Clinical implementation of high precision radiotherapy for urogenital tumours

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Chapter 9

General discussion and future perspectives
Improvement of radiotherapy treatments

The aim of curative external beam therapy is to deliver a dose distribution to the patient, which results in an optimal clinical outcome in terms of tumor control and toxicity to healthy tissue. The best outcome is expected when the tumor cells are irradiated to a high dose while simultaneously the surrounding healthy tissue receives no dose at all. Unfortunately, such a dose distribution cannot be delivered due to two major restrictions. Firstly, we don’t know the exact shape and location of the tumor. Even if we would know the geometry of the tumor in the treatment preparation phase, due to organ motion the position and shape of the tumor may be different in the treatment delivery phase. Secondly, if we would know the exact tumor location in the treatment delivery phase, we are still not able to deliver a high dose to the tumor and zero dose elsewhere in the body due to technological restrictions and due to the physical laws that govern the energy deposition of photon (or electron) beams. This means that in practice we aim at a delivery of a physically and technically feasible dose distribution to a patient that yields the highest probability of a complication free tumor control. In the process of improving the 3D dose distribution delivered to the patient, we are often guided by the

Figure 9-1: Schematic drawing of the links involved in the improvement of radiotherapy treatments. The dashed boxes point out the relationship between the various chapters in this thesis and the corresponding processes of improvement.
Chapter 9

results of clinical studies, technological developments, progress in radiobiological understanding and new insights in the shape and position of both targets and organs at risk (Fig. 9-1).

Dose escalation studies and randomized trials lead us to refined dose prescriptions. Modern imaging techniques like CT, MR and PET contribute to a more accurate delineation of the tumor volume. Immobilization devices and portal imaging protocols allow smaller volumes to be irradiated to a high dose, while maintaining the local control probability. The introduction of 3D conformal radiation therapy and intensity modulated radiotherapy (IMRT) made it possible to increasingly spare healthy tissues.

**Improvement of treatment planning of prostate cancer**

A higher dose to the target seems to improve the outcome of external beam radiotherapy of prostate cancer (1-3). This, however, leads in general to a higher normal tissue dose and an increased risk of complications. At present, radiation induced rectal complications are the dose-limiting factor. To allow for a safe dose escalation, radiation induced rectal complications in relation to the received dose distribution need to be analyzed. The most common way to assess this relationship is by means of dose-volume histograms of the rectal wall. Chapter 4 describes a mathematical model for the rectal wall incorporating the stretching of the rectal wall due to variable rectal filling and neighboring structures. The main objective of the model is to determine the thickness of the rectal wall in each wall element or to obtain the inner surface of the rectal wall from the outer surface. The wall volume in between the two surfaces can be used as input for the DVH of the rectal wall. Parameters extracted from the DVH, such as volume points at certain dose levels, the mean dose, the Equivalent Uniform Dose (EUD) (4,5), or some form of Normal Tissue Complication Probability (NTCP), are commonly used to model and predict rectal complications (6-8). A fundamental restriction of this approach is that the spatial information of the dose distribution in relation to the 3D anatomy of the rectal wall is lost. This implies that two identical DVHs originating from two different dose distributions yield identical NTCP values, whereas in reality the rectal damage may not necessarily be the same because the spatial distribution of the dose over the rectal wall is different.

The concept of a dose map, developed by Hoogeman et al., condenses the 3D dose distribution and the 3D anatomy onto the 2D map while preserving the spatial information (9). In short a dose map is constructed as follows. Firstly, the rectal wall (and the dose distribution 'plotted' on the rectal wall) is straightened and smoothened using the model described in chapter 4, until a cylinder is developed. Secondly, the cylindrical rectal wall is opened on the dorsal side. In the third and final step the rectal wall and its dose distribution are unfolded to a rectangular dose map (Fig. 9-2).
General discussion

Starting from the model described in chapter 4 this means that cell density is uniform over the complete dose map. The advantage of this geometrical reconstruction is that, in principle, the same rectal tissue is projected on the same map position irrespective of rectal volume differences. This means that, unlike DVHs, dose maps of different CT scans of the same patient can be added. Preliminary results of a study of 266 prostate patients irradiated with a dose of 66 Gy have shown a correlation between percentage of the superior part of the rectum that receives a dose higher than 60 Gy and rectal bleeding, whereas no dose-response relationship for rectal bleeding was found for the inferior part of the rectum (10). This illustrates that dose maps are useful to study localized dose-effect relationships, although the true potential of dose maps presumably manifests in the analysis of rectal complaints of a population of prostate patients irradiated to higher prescribed doses (e.g. 78 Gy).

Improvement of treatment planning of bladder cancer

Radiotherapy is the primary treatment modality for bladder cancer in patients not fit for radical cystectomy. The aim of conformal radiotherapy is to irradiate the clinical target volume (i.e. bladder wall) expanded with a margin to account for geometrical uncertainties. In chapter 3 of this thesis, all geometrical uncertainties involved in the irradiation process of bladder cancer were assessed and based on the uncertainties, an estimate of an appropriate margin was established. It turned out that, in order to assure adequate dose coverage, a margin of about 2.5 cm is needed at the cranial side of the CTV. Similar findings on bladder margins have recently been reported by Muren et al. (11). This margin is predominantly due to organ motion of the bladder and cannot be diminished by a setup correction protocol. If we apply the margins as derived in chapter 3 to a CTV of 65 cm³, then this yields a PTV of approximately 400 cm³. This of course limits the feasibility of high precision techniques such as intensity-modulated radiotherapy. For this reason, dose escalation to improve outcome is hardly possible. So the task is to minimize the uncertainty in the position of the bladder during the delivery of external beam radiotherapy. Portal imaging can be utilized to measure organ motion by means of the detection of radio-opaque markers, implanted in or near the target volume. Balter et al. (12) studied the use of radio-opaque markers implanted around the prostate for 10 prostate cancer patients. Transformations in terms of translations and rotations were detected in 70% of all cases. The same authors have used implanted markers to perform online repositioning of the patients. In a similar study for bladder and prostate cancer patients Shimizu et al. (13) implanted gold markers in or near the clinical target volume. Using two sets of diagnostic X-ray television systems in the linear accelerator room, the patient position was corrected by shifting the actual
position of the gold marker to the planned marker position. One of the remaining problems of using radio-opaque markers is the failure to detect organ shape changes. For the prostate gland this may not be too serious because its position and shape can be reasonably well described by translations and rotations with respect to the apex (14). However, bladder shape changes are much more extensive, and the relation between the markers and the tumor may be ill-defined (13). Furthermore, it is difficult to implant markers in the thin bladder wall. Also the flexibility of the bladder wall causes these markers to drift or get loose. However, the recent development of cone beam CT integrated with a linear accelerator has the potential of visualizing soft tissues on the treatment table (15,16). This offers the possibility to improve the localization of the bladder during radiotherapy thereby allowing safe dose escalation.

Another and possibly superior way of visualizing soft tissues on the treatment table may be established by integrating a MR system with a linear accelerator (17). Even though current feasibility studies show optimistic results, it takes several years before a clinical prototype of such a machine will be available. In any case, manual delineation of the bladder in the CT or MR scans is a time consuming task and computer algorithms are needed to reliably estimate the size, shape and position of the bladder, for example by the use of region growing techniques. Both cone-beam CT or MR-guided radiotherapy, combined with on- or off-line correction protocols, allow substantial improvement of localization of the bladder and therefore margins smaller than 1 cm could possibly be applied, allowing safe dose escalation.
Quality control of medical accelerators to improve dose delivery

In order to derive the optimal dose distribution from clinical studies, it is of great importance that the actual dose distribution delivered to the patient is in agreement with the intended planned dose distribution. The implementation of an intensive quality control (QC) programme plays a crucial role in establishing good agreement between planned and delivered dose distribution. Chapter 6 describes the results of a project aiming at the achievement of consensus in the different QC programmes in The Netherlands. A set of minimum requirements was formulated for linear accelerators, containing more than 30 test procedures including test frequencies and action levels. The implementation of the requirements in the radiotherapy institutions lead to an average increment in test frequencies of about 8 tests with a maximum of 17 but did often not require much increase of the total amount of time spent on QC. As a consequence, the large variation in test frequencies and test parameters decreased in time which in turn may have improved the quality of the irradiation process on a national scale.

The project did not focus on QC of multileaf collimators (MLCs), since at the time of the investigation only very few linear accelerators were equipped with MLCs. Hounsfield and Jordan (18) and Mubata et al. (19) suggest that standard use of the MLC only adds an extra half an hour of QC time per accelerator. These QC procedures are mainly related to the positional accuracy of the leaves and their relationship to the back-up collimators, leakage considerations, the relationship of X-ray to light field and the influence of gravity on the positioning and leakage characteristics of the leaves. These tests are therefore of main importance for segmented (IMRT) MLC dose deliveries.

More extensive QC procedures are required when dynamic MLC dose deliveries are implemented. Chui et al. (20) describe a routine QC test for leaf position accuracy in which the leaves move dynamically and then stop to form 1-mm slits at a series of different positions; any variation in slit width indicates a position error. They also describe measurements of stability of leaf speed, leaf acceleration and deceleration and leaf position accuracy both for commissioning or occasional use. LoSasso et al. (21) and Budgell et al. (22) suggest using periodic ionisation chamber measurements of a moving 5 mm or 10 mm slit to verify the leaf positioning. The delivered dose is very sensitive to leaf position accuracy; a 1-mm change in slit width leads to a 10% change in dose. A more sophisticated approach to verify all leaf positions during dynamic multileaf collimation is described by Vieira et al. (23). They developed a two-dimensional method for daily leaf verification using an electronic portal imaging device (EPID). Deviations in a 0.5-cm wide sliding gap width are detected as deviations in gray scale value profiles derived from EPID images. Local experience is needed to decide which of these, or other
tests, is most suitable for a specific institution, and what will be an action level and test frequency. However, since all these tests are neither complicated nor time-consuming it seems likely that a set of tests can be implemented without much workload, which enables the routine clinical use of dynamic MLC.

The role of in vivo dosimetry to improve high precision treatments of prostate cancer

In vivo dosimetry in clinical practice

In vivo dosimetry has been used for several years to assess the uncertainty in dose delivery during the treatment of patients. Different methods and philosophies are applied as discussed for instance in an extensive overview of the current practice of patient dose verification presented by Essers and Mijnheer (24). Chapter 7 and Chapter 8 describe the results of an accurate in vivo dosimetry protocol as part of a quality assurance programme for prostate patients irradiated to a high dose. For each patient, diode measurements are performed during two irradiation fractions at the beginning of the treatment, which is sufficient considering the good reproducibility of the measurements. Due to the high accuracy, we were able to maintain a narrow action level of 2.5%. Experience with measurements performed at more than 500 patients revealed that the measurements were very reliable and, if necessary, the number of monitor units was adjusted even if no explanation could be found for the deviation. During the first few years, a number of systematic dosimetric errors were traced by in vivo dosimetry measurements. These errors were successively restored and consequently, the amount of newly observed errors decreased with time. Hence, the in vivo dosimetry results remained stable in the latter period, making it possible to trace minor imperfections, smaller than 1%, in the dosimetry chain using statistical analysis of the results. This observation has previously not been described in the literature on in vivo dosimetry. Measurements at 8 patients out of 225 patients (3.5%), exceeded the action level of 2.5% but none of the dose measurements showed a deviation larger than 5%. Based on these findings, it is now argued whether it still is necessary to perform in vivo dose measurements at each prostate patient, as long as all the links in the treatment chain remain unaltered. Such a decision is even more justified if we consider that all patients found outside the action level in the study described in Chapter 8 were characterized by unusual dense femoral heads. Prolonged experience over many years with in vivo dosimetry protocols has improved the quality of the treatment process in such a manner, that dose deviations larger than 2.5% only occur for a small subpopulation, which can easily be identified prior to the treatment. Consequently, one may suggest to maintain
the in vivo dosimetry protocol for a selected group of patients (in our case, patients with dense femoral heads) to identify dose discrepancies over 2.5%. In addition, in vivo dosimetry for a random sample of the remaining population is still useful to detect possible time trends in the future.

**In vivo dosimetry during IMRT**

The use of IMRT has been shown to enable the delivery of highly conformal dose distributions. Verification of IMRT treatments is required because of the special delivery conditions of IMRT (e.g. small off-axis fields, moving jaws). The first approach to verifying IMRT treatments was to deliver the patient-optimized intensity modulated beams to anthropomorphic or simple geometric phantoms and to measure the resultant dose distribution using film (25,26). The measured dose distribution is then compared with distribution of the patient-optimized beams and recalculated using the particular patient’s geometry. In this way the dose delivery can be verified at relevant points, along lines or in planes of importance for the correct performance of an IMRT technique. By combining the information in a set of films, in combination with ionisation chamber measurements for the determination of the absolute dose, it is even possible to get an approximate verification of the three-dimensional (3D) dose delivery in that particular phantom. The use of electronic portal imaging devices (EPIDs) is also of interest for IMRT verification. Studies of the basic dosimetric performance of EPIDs have been presented for liquid-filled ionisation chamber-based (27,28), camera-based (29,30) and amorphous silicon flat-panel (31,32) systems. A number of groups reported on pre-treatment verification of small static and dynamic IMRT fields (33-37), but the use of EPIDs for in vivo dose verification is still in an experimental phase. The use of liquid-filled ionisation chamber-based EPIDs is not very attractive for this purpose, because it is not an integrating dosimeter and furthermore relatively long acquisition times are required. Also in vivo dosimetric verification with camera-based systems has not yet been reported, probably because of the more complicated algorithms required for deriving the patient dose from the EPID response for small fields. Due to the improved characteristics, the use of amorphous silicon type of EPIDs has been proposed for IMRT verification. Partridge et al. (38) described a method where they converted the measured fluence of a multiple segment field into the primary fluence at the plane of the amorphous silicon detector. This primary fluence is back-projected through a CT model, with inverse attenuation correction, to yield an input fluence map. The input fluence maps are then used to calculate a reconstructed dose distribution using the same algorithm as for the original planning. In their paper the authors use the actual megavoltage CT data to account for setup errors and organ motion. This extra step is useful for IMRT verification in the head-and-neck region, but for
prostate IMRT verification, this step does not seem to be necessary. The weak element is that the same dose calculation algorithm is used for both the treatment plan and the verification of this plan. Deficiencies in the dose calculation algorithm can therefore not be detected with this method, but in combination with other pre-treatment verification methods (e.g. phantom measurements), this procedure may lead to an accurate dose determination for each individual IMRT treated patient.

**Some radiobiological considerations of in vivo dosimetry**

In this paragraph, biological modeling of the tumor control probability (TCP) is used to estimate the possible effect of in vivo dosimetry on the therapy outcome in terms of local control. For a homogeneous dose distribution the TCP according to the Poisson model of Webb and Nahum (39) as a function of the delivered dose $D_{del}$ is expressed as:

$$TCP(D_{del}) = \frac{1}{\sigma_a \sqrt{2\pi}} \int \exp\left(-\rho \cdot V \cdot \exp(-\alpha' \cdot D_{del})\right) \cdot \exp\left(-\frac{\alpha - \alpha'}{2 \cdot \sigma_a^2}\right) d\alpha', \quad (1)$$

where $\rho$, the clonogenic cell density, $V$, the volume of the tumor, $\alpha$, the effective value of alpha in the LQ model (the quadratic term beta was set to zero) and $\sigma_a$, the standard deviation of $\alpha$. If we assume that the dose delivered to each patient is a random sample from a normal distribution with a mean of the prescribed dose and a standard deviation of $\sigma_{D_{del}}$, then the TCP of a population is expressed as:

$$TCP_{pop}(D_{pc}) = \frac{1}{\sigma_{D_{del}} \sqrt{2\pi}} \int TCP(D_{del}) \cdot \exp\left(-\frac{(D_{pc} - D_{del})^2}{2 \cdot \sigma_{D_{del}}^2}\right) dD_{del} \quad (2)$$

For the TCP computations, we assume that the CTV (prostate plus seminal vesicles) contained tumor with a uniform cell density of $10^7$ cm$^{-3}$, and we use an effective value of $\alpha$ of 0.29 Gy$^{-1}$ with a standard deviation of 0.07 Gy$^{-1}$ over the population of patients as proposed by Sanchez-Nieto and Nahum (40). Figure 9-2 now shows that the TCP calculated for a population of prostate patients is very insensitive for random variations in dose delivery. An uncertainty of approximately 5% (1 SD) in the dose delivery has no effect on the TCP$_{pop}$.

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*The value of $\sigma_a$ will be slightly smaller than 0.07 Gy$^{-1}$ with the introduction of $\sigma_{D_{del}}$, since $\sigma_a$ is derived from clinical dose-effect relationships that do not take into account the uncertainty in dose delivery.*
Figure 9-3: Tumour control probability of a prostate patient population as a function of the prescribed dose with an uncertainty in the delivered dose of $\sigma_\beta=0$ Gy (solid curve) and $\sigma_\beta=3.5$ Gy (dashed curve).

The reason for this finding is that the uncertainty in dose delivery leads to a gain in TCP for the population that receives a higher than average dose and simultaneously leads to a loss in TCP for the population that receives a lower than average dose. Since the TCP curve is approximately linear within each dose domain of 7 Gy (2 SDs), the net effect on the TCP_{pop} is almost zero. Conversely, this means that a reduction of the variation in dose delivery in a randomized trial with two dose levels probably not increases the power of the study. Furthermore, if the aim of the study is restricted to detecting a difference in local relapse probability, then even systematic differences between prescribed and delivered doses do not have an influence on the power of the study, for most dose levels, as long as the difference between the average delivered dose levels is preserved. Since it is most likely that curves representing the normal tissue complication probability (NTCP) of the rectum and bladder can also well be linearly approximated in each dose domain of 7 Gy, (even in the non-linear parts of the curve,) similar results hold for the NTCP_{pop}. After stratification for intrinsic radiosensitivity, reduction of dose uncertainties have an effect for the TCP_{pop}-curves for each cohort of patients, although still limited (Fig. 9-3). Uncertainties in the dose delivery yield a
decrease in TCP\textsubscript{pop} if TCP\textsubscript{pop} is larger than 50\%, whereas an increase can be observed for TCP\textsubscript{pop} values smaller than 50\%.

Consequently, one may conclude that the true merit of an in vivo dosimetry protocol for prostate cancer patients is not to reduce the random errors within a patient group. Although a dosimetric error for a single patient may increase or decrease the TCP for this patient substantially, the overall effect of a random spread in dosimetric errors over a patient population is negligible. The true value of an in vivo dosimetry protocol therefore lies in detecting a systematic deviation between the desired and the actually delivered dose averaged over a patient population, since a systematic deviation yields a different TCP\textsubscript{pop}. Therefore, it is argued that once the random variation in dose delivery is assessed and found to be acceptable and all major sources of systematic deviations were traced and accounted for, one should consider changing the in vivo dosimetry protocol in two ways. First, one could restrict the in vivo dosimetry measurements to randomly assigned patients instead of the whole patient group. The sample size of this randomly assigned patient group depends on random variation and the magnitude of the systematic deviations that one wants to detect in the future. Secondly, one should consider \textit{not} correcting the number of monitor units for a patient in the randomly assigned group that is found to receive a dose outside the action level, because one cannot tell beforehand whether this particular patient benefits from this correction. Furthermore it is not ethical to submit one patient group to a correction protocol and the remaining patients not. Of course questions arise how to respond to an unexpected deviation of for instance 5\%. It seems reasonable to correct this patient and if the cause of the error can be traced, one should check whether the patients that were not in the measured group were subject to a similar error.
Figure 9-4: TCP versus dose after stratification for intrinsic radiosensitivity for 5 homogeneous populations of patients with an uncertainty in dose delivery of 0 Gy and 3.5 Gy (1 SD). As an example, the curves marked ‘10%’ are the hypothetical tumor control curves for a patient population whose radiosensitivity is equal to the 10th percentile of the distribution of radiosensitivities. The steepest curves are the tumor control curves when there is no uncertainty in dose delivery.
Future perspectives

The purpose of studies in this thesis are related to the assessment and minimization of geometrical and dosimetric uncertainties in the radiotherapy process of predominantly urogenital tumours. With regard to the dosimetric uncertainties, it turned out that for conformal irradiation techniques, the prescribed dose could be delivered within a narrow action level of 2.5% for the fast majority of all patients. For new IMRT techniques, such a high degree of accuracy is not easily achieved, due to the complexity of the treatment delivery (i.e., a large number of small segments or moving MLC leaves). The advent of Monte Carlo and convolution/superposition calculation techniques will increase the accuracy of dose distributions, but it is at least questionable if commercial treatment planning systems will eventually incorporate tongue and groove effects or interleaf leakage in the dose calculation. Extensive QC procedures are required during the introduction of new IMRT techniques and demand a lot of physics manpower. For example, multiple 2D film measurements in anthropomorphic and/or cubical phantoms are useful to get experienced with the dosimetric uncertainties in the IMRT treatment delivery. Nevertheless, it seems that the current geometrical errors are a greater element of concern in the IMRT treatment of urogenital tumours. In chapter 3, it is shown that for bladder tumours large margins (up to 25 mm) are needed to assure adequate dose coverage for a bladder CTV. For prostate tumours smaller margins suffice, due to the solid nature of prostate gland, but margins of 10 mm are nevertheless required, even if the systematic component of the setup error is minimized by a portal imaging protocol. Smaller margins can only be compensated in terms of tumor control by a dramatic increment in dose (41). A prostate of 50 cm$^3$ that is expanded with a 1 cm margin yields a PTV volume of approximately 200 cm$^3$. This means that as much as 75% of the PTV is in fact healthy tissue and no CTV. The reason that this healthy tissue is part of the PTV is because of our limited knowledge of where the CTV is located at the time of the irradiation. The true potential of IMRT, that is sculpting high dose gradients around a complex shaped target volume, is therefore bounded by the mobility of the malignities and organs at risk in the pelvic region. Consequently, the benefit of IMRT for prostate and bladder can only show full advantage if the both the clinical target volume and the organs at risk are defined during the actual treatment position. New technological developments that may allow online segmentation in the treatment of target and risk volumes are cone beam CT and MR integrated with a linear accelerator, although the latter is still not in the stage of construction. Ideally, a full IMRT plan should be optimized based on the geometrical information.
of that day, but for reasons of efficiency, an appropriate pick out of class of different (pre-)optimized IMRT plans seems more realistic for near future. Besides the online determination of the CTV at the linear accelerator, new biological imaging methods seem promising for the future. The improved capabilities of nuclear magnetic resonance imaging and spectroscopy and of positron emission tomography, are beginning to provide physiological and functional information about the tumor and its surroundings (42). In addition, molecular imaging promises to reveal tumor biology at the genotype and phenotype level (43,44). All this new biological information may be of assistance in how to sculpt our dose distribution within the patient or even within the CTV. The combination of all the developments of imaging techniques, may eventually improve the efficacy of radiation therapy in the future.

Reference List


