several existing methods in a novel way (chapter 6). Finally, the dose distribution was calculated retrospectively on CBCT scans of 10 NSCLC patients who were treated with a stereotactic treatment, in order to determine whether on-line recalculation and evaluation of the actual dose distribution can improve decision making (chapter 7). We found that recalculation of the dose is the preferred method over estimating the dose by assuming invariant dose distribution. Especially when the set-up error is larger than the ITV-PTV margin or when the shape of the patient has changed.

With on-line dose recalculation and evaluation it is easy to determine whether an organ is at risk or not. When an overdosage does occur one has to decide how to cope with the situation. Currently it is not possible to adapt the treatment plan on-line. An alternative would be to perform the desired position correction partially. Chapter 7 shows that with a set-up error up to 5 mm, which is equal to the ITV-PTV margin we applied, the target is still sufficiently covered and this might be just enough to prevent an overdosage to an OAR. If a partial position correction does not solve the problem, the patient can be asked to stand up and to be repositioned again. There is still little knowledge about how and why the baseline shift occurs, so it is unsure whether this will help. In case this does not help the decision can be made to have the patient come back on another day for the treatment. Ultimately, one can decide to acquire a new planning CT and to create a new plan.

The baseline shift is not the only change that can occur. During the course of the treatment, atelectasis can develop, or atelectasis that is already present can decrease.

With on-line dose evaluation the impact on the dose in the target can be evaluated and one can decide whether replanning is necessary.

8.4 Future directions

8.4.1 Adaptive radiotherapy and on-line plan adaptation

Adaptive radiotherapy (ART) is currently a hot topic. ART usually includes multiple imaging sessions in order to make a patient specific margin and treatment plan, instead of a plan and margins based on the population. The concept of ART was introduced by Yan *et al.* in 1997 [106]. They defined the goal of ART as ‘to incorporate the position variation of the individual patient into the treatment optimization process during the course of radiotherapy’. In practice this means that the variation in tumor position, orientation or shape detected during the first treatment fractions by EPID or CT is used to optimize the treatment for the remaining fractions.

Currently, ART is applied broader than for determining patient specific margins. Another application that is also called ART is the creation of multiple treatment plans: a plan library. Based on the imaging at the start of each treatment fraction is decided which treatment plan to use. This is, among others, applied for the bladder. Foroudi *et al.* describe a procedure that uses the CBCTs of the first five treatments to create three PTVs: small, medium and large [107]. These PTVs are used to create three new adaptive treatment plans. On the remaining treatment days the most suitable of the four plans (the three adaptive plans and the initial plan) is chosen, based on the CBCT of that day. They showed that the target coverage was similar as with conventional planning, but the amount of irradiated healthy tissue was smaller, because the treatment margin with the conventional plan was larger. Lalondrelle *et al.* presented a similar procedure [108]. They created the small, medium and large PTVs based on CT scans made 0, 15 and 30 minutes after voiding the bladder, so they don’t have to wait for five treatment fractions before the adaptive treatment can be started. In 51% of the treatment fractions presented in this study, the target coverage was below 95% without adaptive plans, which means that the smallest PTV was used. However, 73% of the fractions would be sufficiently covered with one of the adaptive plans, but the remaining 27% would still be covered insufficiently. This implies that the plan library should consist of more than three plans.

In the studies described above, the whole bladder is the target. A plan library and on-line plan selection can be very beneficial for a target that might change in volume. For a relatively rigid target on-line position correction should be sufficient. In our situation we

could use on-line position correction for the boost, but we would have to create a plan library for the elective field, which contains the remaining part of the bladder.

The method of ART with a plan library has a few drawbacks. The first is the increased workload. All steps of the preparation phase of the treatment have to be done multiple times: acquisition of the scan, delineation of the structures and creation of a treatment plan. Also, it requires some training to pick the correct plan from the plan library. Taylor *et al.* have shown that the concordance with the 'golden standard', i.e. the selection of the physician, is 76 % without training, while the concordance is 92% after training [109]. Most drawbacks can be overcome when parts of the process can be automated. This makes implementation of using a plan library on a larger scale feasible.

When a plan library is created, it is always uncertain whether these extra plans are necessary. Lalondrelle *et al.* have shown that the additional plans were not used in 5 out of 15 patients [108]. They also showed that in 27% of the cases where an adaptive plan was required, none of the plans was sufficient. With a dose calculation on CBCT as described in chapter 5 it becomes possible to recalculate the plan on-line and adapt it when necessary. One possibility would be to adapt the position of the MLCs, so that the leaves enclose the target again. Other options would be to change beam angles or beam weights. However, this option would only work for relatively simple treatment plans, but not for a complicated technique such as IMRT.

In two studies the feasibility of on-line plan adaptation is investigated [101,110]. Ahunbay *et al.* show a procedure making an adapted plan in ten minutes, including the delineating [101]. However, the time span of ten minutes is probably too long to ensure that the patient position has not changed within that time. Mestrovic *et al.* use a completely different approach [110]. They reconstruct partial CBCTs, using only the projections between two successive treatment angles and based on that they adapt the treatment plan before each beam. However, this proof of principle was based on a digital phantom. For most targets it is not realistic that the quality of a CBCT that is reconstructed only from the projections between two treatment angles is sufficient for automatic target delineation. Even when these concerns are solved, there are some other obstacles. In the normal workflow, there are a number of quality assurance procedures to detect possible errors before a plan is actually irradiated. If the treatment plan is adapted on-line, there is no time to go through these procedures. Hence, new quality assurance procedures and tools have to be developed to ensure the quality of the procedure and to prevent human errors.

An adaptive strategy is probably not beneficial for early stage NSCLC patients who are treated with a stereotactic treatment. The treatment consists of a small number of fractions and therefore it is not feasible to make a patient-specific margin. Because of the short treatment time it is unlikely that tumor regression occurs between the first and last fraction. When a large change in lung tissue is seen, for example development of atelectasis, it is mandatory to take action. This happens in only a small fraction of the patients and therefore this can be an ad-hoc decision.

8.4.2 Dose evaluations, accumulations and complications

For patients who survive cancer the quality of life after treatment is a very important aspect. Quality of life is highly correlated to complications as a result of toxicity of the treatment. Toxicity is discriminated in two categories: acute and late toxicity. Acute toxicity occurs right after or during treatment and is reversible in most occasions. Late toxicity occurs later and is usually more permanent. The late toxicity affects quality of life most.

The risk on complications can be estimated based on the DVH using the normal tissue complication probability (NTCP) [111]. Parameters that are used to describe the risk of complications are the tolerance dose (TD) $TD_{5/5}$ (5% complication risk within 5 years after radiotherapy) or $TD_{50/5}$ (50% complication risk within 5 years after radiotherapy). The normal tissue tolerance doses are defined for organs uniformly irradiated for 1/3 and 2/3 of the volume and the whole volume. Known data are in general based on conventional fractionation schedules of 1.8 – 2.0 Gy/fraction and five fractions a week. In 2005 Kehwar made an overview of all published data on NTCP [47]. Most data are obtained by Emami *et al.* in 1991 [112] and it was supplemented with results of other studies. Kehwar states that 'survey of the literature reveals that there is a wide scattering in the normal tissue tolerance doses and no consensus on the issue among the radiation oncology community' [47].

Most data considering normal tissue tolerance doses were collected before the IGRT and IMRT era and some data are based on 2D dose calculations [112]. Because the human body is very dynamic, which was not corrected for at the time, the DVHs that were planned were probably quite different from the dose actually delivered in the healthy tissue. Besides, $TD_{5/5}$ and $TD_{50/5}$ are defined in uniformly irradiated volumes, while the dose outside the target is not uniform with modern irradiation techniques. Nevertheless, the 20-year-old data from Emami are still used as a guideline.

With the current position verification and correction techniques the actually delivered dose shall be much closer to the planned dose than 20 years ago. Moreover, the same position verification tools can be used to determine the deviations with respect to the treatment planning situation. The dose of the day can be calculated on the CBCT (chapter 5 and 7). Deformable image registration can be used to determine the corresponding points on the CBCTs and the planning CT and this information can be used to accumulate the dose. When the actually received dose is known and the patients are followed for several years, new models can be made that are probably more accurate.

8.4.3 Reducing treatment time using VMAT

Volumetric modulated arc therapy (VMAT) is a new delivery technique that has gained popularity in the last couple of years. VMAT is an arc technique, which means that the patient is not irradiated with a predetermined number of static beams, but that the gantry rotates with the beam on. With VMAT, the field shape, dose rate and gantry speed can be varied during this rotation [113]. The dose distribution produced with VMAT is comparable, or sometimes better, than with IMRT. The main advantage compared to IMRT is the gain in speed of the treatment. IMRT usually includes a number of small fields and is therefore associated with a high number of monitor units. Moreover, with a conventional or IMRT treatment, the gantry also has to rotate between the different treatment angles. With VMAT, the beam is on during the rotation. These two effects together accomplish a large reduction in treatment time. Several studies have compared VMAT with IMRT. The treatment time for targets in the pelvic area (prostate, anus, rectum and cervix) when VMAT is used is on average 20-40% of the treatment time of an IMRT plan [114]. The reduction in treatment time depends both on the number of beams of the IMRT plans and on the number of arcs in the VMAT plans that are compared. McGrath *et al.* show that VMAT reduces the treatment time for SBRT for NSCLC patients by 37-63% compared with 3DCRT [115].

The gain of several minutes per patient is not only beneficial from an economic point of view, but it also increases the accuracy of the treatment. Because of the high fraction dose, the irradiation time of a stereotactic treatment for NSCLC patients is relatively long. Because of this long treatment time, the protocol in our department is to acquire a CBCT halfway during treatment, in order to check whether the patient has not moved. When the treatment time is approximately halved by introducing VMAT, the scan halfway during treatment is unnecessary, saving even more time. In bladder cancer patients one of the uncertainties of the treatment is the bladder filling that occurs during treatment. With a reduced treatment time, this uncertainty will also be reduced. However, the increased

complexity of the treatment plan results in a higher calculation time, when calculating the dose distribution. With current computer speed, the dose calculation of a VMAT plan is too time-consuming for on-line recalculation of the dose distribution.

8.4.4 Improving treatment using pre-treatment imaging

Daily position verification solves a large part of the uncertainty of the tumor position. Together with an improved dose distribution this improves the treatment, i.e. the survival probability increases and the complication rate decreases. However, delineation uncertainty is one of the uncertainties that remains to be solved. On CT it is often hard to discriminate between the tumor and the healthy tissue and it is impossible to determine the microscopic extension. The margin that is used for microscopic extension is based on pathological studies and statistics, which results in a margin that is too small for some patients and too large for others. The interobserver variation between the radiation oncologists, when asked to define the same target on the same scan, is large. When magnetic resonance imaging (MRI) is used for delineation of the prostate, the interobserver variation is reduced significantly [116,117]. Compared to CT, MRI has a superior soft tissue contrast and therefore the use of MRI has increased over the last years. A combination of MRI with a linear accelerator is currently under development [118]. This leads to new applications for radiotherapy [119].

Positron emission tomography (PET) is a well known example of molecular imaging. The tracer that is most commonly used for PET scans for oncological purposes is glucose which is labelled with a radioactive isotope: [¹⁸F]-fluorodeoxyglucose (FDG). Tumor cells have a high glucose metabolism and therefore the FDG will accumulate in the tumor. The PET scanner detects the gamma rays that are emitted by the FDG. When the information of PET imaging is combined with the CT information, the delineation variation between observers decreases compared to delineation based on CT alone [120]. A disadvantage of FDG is that it is not tumor specific. All cells in the body use glucose and an area with a high glucose concentration can also indicate an inflammation. Besides FDG there are quite a lot of other tracers that are potentially suitable for oncological imaging [121]. There are tracers to detect different processes, for example DNA synthesis, lipid synthesis, hypoxia and angiogenesis.

The developments in the field of PET tracers are beyond the scope of this thesis. However, when the development of these tracers improves tumor definition or even determination of the activity in different parts of the tumor, this will trigger a new range of

developments in radiotherapy, for example dose painting, which is defined as the prescription of a non-uniform radiation dose distribution to the target [122].

8.5 Conclusion

In this thesis we have applied IMRT and IGRT in order to improve radiotherapy for bladder tumors and lung tumors. The application of IMRT for bladder cancer reduces the dose in the organs at risk, especially the small intestines (chapter 2). Simulations have shown that it is safe to implement on-line position verification, even when set-up errors as large as 2 cm occur, and that it is possible to apply separate correction protocols for the tumor and for the elective volume (chapters 3 and 4). We have also shown that it is possible to calculate a dose distribution for NSCLC patients on CBCT (chapters 5, 6 and 7). This technology can be used for on-line recalculation of the dose distribution. Recent and future developments, such as VMAT and improved target definition, can improve the radiotherapy treatment even further.