Exploring and exploiting the potential of pelvic IMRT to spare the bowel

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'When a measure becomes a target,
it ceases to be a good measure.' [1]

[1] Goodhart's law warn us against the focus on impact factors. From Arnold and Fowler 2011; Nefarious numbers [3]

Scientific Environment

The work of this thesis has been carried out at the Section of Medical Physics, Department of Oncology and Medical Physics at Haukeland University Hospital in Bergen, Norway as well as at the Section of Biomedical Physics at the University Clinic for Radiooncology, Tübingen, Germany. The candidate has formally been connected to the Institute of Biomedicine, Faculty of Medicine and Dentistry at the University of Bergen during the PhD-period. The work has been supported financially by Western Norway Regional Health Authority.

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Summary

The work presented in this thesis explore the potential of pelvic intensity-modulated radiotherapy (IMRT) to spare the bowel and contributes to the tools to allow for more robust RT planning for patients with prostate, bladder, rectal and gyneacological cancer. Due to its radiosensitivity and proximity to the pelvic lymph node target, the bowel is often the dose-limiting organ-at-risk (OAR) in these patients. Furthermore, this organ is difficult to handle in treatment planning because of large amplitude motion and unclear correlation between the planned dose-volume histogram (DVH) and small bowel adverse effects.

Convential RT planning is based on a computed tomography (CT) scan of the patient acquired about one week prior to treatment start, while RT is administered in daily fractions over several weeks. Since this image information differs from the exact geometrical configuration realised during treatment, uncertainties in the delivered dose excist. In the pelvis, organ motion is the major contributor to these uncertainties. Population-based treatment planning margins are used around the target volume to make sure the prescribed dose is delivered to the tumour despite these uncertainties. The transition from conformal to intensity-modulated RT has emphasized the need for methods to also account for OAR motion.

In this thesis we have investigated the benefit of moving from 3D conformal RT (CRT) to IMRT for prostate cancer patients who receive RT to the prostate, seminal vesicles and pelvic lymph nodes. Furthermore, the influence of organ motion on both techniques was assessed in order to picture the robustness of todays planning procedures. These studies showed that although IMRT allows for reduced bowel doses compared to CRT, optimization based on the bowel contour from a single CT scan might result in unacceptable bowel doses in some patients. These findings thus emphasized the need for methods to account for bowel motion in planning of pelvic IMRT.

In this thesis we have therefore also suggested and evaluated two different bowel planning concepts. The first concept was an empirical estimation of a population-based planning OAR (PRV) margin for the bowel, which was shown to be rather unspecific because of large amplitude motion and inter-patient variation. The last part of the thesis therefore focused on developing a patient-specific small bowel (SB) planning concept which was based on coverage probabilities (CPs). Patient-specific concepts rely on repeat image information which is laborious. We therefore aimed at developing a statistical method that made the best out of the information captured in a few repeat CTs. Compared to commonly used SB planning volumes, the patient-specific SB PRVs were either similar or better in predicting for SB voxels, and at the same time they occupied a smaller or similar volume in the patient. They thus show promise for use in RT planning and might produce DVHs which better represent the delivered SB dose. Furthermore, the SB CPs generated with this method could be used for pinpointing conflicting regions of target volume and SB and for finding a compromise for dose to these regions in robust optimization of IMRT.

To summarize, the current work provides new solutions for handling the bowel in RT planning which is central for improving pelvic RT by fully exploiting the potential of IMRT.

List of papers[2]

I Muren LP, Wasbø E, Helle SI, Hysing LB, Karlsdottir Á, Odland OH, Valen H, Ekerold R and Johannessen DC: *Intensity-modulated radiotherapy of pelvic lymph nodes in locally advanced prostate cancer: planning procedures and early experiences.* Int J Radiat Oncol Biol Phys 71(4), 1034–41, July 2008.

II Hysing LB, Skorpen TN, Alber M, Fjellsbø LB, Helle SI and Muren LP: *Influence of organ motion on conformal vs. intensity-modulated pelvic radiotherapy for prostate cancer.* Int J Radiat Oncol Biol Phys 71(5), 1496–503, August 2008.

III Hysing LB, Kvinnsland Y, Lord H and Muren LP: *Planning organ at risk volume margins for organ motion of the intestine.* Radiother Oncol 80(3), 349–54, September 2006.

IV Hysing LB, Söhn M, Muren LP and Alber M: *A coverage probability based method to estimate patient-specific small bowel planning volumes for use in radiotherapy.* Radiother Oncol. (Conditionally accepted)

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Contents

Chapter 1

Introduction

About 26 000 norwegians were diagnosed with cancer during 2008 [13]. This corresponds to an estimated accumulated risk of about 30% of developing cancer at the age of 75 years. Radiotherapy (RT) is used both for curative as well as palliative treatment of a large fraction of cancer patients, either alone or in combination with other modalities, such as surgery, chemotherapy, hormonal therapy, anti-angiogenetic drugs or hyperthermia. Survival from cancer is highly dependent on cancer site, but overall, RT together with other modalities cure about 65% of all cancer patients [13].

The aim of curative RT is to inactivate all cancer cells, and at the same time minimize damage to surrounding healthy tissue. Nevertheless, being cured from cancer often comes with the price of adverse side effects. During and after pelvic RT, such complications are often related to the bowel. As much as 90% of patients treated with pelvic RT develop permanent changes in gastrointestinal physiology [2]. In 20-40% of patients, these changes moderately or severely affect their quality of life [2].

RT has been used in cancer treatment for more than 100 years. The ability to cure the patient while keeping the risk of side-effects on an acceptable level has changed dramatically with technological development. Megavoltage linear accelerators (linacs) [95] developed in the 1930ies are still essential in external-beam photon RT for their penetrating energies. The development of computed tomography (CT) scanners in 1972 [9] made individual treatment planning possible by providing information about internal geometry and tissue density. Also the introduction of the multileaf collimator (MLC) [86] has contributed significantly to improving the precision of external beam RT. A MLC consists of many individual leaf pairs made from a high atomic numbered material like tungsten. It replaced customized lead blocks to shape the radiation field by blocking the beam and thereby shielding surrounding normal tissue.

The beam's eye view concept [58] for visualizing the geometry of the contoured tumour (target volume, TV) and nearby critical organs (organs at risk, OARs) as seen on the CT scan has also played an important role in RT planning. By applying several beam directions, and using the MLC to shape the field such that it fits to the projection of the TV as seen on the CT scan through each beam, highly customised dose distributions are produced with 3D conformal RT (CRT).

The introduction of modulated instead of homogeneous beams through so-called intensity-modulated RT (IMRT) has further increased the possibilities of conforming the dose distribution to the TV and to spare the OARs by redistributing the dose in the patient. Different systems are used for delivery of IMRT [1]. With a standard linac, IMRT is delivered from multiple beam directions by either dynamically moving the MLC leaves during irradiation or

by delivering the radiation in several steps with different MLC configurations. The fluence distributions of the modulated beams are optimized by a computer algorithm based on objectives given by the planning expert. These objectives directly or indirectly reflect the probabilities of tumour control (TCP) and normal tissue complications (NTCP). Optimal use of IMRT thus rely on specific knowledge of the correlation between the planned TV/OAR dose distribution and TCP/NTCP.

Geometrical uncertainties are a major issue in CRT as well as for IMRT [90]. They occur because the planning CT information about the position and shape of the TVs and OARs differs from the exact geometrical configuration during treatment. RT is delivered in fractions, typically once per day, five times a week and over several weeks in order to maximise biological effect to obtain more cell kill in the tumour than in the surrounding normal tissue. During this period, typical sources of uncertainties such as differences in the position of the patient relative to the treatment machine (setup uncertainties) and internal organ motion relative to the patient's bony anatomy occur. In pelvic RT, organ motion is extensive and thus the biggest challenge of these two.

Traditionally, geometrical uncertainties in tumour position has been handled by expanding the clinical target volume (CTV) by a margin to create the larger planning target volume (PTV) [39]. By planning using the PTV, the CTV will certainly receive the prescribed dose despite geometrical uncertainties, given the margin is big enough. Because the knowledge about individual uncertainties are incomplete prior to treatment, margins are usually population based [83, 90]. In case of OARs, geometrical uncertainties were usually not considered for planning of CRT. With the introduction of IMRT, however, the ICRU report no 62 addressed this topic by introducing the planning OAR volume (PRV) [38]. In analogy to the PTV, the PRV should account for geometrical uncertainties in OAR position by adding a margin around the organ. Compared to the PTV, the PRV concept has so far received less attention.

Margin reduction by either reducing uncertainties or by treatment individualisation is an important topic in RT research. Reduced margins around the CTV lead to smaller high-dose volumes and consequently less normal-tissue damage which in turn can allow for dose-escalation to the tumour within the PTV concept. This has driven major developments in image technology to allow for image-guided RT (IGRT) by tumour localization prior to or during treatment sessions. IGRT can optionally be used together with adaptive RT (ART) by methods for individualizing margins based on repeat image information that becomes available throughout the treatment course [99].

Hard margins through the PTV/PRV concepts are problematic in optimization of IMRT because they result in overlapping regions of conflict [7]. Finding alternative methods to fully exploit the potential of combining IMRT with IGRT and ART is therefore warranted [1]. Because these methods rely on repeat volumetric imaging data, image processing has recently become a relevant topic for RT. It is focused on developing methods for automatic or semi-automatic segmentation [52], deformable registration and organ motion modelling. Despite increased availability, repeat image information is still laborious. A challenge in this context is therefore how to extract useful information about patient-specific organ motion from few available samples.

In summary, this Phd-project contributes to improving pelvic RT by adressing: 1)the use of conventional IMRT compared to CRT to spare the bowel, 2)the influence of organ motion on delivered dose and 3)methods to account for bowel motion in planning and evaluation of pelvic RT. The latter includes methods for calculating bowel PRVs, use of repeat imaging data for individualization of bowel PRV margins as well as an alternative method for representing patient-specific bowel motion.

Chapter 2

Background

For RT of the pelvis in case of prostate, bladder, rectum or gynaecological cancer, the main motivation for exchanging CRT with IMRT has been to reduce the incidence of gastrointestinal (GI) adverse effects. This was also our main motivation when introducing IMRT at Haukeland University Hospital in September 2005 (Paper I). Patients with locally advanced prostate cancer were chosen for our IMRT start-up, and consequently the current thesis is based on the same group of patients, although the developed methods and principles are general.

Locally advanced prostate cancer patients with a risk (estimated to $> 15\%$ by [71]) of lymph node involvment are routinely given irradiation to the proximal pelvic lymph nodes in addition to the prostate and seminal vesicles in ours as well as other institutions. Irradiation of pelvic lymph nodes could theoretically sterilise subclinical metastasis and thereby increase the survival in a subgroup of patients. The costs versus benefits of whole pelvic RT has been debated for more than two decades for a number of reasons [4, 20, 56, 70, 78, 92]: A) Selecting the right subgroup of patiens (i.e. with advanced disease but no distant metastasis) is difficult [20, 71]; B) Identifying which lymph nodes to irradiate is challenging and currently based on population data which carries the risk of geographical miss [29]; C) Whole pelvic RT is associated with increased GI adverse effect rates compared to prostate only RT because larger volumes of small bowel were included in the field [20]; D) The pelvic doses are limited to 45-50 Gy to keep the risk of GI complications at an acceptable level and this might not be sufficient to sterilise the cancer cells [30].

A key to improve treatment outcome of whole pelvic RT is therefore the challenge of reducing and controlling small bowel related complications. This is challenging because: 1) knowledge about the radiobiologic mechanisms behind GI adverse effects are limited, and 2) the mobility of the pelvic organs is considerable, especially for the bowel, such that estimates of both the applied dose and the dose prescription for optimization are uncertain [35, 36, 45, 62, 67, 77]. The current project has investigated the potential of pelvic IMRT to spare the bowel as compared to CRT, but also challenges and solutions for better exploiting this potential.

2.1 Potential and challenges of intensity-modulated radiotherapy

The idea and concepts of using modulated instead of homogeneous beams evolved in the 1980s [37]. Different techniques for delivering modulated fields were developed during mid 1990ies [37]. The first IMRT treatment with a dynamically moving conventional MLC was delivered at the Memorial Sloan-Kettering Cancer Center in New York in 1995 [49]. During the last decade, IMRT has spread to most RT departments worldwide [93]. This rapid clinical implementation was driven by numerous planning studies showing the potential of IMRT for

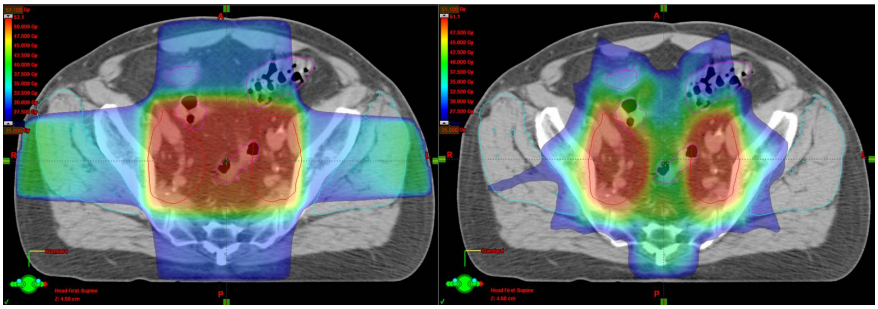

Figure 2.1: Example of prostate pelvic dose distribution as produced with four-field CRT (left) and seven-field IMRT (right). Dose colour wash is from 25 Gy (blue) to approximately 50 Gy (red). Target volumes are shown in red and bowel in pink. From Paper I.

reducing toxic effects, but happened despite incomplete knowledge about the challenge of IMRT planning, delivery and quality assurance [93]. In the following, our focus will be on potential and challenges in IMRT planning with respect to geometrical uncertainties.

Planning of RT is based on our clinical experience. The most intuitive way of using IMRT is thus to mimic the concept of CRT, but exploiting the technique to better conform the dose to the PTV (Figure 2.1). Nutting and colleagues were the first to demonstrate the advantages of pelvic IMRT [66]. In a planning study comparing pelvic IMRT and CRT, they showed a reduction from 18% to 5% in the volume of small bowel receiving more than 45 Gy. Many other investigators have later confirmed this potential of IMRT to spare the bowel [5, 15, 29, 32, 41, 48, 50, 53, 63, 66, 69, 74, 75, 94].

In order to achieve a good compromise between risk of normal tissue complications and tumour control, IMRT dose distributions are often tightly tailored to the patient geometry as imaged on the planning CT scan. One concern has been how organ motion and set-up uncertainties influence delivery of such dose distributions. This has also been a topic for CRT [43, 46, 54], but is even more pertinent with IMRT because tightly tailored dose distributions tend to be less robust to geometrical uncertainties [7, 40, 98]. Yan and colleagues demonstrated that prostate IMRT actually required larger PTV margins compared to CRT [98]. Also Löf and colleagues pointed out that optimized dose distributions could easily loose their advantages because of uncontrolled changes in set-up, patient geometry, or beam profiles [51]. As a consequence of geometrical uncertainties, 'better' in planning does not necessarily stay 'better' in application for all patients.

Geometrical uncertainties are often classified as systematic or random. Systematic errors occur if the geometry configuration on the CT scan used for treatment planning deviates from the mean of the geometries realized throughout the fractionated treatment. Random errors are variations around this mean deviation occuring with different magnitude at each treatment fraction. Systematic and random uncertainties have a different impact on the delivered dose distribution [83, 84]. Common PTV margin recepies are therefore derived from dosimetric rather than geometrical criteria [83]: i.e. the CTV margin should be big enough to ensure that the achieved treatment dose and the prescribed dose are in agreement for a large number of patients. Provided that the margins are adequate, the PTV concept thus ensures robust treatment plans for the CTV [7].

A competing demand is to control the risk of normal tissue complications. Consequently, the dose distribution should also be robust for the OARs. To cope with this problem in opti-

mization of IMRT, ICRU report no 62 introduced the planning OAR volume (PRV) in 1999 [38]. McKenzie and colleagues were the first to explore the PRV concept by seeking margin recipes analogous to a common CTV→ PTV margin approach [57, 91]. They chose a criteria such that the DVH of the PRV should not underestimate the high-dose volumes in the OAR in 90% of cases. Such a dosimetric criteria led to different margin recipes depending on the type, size and position of the OAR relative to the high-dose region. Muren and colleagues later used an empirical approach to determine margins around the rectum to encompass different degrees of rectum motion as seen in a series of repeat CT scans of bladder cancer patients [60]. In contrast to McKenzie and colleagues, the approach presented by Muren was purely geometrical. Stroom and Heijmen followed by discussing the limitations of the PRV concept in a paper where they also investigated a similar but alternative method to McKenzie for deriving PRV margins around organs with a maximum dose constraint [85]. One limitation of the PRV concept is that the derived margin recipes are strongly dependent on the case and definition of max dose, and it is therefore difficult to define a general recipe in analogy to the target. Furthermore, it is challenging how to translate dose-volume constraints applied for an OAR to the much larger PRV. Despite these limitations, Stroom and Heijmen acknowledged that PRVs can be a useful tool in treatment planning to avoid high doses in proximity to serial OARs.

Planning of IMRT is an optimization process where knowledge- and experience- based treatment goals of a clinician has to be communicated to the optimization algoritm. The abstraction of these goals through the objective function is therefore crucial [1]. The purpose of the objective function is to control the shape of the dose-volume histogram (DVH), e.g. take a volume from one bin, reduce the dose and put it in a lower bin. Most commersially available treatment planning systems use cut-off volumes from the cumulative DVH as objectives (i.e. the volume receiving more than xGy, V_x). This might not be optimal because: 1) a single DVH point does not sufficiently control the dose distribution in an organ and 2) multiple DVH points might be overly restrictive [1]. Biological measures like tumour control probability (TCP), normal tissue complication probability (NTCP) and equivalent uniform dose (EUD) might be better suited because they seek to describe the effect of the whole DVH [1].

The most widely accepted NTCP model is the phenomenological Lyman-Kutcher-Burman model [10, 44]. At the core of this model lies the ability to map an inhomogenious dose distribution in an organ to standard conditions of partial organ volume irradiation with an homogeneous dose, allowing for extrapolation of published dose constraints [21]. Closely connected to this DVH reduction to an effective partial volume, is the concept of reducing the DVH to a generalized EUD or effective dose [44, 65]. The generalized EUD relies on a tissue-specific parameter k incorporating the volume-effect of the organ in question. It represents the dose that causes the same radiobiological effect as the inhomogeneous dose distribution if applied homogeneously to the entire organ.

The direct use of EUD/NTCP or cut-off volumes in optimization of IMRT has stimulated attempts to establish dose-volume-toxicity relations, also for the bowel [22, 72, 76, 93]. Notably, the RT technique can influence the correlation between planned dose and incidence of specific adverse effects, and consequently toxicity relations established with CRT cannot uncritically be applied in IMRT optimization [80]. EUD models have been shown to be less prone to such statistical bias caused by correlations of DVH dose bins [82].

Another challenge with establishing dose-volume-toxicity relations is the limited ability of the planning DVH to represent the actual accumulated dose in an organ throughout the treatment course [24]. Furthermore, dose-volume constraints derived from an OAR DVH cannot directly be applied to the often much larger PRV [85]. Some investigators have therefore attempted to correlate the PRV DVH to toxicity [22, 61, 76, 88]. The sensitivity and specificity

of the PRV is crucial in this context. A PRV is sensitive if it contains a large fraction of voxels which will be visited by the OAR in future. It is unspecific if it also contains large volumes which will never be visited by the OAR. Unspecific PRVs are problematic in RT planning because they produce unreliable DVHs, unreliable estimates of evaluators of plan quality, and difficulties to achieve treatment planning dose-volume constraints because of large volumes of overlap between PRV and PTV.

Planning and delivery of IMRT offers increased degrees of freedom for shaping the dose distribution which could be exploited beond tailoring the dose to the PTV [37]. One interesting way of exploiting this freedom is to abandon the PTV/PRV concepts by directly incorporating geometrical uncertainties of the CTVs and OARs in robust optimization. Robust optimization refers to methods aiming to produce dose distributions which result in CTV and OAR doses which are predictable within an acceptable uncertianty. This is in contrast to PTV/OAR based optimization which are robust with respect to the CTV only, and to PTV/PRV based optimization which result in overlapping regions of conflict between PTV and PRV.

The most basic robust optimization methods are based on coverage probabilities (CPs) [83]. A CP matrix is defined on a voxel grid, with each voxel containing the probability of being occupied by the TV or OAR in question. Baum and colleagues used TV and OAR CPs as weights for the objective function to compromise the dose in conflicting TV/OAR voxels. Witte and colleagues used a similar concept for optimizing expected TCP and NTCP [96]. More sophisticated methods replace the common static patient model with a dynamic patient model for optimizing the dose to moving volume elements of TVs and OARs (see e.g. [11, 79, 89]). The latter methods are only possible with deformable patient models at hand.

To summarize, IMRT has a great potential for reducing GI toxicity, but this potential might be jeopardised by geometrical uncertainties. Due to tightly tailored IMRT dose distributions, the impact of geometrical uncertainties are potentially larger as compared to CRT. Therefore, methods are required to ensure robust dose distributions both with respect to CTV and OARs. The PRV concept has been suggested to account for OAR uncertainties in planning of IMRT. However, it is not straight-forward how to define clinical useful PRVs. Furthermore, PRVs do not necessarily lead to robust dose distributions because they often produce overlapping PTV/PRV regions which are difficult to handle in IMRT optimization. Alternative methods to PTV/PRV based optimization have been suggested. These are based on methods for organ motion modeling.

2.2 The bowel as organ-at-risk

The bowel is a radiosensitive organ and pelvic RT therefore often leads to both acute and chronic changes in gastrointestinal physiology [2]. While acute symptoms often start during the second week of treatment, chronic symptoms might not become evident until years after treatment [2]. The most common sympthoms are abdominal pain, diarrhoea, tenesmus (a feeling of repeatedly needing to open the bowels), incontinence (leakage/soiling), excessive flatulence and passing blood or mucus when opening the bowels [2]. Severe complications like ulceration (a sore area that doesn't heal), obstruction (blockage of the bowel) and perforation (a hole in the bowel wall) are rare (below 5%) when pelvic doses are limited to 45-50 Gy over 5 weeks [47]. Experience have shown that doses above this limit can increase the risk for obstruction from 5% to 37% and risk of chronic diarrhoea with up to 40% depending on the volume of irradiated small bowel [47].

Complications have traditionally been scored according to the lower gastro intestinal (GI) RTOG/EORTC acute and late radiation morbidity scoring criteria, which grade vari-

ous radiation-induced complications from 0-4 depending on to their severity as judged by the physician [17]. More specific criteria for acute GI complications have been publised by CTC (common toxicity criteria) [14]. Also methods for patient-graded complications excist through the LENT SOMA system [73].

The relationships between planned bowel DVHs and Grade $\geqslant 2$ GI complications are unclear. Recent reviews by Fiorino and colleagues and the QUANTEC initiative show that prospective studies are lacking [23, 42]. Based on results from mostly retrospective studies [6, 31, 34, 72, 87], QUANTEC recommend DVH constraints for the cut-off volume receiving $\geqslant 15$ Gy (i.e. V_{15}) when contouring specific bowel loops and V_{45} when the entire cavity (i.e. the intestinal cavity, IC) in where the bowel can move is delineated (Figure 2.2) [42]. In addition, high doses should be minimized. Fiorino and colleagues, explain the correlation between V_{15} and acute toxicity with what they call 'geometrical factors' from use of conformal techniques [23]. Tho and colleagues and Baglan and colleagues also noted that the effect of low-dose RT was impossible to isolate from these studies because V_{15} was correlated to the high-dose cut-off volumes due to limited DVH variability with conformal techniques [6, 87]. Due to these findings, Fiorino and colleagues warn against using constraints to limit V_{15} in optimisation of IMRT without considering $V_{30} - V_{50}$ [23].

There are probably many reasons why it is difficult to establish a clear correlation between the planned bowel DVH and toxicity. Factors and diseases like previous abdominal surgery, diabetes, hypertension, inflammatory bowel disease, HIV, connective-tissue disorders, concomitant chemotherapy and smoking can increase the risk of acute and late complications and are not always corrected for when analysing the data [2]. Furthermore, the RTOG/EORTC scoring criteria is rather unspecific because different symptoms are pooled. Even with specific sympthoms at hand, finding the exact causes of these are complex - e.g. as much as 13 different mechanisms reflecting changes of different parts of the GI tract lead to diarrhoea [2].

Another potentially important factor leading to a blurring of the correlation between the planned bowel DVH and toxicity is the excessive mobility of the bowel, which is the topic of the current thesis [24, 45, 47]. It is a premise of the current work that a clearer correlation between the planned bowel DVH and toxicity can only be achieved if motion information is included in the bowel DVH. Studying bowel motion is therefore essential for improving pelvic RT.

Gallhager and colleagues investigated the volume, distribution and mobility of the small bowel from orthogonal radiographs [28]. They found that patients with previous ab-

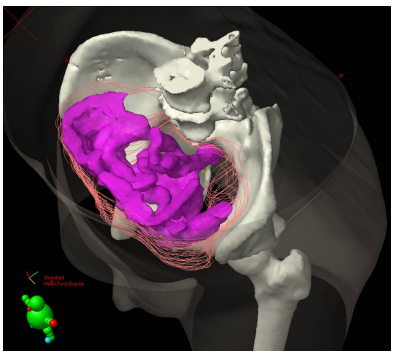

Figure 2.2: Volume rendering of the segmented bowel (solid magenta) and the intestinal cavity (contour pink).

dominoperinal resection had a greater volume of less mobile small bowel positioned in the lower pelvis explaining a higher risk for RT-induced obstruction in these patients. They also investigated different surgical techniques and patient-positioning methods in order to displace the small bowel from the pelvic RT treatment field and found that a combination of bladder distention and compression of the anterior abdominal wall in prone position could displace the small bowel without causing patient discomfort. Such patient position also reduced the incidence of acute diahorrea. The latter findings have been confirmed by Mak and colleages which found that an open table top, or a so-called belly-board, shifted the small bowel away from the field and thereby reduced the risk of late small bowel obstruction [55].

Nuyttens and colleagues throughly investigated changes in the position of the small bowel in a group of rectal patients by measuring distances between bony structure and the nearest contrast enhanced small bowel loops as seen in 12 patients with 4-7 repeat CT scans each [67]. They found a considerable standard deviation in small bowel position of 2.7 cm at 5 cm below the sacral promontory in preoperative patients. In patients with low anterior resection and abdominoperineal resection (APR), the standard deviations were smaller (1.4 cm and 0.2 cm, respectively). Furthermore, there was a correlation between the most inferior small bowel position and the bladder volume (except for APR), but no correlations with the anterior and posterior positions.

Kvinnsland and Muren later studied the impact of bowel motion on conformal bladder RT DVHs in 10 patients with 6-8 repeat CT scans [45]. They found that in 6 out of the 10 patients, the volume occupied by the bowel in one scan only was bigger than the volume occupied in all CT scans. Bowel motion translated into large DVH (and NTCP) uncertainties for individual patiens, but even larger variability was found between patients. Based on these findings, Kvinnsland and Muren accentuated that bowel dose-volume constraints for optimisation of IMRT shoud be used with care.

Due to the mobility of the bowel and uncertainties in DVH constraints it is not straightforward how to include this OAR in optimization of IMRT. Optimization based on the bowel contour from a single planning CT could potentially lead to an illusionary low dose to the bowel. Because of large deformations and a complex motion pattern, calculating a bowel PRV with the McKenzie or Stroom and Heijmen approaches is infeasible. A commonly used PRV for the bowel is therefore the physical boundary in where the bowel is free to moove, i.e. the intestinal cavity (IC) (Figure 2.2) [15, 18, 29, 50, 74]. By minimizing the dose to the IC volume, a low and homogeneous dose is secured to the bowel itself. Although this bowel PRV is highly sensitive in predicting for future bowel voxels, it is highly unspecific due to its size.

2.3 Organ motion modelling

In order to find alternative methods to account for bowel motion in optimization of IMRT, various organ motion modelling methods and their applicability for the bowel are discussed in the following. Modelling of organ motion uncertainties is one of the main focus areas in RT research. A number of relevant recipes have been published [7, 19, 25, 26, 33, 81, 83, 97]. Some of these neglect deformations by assuming rigid body motion [19, 83]. This would probably not be valid for the bowel where peristalsis waves displace the bowel wall with a mean amplitude of around 7 mm occuring about 11 times per minute [27].

Hoogeman and colleagues simulated rectum deformations by stochastic sampling of a set of shape and shape-change parameters defined on a slice-by-slice basis from the probability distributions of these parameters as estimated in a group of reference patients [33]. However, a slice-by-slice based approach would not be feasible for the bowel because it can move more or

less freely within the pelvis, also in the cranio-caudal direction. Both of the above-mentioned methods are examples of using population-statistics to estimate uncertainties in organ position or shape. Adaptive approaches, on the other hand, seek to include patient characteristics by measuring individual uncertainties.

Yan and colleagues have shown that the convex hull (union) of the CTV (i.e. prostate and seminal vesicles) from a few repeat CT scans capture a large degree of organ motion and can be used to construct a much smaller PTV than a single CTV pluss a population based margin, while maintaining the same dosimetric criterion [98]. By including more planning CTs, the systematic uncertainty is reduced in a simple manner. More sophistically, Yan and colleagues also modelled individual organ shape changes from repeat CT scans by using a biomechanical finite element model driven by user-placed fiducial landmarks on the organ surface to generate groups of intermediate organ shapes by interpolation between the surface point positions in the measured geometries [97]. Söhn and colleagues [81] refined this approach by using a point distribution model to reduce the large dimensionality of the geometrical information from repeat CTs into a few statistical parameters which describe correlated displacement of the organ surface points around the mean organ shape. Others have presented different approaches also acting on corresponding points [25, 26]. Because it is impossible to distinguish between bowel segments in CT images and hence to define fiducial landmarks on the bowel wall, no point-correspondence model can be made for this organ. This is the major challenge in modelling bowel motion and is one of the main reasons why this organ is treated seperately in the present work.

An alternative and common way to represent organ motion is by coverage probabilities (CPs). CPs were first introduced by Stroom and colleagues [83] who used it to model the impact of systematic uncertainties on the CTV DVH and to establish a PTV margin recipe. Because the CP matrix is a static patient model, it doesn't rely on point correspondence models. Coverage probabilities were thus a natural choice for representing bowel motion in the current work. Baum and colleagues sampled CPs by estimating the relative frequency of coverage of an organ as outlined in multiple CT scans [7]. This approach have been demonstrated for prostate, rectum and bladder, but is in principle also applicable for the bowel. However, when applied to organs with large amplitude movements the approach converges very slowly to the true CP matrix. Consequently, the CP matrix might contain holes where the optimization algorithm is free to deposit high doses when based on a few CT scans [7].

Chapter 3

Aims of the project

The aim of this thesis was to study the potential of conventional pelvic IMRT to spare the bowel and to develop methods for further exploiting this potential. Specifically, we aimed at:

- Comparing IMRT to CRT in locally advanced prostate cancer patients (Paper I and II).
- Studying the influence of organ motion on the planned dose distributions in treatment of locally advanced prostate cancer patients (Paper II).
- Defining clinical useful bowel PRVs (Paper III and IV).
- Developing a statistical method for making the best use of scarce imaging data to generate patient-specific small bowel PRVs based on coverage probabilities (Paper IV).

Chapter 4

Materials and methods

This chapter gives an overview of the applied patient materials as well as the methods which were used and developed to fulfil the aims of the project. Further details can be found in the corresponding papers (Papers I-IV).

4.1 Patient materials

The methods developed in the project are relevant for all patients receiving pelvic radiotherapy. That includes patients with prostate, bladder, rectum and gynaecological cancer where the lymph nodes are part of the target volume. However, the studies were mainly performed on patients with locally advanced prostate cancer who received pelvic external beam radiotherapy at Haukeland University Hospital. These patients had two clinical target volumes (CTVs) defined. Both CTVs consisted of the prostate and seminal vesicles, while CTV1[1] also included the relevant lymph nodes. Two planning target volumes (PTVs) were constructed by adding margins around the CTVs. A 15 mm margin was used around the prostate and seminal vesicles except towards the rectum, where a 10 mm margin was used. For the lymph node volume, an isotropic 10 mm margin was used.

In order to include information about organ motion, two different datasets of patients with CT scans acquired once or twice a week during the treatment period were used. One of these datasets consisted of the CT data of totally 20 male bladder cancer patients which had 6-9 CT scans each. Out of these, 14 patients were treated at Haukeland University Hospital in the period from January 2000 to October 2001 and 6 patients were treated at Edinburgh Cancer Centre during 2003. The other dataset consisted of 3 prostate cancer patients treated at Haukeland University Hospital during May/June 2007. The CT data of these three patients were taken from a dataset of totally 40 patients with 10-11 CT scans each which was collected within the present project for use in current and future studies about bowel motion.

In some of these datasets, one bowel volume consisting of both the large and small bowel was contoured, while in the other dataset the large and small bowel were contoured seperately. When using the term bowel we therefore refer to the volume containing both the large bowel (LB) and the small bowel (SB).

[1] This 'outdated' nomenclature was chosen for concictency with Papers I-II, despite the recent ICRU 83 recommendations [40].

4.2 Conformal vs. intensity-modulated prostate pelvic RT

Two of the studies were planning studies where we compared CRT with intensity-modulated prostate pelvic RT. The procedures for treatment planning and evaluation are outlined in the following and more details can be found in Papers I-II. One CT scan of the patient was used for treatment planning.

4.2.1 Planning of conformal and intensity-modulated prostate pelvic RT

CRT planning of prostate pelvic radiotherapy was performed according to the routine practice at Haukeland University Hospital as until September 2005. The treatment of these patients then consisted of two phases; first, 50 Gy was delievered in 25 fractions to the prostate, seminal vesicles and relevant lymph nodes with margins (i.e. to PTV1), and second, 20 Gy was delivered to the prostate and seminal vesicles with margins (i.e. to PTV2) in 10 fractions. Both CRT plans consisted of four beams with gantry angles of 0°, 90°, 180°and 270°. A PTV dose variation within 95% and 107% of the prescribed dose was aimed for, but a minimal point dose of 90% of the prescribed dose was accepted in the posterior part of the PTV to avoid an unacceptably high rectum dose.

IMRT planning of prostate pelvic radiotherapy was performed using the treatment planning system available at Haukeland University Hospital (Eclipse, Varian Medical Systems, Palo Alto, CA)). This planning system uses dose-volume objectives with priorities for both the PTV and OARs. As for CRT these patients were still treated in two phases, but with the first phase of treatment (up to 50 Gy) delivered with IMRT. In the initial phase after moving from CRT to IMRT, the objectives were based on what could be obtained with CRT for the patient in question. With IMRT, we aimed at reducing the volume of rectum, bladder and bowel receiving more than 30, 40 and 50 Gy by 25%, 25% and 50% compared to CRT, respectively. The IMRT plans consisted of seven coplanar beams with gantry angles of 0°, 51°, 103°, 154°, 206°, 257°, and 309°. During the optimization, the highest priority was given to the minimal dose criterion of 95% of prescribed dose to the PTV.

No attempt was made to account for OAR motion neither for the CRT plans nor for the IMRT plans.

4.2.2 Evaluation of conformal and intensity-modulated dose distributions

To compare the treatment plans, we first reduced the 3D dose distribution to dose-volume histograms (DVHs), both for the PTVs and the most relevant OARs (i.e. bowel, bladder, and rectum in case of Paper I and II, as well as the penile bulb, hip joints, and hip joint muscles in case of Paper I). For the OARs, dose cut-off volumes from 20 Gy to 70 Gy in intervals of 10 Gy were compared in Paper I. In Paper II, we only compared the dose distributions resulting from the first phase of the treatment (i.e. up to 50 Gy).

Also the generalized equivalent uniform dose (gEUD) [65] was used (in Paper II) to compare bowel, bladder and rectum doses. Normally, the gEUD is calculated relative to the volume of the whole organ, but in case of bowel, only the part of the bowel within the lower pelvis was contoured. We therefore extended the gEUD concept of Niemierko to calculate the gEUD relative to an absolute reference volume (V_{ref}):

$$gEUD = (\frac{1}{V_{ref}} \sum_i v_i D_i^k)^{\frac{1}{k}} \tag{4.1}$$

where (v_i, D_i^k) denotes the ith bin of the differential DVH, and k is associated with the volume effect of the organ considered. For the bowel, we used a V_{ref} equal to 200 cm^3 and a volume effect parameter $k = 4$, while for the rectum and bladder, we calculated gEUD relatively to the whole organ volume with $k = 12$ and 8, respectively [82]. A $k = 12$ practically only considers the volume elements receiving $\geq 80\%$ of the maximum dose (i.e. a small volume effect), while a reduction with $k = 4$ would also consider the volumes receiving intermediate doses ($> 50\%$) but would weight these against greater dose volumes (i.e. a larger volume effect).

4.2.3 Influence of organ motion on CRT vs. IMRT

In order to investigate the influence of organ motion on CRT compared to IMRT in Paper II, we used the dataset of 20 male patients with 6-9 CT scans each to estimate the mean treatment bowel, bladder and rectum gEUDs and dose cut-off volumes. The dose distribution was not recalculated on each of the treatment CT scans, because only the contoured bowel, bladder and rectum volumes were available (and not the CT scans themselves). The gEUDs calculated from the planning DVHs were denoted $gEUD_{plan}$ and the mean of the gEUDs resulting from the CT scans acquired during treatment were denoted $gEUD_{treat}$. Correspondingly, the dose cut-off volumes were denoted Vx_{plan} and Vx_{treat}, where x $\in$ [25, 30, 35, 40, 45, 50] Gy was the cut-off dose. In order to investigate if IMRT was superior to CRT also when considering OAR motion, we compared $gEUD_{treat}$ and Vx_{treat} from the CRT dose distribution with the IMRT dose distribution. We also compared $gEUD_{plan}$ with $gEUD_{treat}$ and Vx_{plan} with Vx_{treat} for both CRT and IMRT to see how robust the dose distributions were towards organ motion.

4.2.4 Statistics

All statistical tests were performed using Statistical Package for Social Sciences, version 13.0 (SPSS, Chicago, IL). All p-values were derived from two-sided tests and a p-value below 0.05 was considered statistically significant. In most cases the paired t-test was used, but in cases where the paired differences of the test variables did not follow a normal distribution, the Wilcoxon test was applied.

4.3 Methods to account for bowel motion for use in radiotherapy

Two different methods to account for bowel motion was developed and tested in the project. The first method (described in Paper III) was a quantification of a population based PRV margin for the bowel, based on the recommedations from ICRU report no 62 [38]. The second method (described in Paper IV) was an estimation of patient-specific small bowel wall (SBW) coverage probabilities (CPs) and PRVs from a few patient-specific CT scans.

4.3.1 Quantification and evaluation of a population-based PRV margin for the bowel

To quantifiy a population-based PRV margin for the bowel we used the dataset of 20 male patients with 6-9 CT scans each. Isotropic margins of 5-30 mm in intervals of 5 mm were added to the bowel contour of the planning CT scan by using the 3D margin tool of the Eclipse treatment planning system. The bowel contours from the additional CT scans were used to create so-called location probability maps, where each voxel was assigned an estimated probability of containing the bowel of 12.5%-100% in intervals of 12.5% (Figure 4.1). The fraction

of patients for which a given PRV encompassed 85%, 90% and 95% of the different location probability volumes was derived. Also the average volume fraction of the PRVs with no probability of containing the bowel was investigated to get a measure of the specificity of the PRV.

4.3.2 A method to estimate patient-specific small bowel coverage probabilities and PRVs

In paper IV we developed a statistical method to estimate patient-specific SB PRVs by exploiting the information about individual SB motion captured in a number n of repeat CT scans. The PRVs were calculated from a CP matrix by thresholding. Voxels with a CP-value above the threshold were included in the PRV and voxels with a lower CP-value than the threshold were excluded from the PRV. The procedure for calculating SB CPs is illustrated in Figure 4.2.

Baum and colleagues modelled CPs by recording the relative frequency of coverage [7]. Our approach is designed to converge towards the Baum approach when the number of CT scans approaches infinity, but extended the concept by adding a soft margin to capture the additional uncertainty in SB position with few CT scans. This should prevent the CP matrix from containing any holes, i.e. voxels which were assigned a CP equal to zero, but still had a risk of being occupied by the SB in future.

In order to estimate the 'soft margin' we considered the variability in SBW position between the n CT scans of an individual patient. Peristaltic waves of the SB, occuring about 11 times per minute and displacing the SBW with an average amplitude of 7 mm represent one of two main effects of SB motion [27]. Another main effect is large amplitude shifts of parts of the SBW or SB due to e.g. change in content and bladder filling. We assumed that patient-specific patterns of large amplitude motion or stability in the SBW will become evident in the accumulation of CT scans. By adding a soft margin around the SBW instances, we further assumed that all voxels with the same distance away from the SBW as seen in one or more CT-scans had approximately the same probability of being visited by the SBW in future.

The soft margin was estimated as a function of the closest distance to any known SBW voxel. Therefore, patients showing a large variability in SBW position got a broader estimated soft margin than patients showing less variability in SBW position. As the number of included CT scans increased, the soft margin got tighter (Figure 4.3). If the number of CT scans approaches infinity, the margin width would approach zero.

The CP matrix was calculated by first smearing out each of the SBWs with the soft margin and later adding up the voxels of the smeared out matrices and multiply with a volume-preserving normalizing constant.

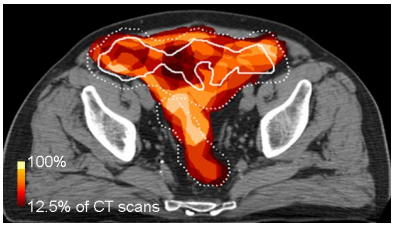

Figure 4.1: Example of bowel location probability map from repeat CTs as well as the planning bowel contour B_0 shown in solid white and B_0+10 mm margin shown in dotted white.

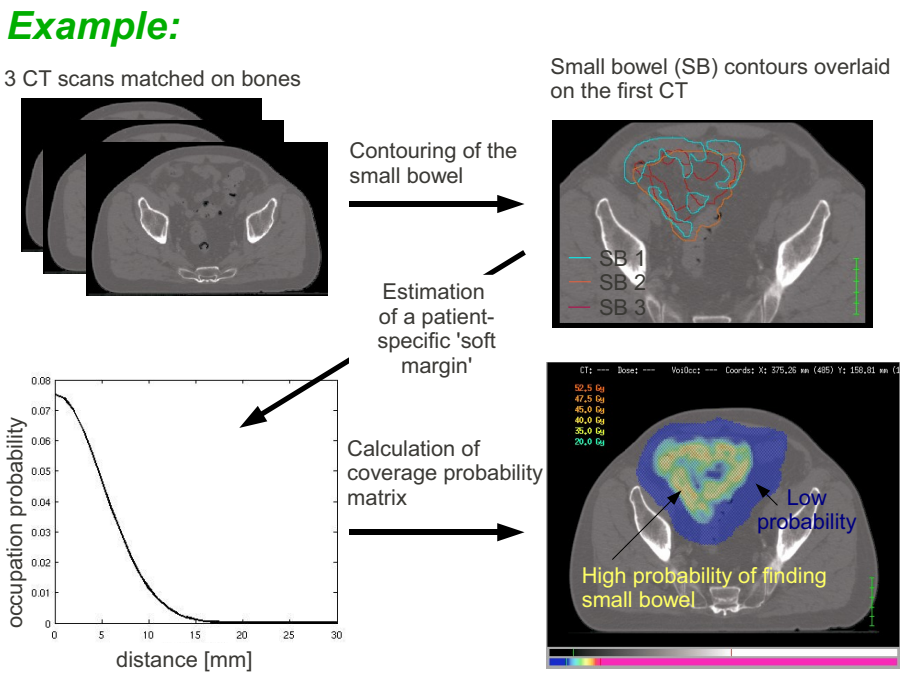

Figure 4.2: Illustration of the procedure for calculating small bowel coverage probabilities (CPs) from $n = 3$ CT scans.

4.3.3 Evaluation of patient-specific SB PRVs

To test the method we applied it on three patients with different degrees of SB motion. Maximum five CT scans was considered clinically feasible, and consequently the PRVs generated from 2-5 CT-scans were evaluated by their sensitivity and specificity with respect to the PRVs from all 10-11 repeat CT-scans. The effect of different CP-threholds and its impact on sensitivity and specificity of the generated PRVs was studied. Based on the sensitivity and specificity study, two thresholds were chosen for comparison of the current concept with conventional methods; CP=0.005 (i.e. generous patient-specific PRVs) and CP=0.03 (i.e. tight patient-specific PRVs) (Figure 4.4). These were compared to an intestinal cavity (IC) approach a a population based PRV approach of 10mm and 30mm isotropic planning margins. Sensitivity was compared by estimating the overlap between the planning volume in question and randomly chosen independent SB- /SBW volumes, while specificity was measured by comparing relative planning volumes (i.e. the volume relative to a boundary composed from the hull of all available ICs of the patient in question).

4.3.4 Future application of small bowel PRVs and coverage probabilities

In principle, the patient-specific small bowel PRVs can be included into any treatment planning system by writing the coordinates to a DICOM RS structure file. Because the PRV volume differs from the SB volume, dose-volume or EUD constraints for the SB cannot be transferred

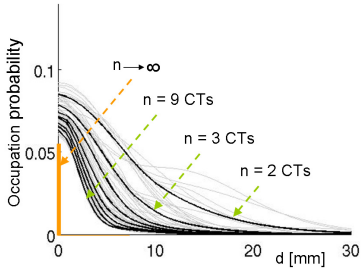

Figure 4.3: Example of estimated soft margins around the SBW for one patient when including $n = 2-9$ CT scans. If the number of CT scans approaches infinity, the margin would approach zero.

directly to the PRV [85]. We suggest to weight the PRV DVH by a factor $V_{SB}^{tot}/V_{PRV}^{tot}$, reflecting a homogeneous SB coverage probability distribution within the PRV.

The SB coverage probability matrix can alternatively be used directly in optimization as described by Baum and colleagues [7]. In the treatment planning system Hyperion, developed at the University of Tübingen, organ specific coverage probabilities are used as an importance weight to each TV and OAR voxel for the objective functions during optimization. Coverage probabilities of the SB can thus be used in combination with the Baum approach to pinpoint conflicting regions of SB and TV and to find a compromise for dose to these regions. See Figure 4.5 for an example of using SB CPs in optimisation of prostate pelvic IMRT in Hyperion.

Furthermore, the SB CPs could be used in evaluation of IMRT by weighting the DVH. The differential volume receiving a dose in the interval ΔD, $pV(\Delta D)$, would then be calculated as:

$$pV(\Delta D) = v \sum_{i,D(i)\in\Delta D}^{N} \widehat{cp(i)}, \tag{4.2}$$

where v denotes the absolute voxel volume, N is the total number of voxels, and $\widehat{cp(i)}$ is the coverage probability of voxel i.

It should be mentoned that the current work (Paper IV) focused on the development and testing of the method rather than application. However, the areas of application described here

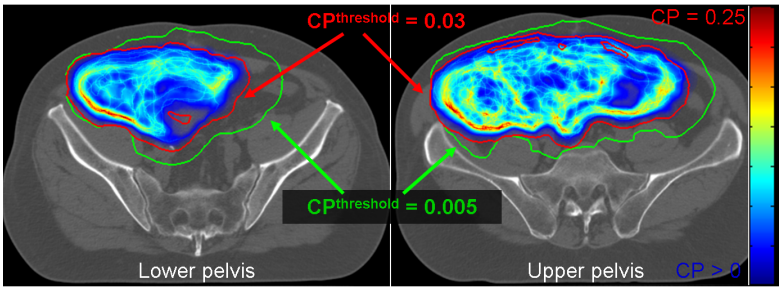

Figure 4.4: Example of PRVs created from 3 CT scans and overlaid on the CP matrix created from all 11 available CTs. A generous PRV (green) was obtained by applying a CP threshold of 0.005, while a tighter PRV (red) was obtained by applying a CP threshold of 0.03.

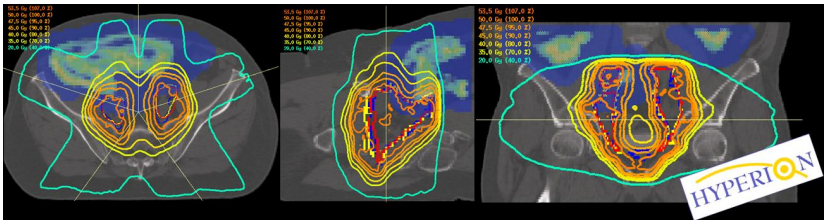

Figure 4.5: Example of using SB CPs in combination with the Baum approach for optimization of prostate pelvic IMRT in Hyperion with three input CTs.

served as an objective while developing the method and furthermore lays the fundation for future work.

Chapter 5

Summary of results

5.1 Paper I

The first paper was a description of our procedures for planning and verification of prostate pelvic IMRT as well as a presentation of our first clinical experiences after moving from CRT to IMRT for this patient group. A DVH comparison of CRT with IMRT in 15 patients showed that moving from conformal to intensity-modulated RT considerably reduced irradiation of bowel, bladder and rectum. At the same time, IMRT improved the target coverage. Also the initial clinical outcome results were promising. With these results, we were in line with others who have emphasized the superiority of the IMRT dose distribution compared to the dose distribution produced with CRT for this group of patients. However, none of these studies considered that the large mobility of the relevant OARs (i.e. the bowel, rectum and bladder) could jeopardize the superior normal tissue sparing obtained with IMRT.

5.2 Paper II

In this paper we investigated the influence of OAR motion on prostate pelvic CRT and IMRT and showed that the examined IMRT approach still allowed for reduced doses to the OARs compared to CRT even when accounting for internal organ motion. Internal organ motion made all dose volume parameters worse compared to the planned dose volume parameters both for CRT and IMRT. This could potentially translate into violation of dose constraints and showed that neither the CRT nor the IMRT dose distributions were especially robust towards OAR motion. Notably, the $gEUD$ was less sensitive towards bowel motion than were the volume parameters. However, large differences between the planned and estimated treatment $gEUD$ were found for the bowel in some of the patients. This means that planning based on one bowel contour can easily translate into greater delivered than planned bowel doses.

5.3 Paper III

This paper was a quantification of an empirical population-based PRV margin for the bowel. We showed that isotropic margins of up to 30 mm were required to account for all bowel motion in 90% of the patients. Smaller margins of 5-10 mm were shown to encompass the major part of volumes which had a probability of bowel occupancy of $\geqq$ 75% in 90% of the patients. Population-based PRV margins for the bowel were further shown to be highly unspecific, meaning that they also included large volumes with no bowel occupancy at all.

With a 30 mm margin, 58-84% of the PRV had no bowel occupancy in the treatment CT scans. With these results we showed that more sophisticated methods are required to account for bowel motion. Due to large differences between patients, individually-based methods should be investigated.

5.4 Paper IV

In this last paper we presented a new method to estimate patient-specific small bowel PRVs based on a few CT scans. The sensitivity and specificity depended on the number of CT scans and the applied CP-threshold. The best trade-off between sensitivity and specificity was obtained at a threshold of 0.03. With this threshold and three CT scans, an average sensitivity of 94-96% and specificity of 86-97% was obtained in the three studied patients. Using a CP-threshold greater than 0.05 resulted in a dramatic drop in sensitivity. It was shown that three or more CT scans were required to secure a good representation of the patient-specific variability in SBW position. As compared to conventional planning volumes, the patient-specific PRVs were either similar or better in predicting for SB voxels, and at the same time they occupied a smaller or similar volume in the patient.

Chapter 6

Discussion

The work presented in this thesis aimed to contribute to the tools to allow for more robust treatment planning of pelvic RT for patients with prostate cancer, rectum cancer, bladder cancer and gyneacological cancer. The benefit of moving from CRT to IMRT for prostate cancer patients who receive RT to the prostate, seminal vesicles and pelvic lymph nodes was investigated and the influence of organ motion on both techniques was assessed in order to quantify the robustness of todays planning procedures. These studies emphasized the need for methods to account for bowel motion in planning of pelvic RT. In the last part of this thesis, we therefore presented and evaluated two different concepts to account for such motion. The first concept was an empirical estimation of a population-based planning organ-at-risk (PRV) margin for the bowel, and the second concept was a method to estimate patient-specific SB CPs and PRVs.

Our work, in line with others [5, 15, 29, 32, 41, 48, 50, 53, 63, 66, 69, 74, 75, 94], has shown that the use of IMRT for prostate pelvic RT better conforms the dose to the PTV and therefore reduces the doses to the major OARs (bowel, bladder and rectum) while at the same time improving target coverage. Nutting and colleagues were the first to investigate the potential benefit of using IMRT in stead of CRT to treat the pelvic lymph nodes. They reported a reduction from 18% to 5% of the bowel receiving more than 45 Gy (V_{45}) when replacing CRT with IMRT [66]. However, IMRT redistributes the dose in the patients such that a reduction in the bowel V_{45} has to be repaid by greater volumes receiving lower doses. It is therefore difficult to conclude about the clinical benefit of moving from CRT to IMRT for these patients based on single CT planning studies.

Knowledge about the correlation between bowel dose-volume parameters and the risk of GI adverse effects, especially diarrhea, is unclear. Although many studies have recognized adverse effects from irradiation of the bowel, only a few studies have reported a correlation with dose-volume data [6, 16, 22, 31, 34, 42, 68, 72, 87]. Furthermore, these findings were ambigious with some studies reporting V_{45} to be the predictive cut-off volume and others reporting lower dose cut-off volumes, especially V_{15}, to give the best correlation with acute diarrhea. Divergent definitions of the bowel (i.e. bowel, SB or LB loops vs. IC) and use of absolute vs. relative DVHs also make comparisons between these studies difficult. It should be noted that consideration of absolute volumes are more relevant than relative volumes for the bowel because only parts of the organ is delineated. The recent review by QUANTEC recommended different DVH constraints depending on the definition of bowel (i.e. V_{15} in case of bowel loops and V_{45} in case of IC). Although OAR DVHs and PRV DVHs are expected to be different [85], it is difficult to understand how QUANTEC could conclude on fundamentally different bowel vs. IC constraints bearing in mind the possibility of correlation between low

and high dose bins with CRT DVHs [6, 23, 80, 82, 87]. A recent study by Perna and colleagues of postoperative pelvic IMRT further question the QUANTEC-conclusion of the importance of V_{15} [68]. They found V_{45} to be the predictive cut-off volume even when investigating the correlation between acute toxicity and the DVH of bowel loops. No correlation was found for V_{15}.

During optimization we used dose-volume objectives at 30, 40 and 50 Gy aiming at controlling the intermediate and high bowel doses. Our calculations of generalized EUD was based mainly on the findings by Roeske and colleagues on Grade 2 acute diarrhoea ($k = 3.2 \pm 1.1$ and threshold volume of 195 cm^3) [72]. We used a volume-parameter $k = 4$ and a reference volume of 200 cm^3, which considered the bowel volumes receiving intermediate and high doses (i.e. $V_{25} - V_{50}$, with more weight on high doses). Our results thus rely on the assupmtion of V_{45} being of higher importance than V_{15}.

Although SB motion has been pointed out as one of the reasons to why a limited correlation has been found between dose volume parameters for the SB and adverse GI complications [23, 24, 45, 47], little has been done to investigate the influence of bowel motion on the delivered dose distribution and to account for bowel motion in RT planning [45, 67, 77]. Nuyttens and colleagues reported considerable variation in SB position during RT in patients with rectal cancer treated with preoperative and postoperative RT [67]. Muren and colleages found large variations in bowel volume between patients, especially in the lower pelvis (below the promontory) [62]. Kvinnsland and Muren later investigated the impact of pelvic organ motion on DVHs in ten bladder cancer patients treated with CRT and found that bowel motion cause large uncertainties in the DVHs for the individual patients [45].

In the present work, we have shown that despite the uncertainties in the bowel DVH due to organ motion, prostate pelvic IMRT optimized using one bowel contour still allows for reduction in bowel gEUD compared to CRT. This has also been confirmed by clinical studies showing reduced GI complications when moving from CRT to IMRT (see the recent review by Veldeman [93]). The advantage of IMRT over CRT was mainly due to a reduction in the total volume receiving $\geq 45Gy$ with IMRT. Bowel motion thus resulted in a significantly larger treatment V_{45} than planned with CRT. With IMRT, the biggest differences between planning and treatment were seen for lower dose cut-off volumes. In terms of gEUD, IMRT did not turn out to be less robust than CRT. Notably, the gEUDs were less sensitive to organ motion than the cut-off volumes. Because these are also less sensitive to correlation between DVH dose bins [80, 82], they should be prefferred over cut-off volumes in optimization and evaluation.

In this study (Paper II), organ motion was included by averaging gEUDs. Hoogeman and colleagues have shown that this is a good way of estimating rectal wall EUDs [33]. Also Baum and colleagues used average EUDs for estimating the effect of organ motion [7]. Methods for accumulation of dose have become more available over the last years and should be preferred over averaged EUDs when available and applicable [64, 97].

Although the influence of organ motion was different for CRT and IMRT, it made dose metrics worse. In some patients this translated into much higher bowel doses than planned for, and treatment planning based on single CT PTV/OARs is therefore not optimal. Sanguineti and colleagues also found increased bowel V_{45} during treatment in 8 out of 9 patients when optimizing whole pelvic prostate IMRT based on the bowel as seen on a single planning CT [77]. This shows that alternative methods accounting for bowel motion are needed. Sanguineti and colleagues further compared three strategies to delineate the bowel for use in optimization of prostate pelvic IMRT: one bowel contour, one bowel contour + a 10 mm isotropic margin and the IC volume [77]. The isotropic 10 mm margin was based on our study, where it was shown to be sufficient to cover 90% of the volume occupied by the bowel in more than half of

the CT scans in 90% of the patients (Paper III). Sanguineti and colleagues found bowel+10mm to be the most sensitive PRV among these, but also the one with the largest volume. These findings were probably influenced by the fact that the PRV was not restricted to within the IC. When applied in optimization, both the bowel+10mm and IC volumes produced dose distributions resulting in a lower bowel V_{45} at treatment as compared to optimization on a single bowel volume [77]. Interestingly, the patient-specific variation in V_{45} between repeat CT scans were similar for all three approaches.

The development of a method for generating patient-specific small bowel PRVs in the present work (Paper IV) was motivated by eliminating the large variability in bowel motion between patients [45, 62, 67, 77, 98]. When compared to population based PRVs (i.e. SB+10mm, IC and SB+30mm), the patient-specific PRVs were either similar or better in predicting for SB and SBW voxels, and at the same time they occupied a smaller or similar volume in the patient. Importantly, they were also more robust in the meaning of being less dependent on the motion pattern of the patient in question. However, patient-specific PRVs are more resource-intensive because they require more than one CT scan as well as the SB and IC contours from these CTs. In cases where target coverage is easily obtained with the IC approach, using the patient-specific SB PRV approach instead might not be worth the additional workload. Nevertheless, using the patient-specific SB PRV instead of the IC volume increases the degrees of freedom for the optimizer which is essential in situations where for instance a dose escalation to the pelvic lymph nodes is warranted [8, 59].

Both PRV concepts investigated in the current project (Paper III and IV) are based purely on geometrical considerations. When ICRU suggested the use of margins around OARs, the PRV was defined in analogy to the PTV, but without any given dosimetric criteria [38]. Stroom and Heijmen pointed out the difficulty of defining a general PRV recipe based on a maximum dose constraint [85], while McKenzie suggested different recepies depending on the characteristics of the dose distribution [57]. IMRT dose distributions are even more difficult to characterize compared to CRT. In contrast to McKenzie and colleagues and Stroom and Heijmen, Muren and colleagues suggested to quantify rectum PRV margins based on organ motion as seen in repeat CT scans [60]. The advantage of the latter approach is that it included data on deformation, the disadvantage is that these findings are difficult to generalize. Both Stroom and Heijmen and Muren and colleagues discussed the problem of transferring dose-volume constraints applied for an OAR to the usually much bigger PRV [60, 85]. Muren and colleagues later studied the association between their rectal PRV DVHs and acute and late GI side effects [61, 88]. For the bowel, several studies have tried to correlate the IC DVH to GI side effects [22, 76]. Because our patient-specific SB PRVs are smaller than the IC volume and at the same time has a comparable sensitivity in predicting future SB voxels, it is likely that patient-specific SB PRV DVHs would better represent the delivered bowel dose than the IC DVH.

All DVHs used for RT planning are surrogates of the real accumulated dose delivered to an OAR during the course of radiotherapy, and constraints used for optimization are defined based on our clinical experiences with these surrogates. Therefore, one could argue that as long as the same surrogate DVH is used for planning and evaluation, it should not matter whether this surrogate is derived from a PRV, the organ volume from the snap-shot of a CT or other representations of this organ such as the organ hull from more than one planning CT or the IC volume in case of the bowel. On the other hand, the amount of bowel within the lower pelvis may be of importance, and this information is lost when replacing the bowel volume with a PRV. A simple approach to retain this information is to weight the absolute PRV DVH by a factor V_B^{tot}/V_{PRV}^{tot}. By doing this, patients with a large amount of bowel within the PRV

would be differentiated from patients with less bowel.

Another drawback of PRVs is that they are 'binary'-approaches in the way that a voxel is either defined as belonging to the PRV (value 1) or not (value 0). This poses a problem in optimization of IMRT, where one has to compromise the dose to regions where the TV and OAR overlap. Adding a margin around both the TVs and the OARs naturally leads to larger regions-of-conflict for the optimizer. Baum and colleagues suggested using CPs rather than static 0/1-volumes as a tool to handle such regions-of-conflict [7] . An alternative to using PRVs is therefore to directly use the CP matrix in robust optimization of IMRT. Also with CP-based optimization there is a question of how to transfer known dose-volume constraints. The most intuitive way of doing it would be to weight the contribution of each voxel with the CP. If the CP matrix reflected systematic uncertainties the CP weighted DVH would then represent the delivered dose in an organ [83], but when reflecting random motion the usefulness of a CP weighted DVH is questionable.

This deficiency of CPs occur because dose is evaluated in dose space of the static patient model, ignoring how different parts of the organ move in relation to one another [81]. Ignorance of correlated motion (both within an organ and between organs) with the static patient model, further constrains the possibilities for dealing with conflicting TV and OAR regions because the probability clouds might have common regions. Sobotta and colleagues recently published a robust optimization method based upon statistical theory (R.O.B.U.S.T) which solves this problem by optimization of distributions of treatment outcome incorporating correlation in geometrical shifts [79]. As this method is based upon point-correspondence models which are extremely hard to establish for the SB, CP based optimization most likely remain the best solution for this OAR. However, with recent development in deformable registration (e.g. [12]), it might be possible to establish such models of the sigmoidum and large bowel despite large amplitude motion.

Chapter 7

Conclusions

This PhD project has shown that use of conventional IMRT for pelvic RT in prostate cancer patients better spares the bowel compared to CRT, while at the same time improving target coverage. The advantage of IMRT over CRT was maintained under influence of bowel motion. However, bowel motion made dose metrics worse both for IMRT and CRT and optimization based on a single bowel contour was not optimal for all patients. Therefore, methods accounting for bowel motion are needed to better exploit the potential of IMRT to spare the bowel.

Two planning organ-at-risk (PRV) concepts for the bowel were developed and evaluated in this PhD. The first concept was an empirical estimation of a population-based bowel PRV. Due to large inter-patient variation, this method produced PRVs which were very large when accounting for all bowel motion in a large fraction of patients. Alternatively, a tighter margin could be used to produce a smaller and thus a more specific PRV, but at the expence of a poorer sensitivity in predicting for future bowel voxels. The second concept was a patient-specific small bowel PRV based on a statistical method for estimating coverage probability (CP) maps from repeat CT scans. By removing intra-patient variability, more specific PRVs could be obtained without compromising sensitivity. The specificity/sensitivity of these patient-specific PRVs was tunable by the CP threshold. Importantly, they were more robust towards patient-specific small bowel motion patterns. Patient-specific small bowel PRVs thus provide a promising tool for use in PTV/PRV based IMRT optimization.

Finally, the method developed in this PhD project further has laid the fundation for CP-based robust optimization of pelvic IMRT with the small bowel as OAR.

Chapter 8

Future perspectives

A natural first step beyond this Phd project will be to investigate the use of patient-specific small bowel PRVs and CPs in robust optimization of pelvic IMRT. We hypothesise that these concepts allow for more robust treatment planning compared to the IC approach. In an IMRT planning study we will therefore compare 1) the PTV + IC approach, 2) the PTV + patient-specific PRV approach and 3) the CP_{TV} + CP_{SBW} approach. The coverage probability matrix for the target volume (CP_{TV}) and for the other relevant OARs could for instance be obtained from the method presented by Baum and colleagues [7].

Evaluation of the estimated CP-values in Paper IV is difficult without knowing the true CP matrix. For the SB this information is difficult to obtain. An interesting project would therefore be to evaluate the CP method in an organ where correlated motion of adjacent surface points excist. Söhn and colleagues has developed a principal component based method which can be used to generate reliable CPs for the rectum [81]. These could be compared with CPs estimated with our method. Although the rectum have similarities with the SB, assuming that all voxels with the same distance from the wall have approximately the same CP value is probably less valid for the rectum because it is fixed at one end. It would also be interesting to compare CP-weighted DVHs/EUDs with accumulated DVHs/EUDs.

The methods developed in Paper IV in the current project require the SB contours from a number of CT scans as input. Currently, these are manually outlined by an expert, which is quite resource-intensive. Methods for automatic or semi-automatic segmentation of the SB would therefore be of great assistance in clinical use of this method. In paralell with this PhD project, a method for semi-automatic segmentation of the large bowel has been developed in a connected PhD project [52]. It would be interesting to develop this method further to also include semi-automatic segmentation of the small bowel.

In order to fully exploit the potential of pelvic IMRT it is crucial to establish reliable estimates of evaluators of plan quality. With the tools developed in the current work, we are able to better pinpoint conflicting areas of SB and TV, but finding a compromise of dose to these regions remain challenging because of an unclear dose-volume relationship. Another main focus area of future work will therefore be to correlate patient-specific SB PRV DVHs and CP-weighted DVHs to incidence of GI adverse effects. With the low GI adverse effects rates seen with IMRT such a study would have to include a large number of patients [63]. Even in a large study, the correlation could be jeopardized by imprecicion of grading, unclear cause-effect relation of specific sympthoms (especially for diarrhea), variability in small bowel radiosensitivity between patients, and limitations of surrogate DVHs to representing the real accumulated SB DVH. Despite these challenges, we believe that the SB planning concepts developed in Paper IV of the current project can safely be used clinically and a clinical im-

plementation of these methods both for locally advanced prostate cancer patients, but also for bladder cancer patients and patients with gyneacological cancer, would therefore be a main focus of future work.

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