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Improving radiation dose delivery for moving targets using image guidance

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**Improving bladder cancer treatment with
radiotherapy, using separate IMRT plans for boost
and elective fields**

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2.1 Abstract

Introduction: The aim of this study is to investigate to what extent IMRT can decrease the dose to the organs at risk in bladder cancer treatment compared to conformal treatment, while making separate treatment plans for the elective field and the boost. Special attention is paid to sparing small intestines.

Methods: Twenty patients who were treated with the field-in-field technique (FiF) were replanned with intensity modulated radiotherapy (IMRT) using 5 and 7 beams respectively. Separate treatment plans were made for the elective field (including the pelvic lymph nodes) and the boost, which enables position correction for bone and tumor separately. The prescribed dose was 40 Gy to the elective field and 55 or 60 Gy to the PTV. For bladder and rectum $V_{45\text{Gy}}$ and $V_{55\text{Gy}}$ were compared and for small intestines $V_{25\text{Gy}}$ and $V_{40\text{Gy}}$.

Results: The dose distribution with IMRT conformed better to the shape of the target. There was no significant difference between the techniques in dose to the healthy bladder. The median $V_{40\text{Gy}}$ of the small intestines decreased from 114 cc to 66 cc ($p = 0.001$) with 5 beam IMRT and to 55 cc ($p = 0.001$) with 7 beam IMRT compared to FiF. $V_{45\text{Gy}}$ for rectum decreased from 34.2% to 17.5% ($p = 0.004$) for both 5 and 7 beam plans, while $V_{55\text{Gy}}$ for rectum remained the same.

Conclusions: With IMRT a statistically significant dose decrease to the small intestines can be achieved, while covering both tumor and elective PTV adequately.

2.2 Introduction

Radiotherapy is a common treatment in the management of bladder cancer, particularly when surgery is not an option. A major problem in focal bladder cancer irradiation is the large day-to-day variation of the position of the tumor [22,37-41]. The position of the bladder wall depends on bladder filling and the position of the bladder as a whole depends on bowel and rectum filling. Large planning target volume (PTV) margins are required to compensate for this uncertainty. Because of these large margins, a considerable amount of healthy tissue is irradiated. Small intestines, rectum and the healthy part of the bladder are the organs at risk.

At the Department of Radiation Oncology of the Academic Medical Center in Amsterdam, in bladder cancer irradiation, the small pelvis is irradiated with an elective field, to include the pelvic lymph nodes and the whole bladder. A concomitant boost is given to the tumor. Previous studies have shown that the local control rate was 56% in 3 years [24,42].

Intensity modulated radiotherapy (IMRT) has several advantages compared to conformal treatment planning. IMRT is capable of handling concave-shaped targets and creates relatively steep dose gradients [43]. Sondergaard *et al.* recently showed that IMRT has a normal tissue sparing effect in comparison to a 3-field box technique [44]. They showed that IMRT decreases the dose to the bowel, bowel cavity, rectum and femoral heads. In their study, the healthy part of the bladder and the pelvic lymph nodes were irradiated too.

However, the steep dose gradients that are used in IMRT are a potential risk for mobile targets such as the bladder tumor. Without on-line position verification the target can be missed. Since 2004, markers are used in our department to guide the delineation of the bladder tumor. These markers are also visible on CBCT. The markers are placed around the tumor and can, therefore, be used as a surrogate for the tumor position. This enables image-guided radiotherapy (IGRT) for bladder tumors. However, the movement of the pelvic lymph nodes with respect to the bony anatomy is relatively small and independent of the movement of the bladder [45]. That means the implementation of on-line position correction might introduce the risk of underdosing the pelvic lymph nodes. In this study we have therefore made two separate IMRT plans, an elective plan and a boost plan, affording us the opportunity to adjust the patient position in between the application of both plans.

The aim of this study is to separate the elective field and the boost in individual IMRT plans and still profit from the benefits of IMRT for the dose in the organs at risk (OARs).

2.3 Methods

2.3.1 Patients

Twenty patients with histologically proven bladder cancer were included in this modeling study: median age: 81.5, range: 66-88 years. All patients were treated with the field-in-field-technique (FiF) in the period 2003-2007 [24]. Starting in November 2004, titanium clips were implanted around the tumor under cystoscopic guidance to serve as reference points for gross tumor volume (GTV) delineation [26]. Contrary to, for instance, prostate markers these titanium clips were implanted around the tumor, to indicate the border between tumor tissue and the healthy bladder wall. One patient had undergone rectum resection in the past, so the results for rectum are for 19 patients.

2.3.2 Delineation

For all patients a planning CT scan with 3 mm slices was acquired while the patient was in supine position. An experienced radiation oncologist (MH) delineated GTV and the unaffected part of the bladder (healthy bladder) on the planning CT. During five consecutive days a repeat CT scan was made of each patient to be able to apply the adaptive margin strategy. The physician delineated the GTV in each repeat CT. The GTVs of all CTs of a patient were summed up to form the GTV_{SUM} . The PTV was constructed with

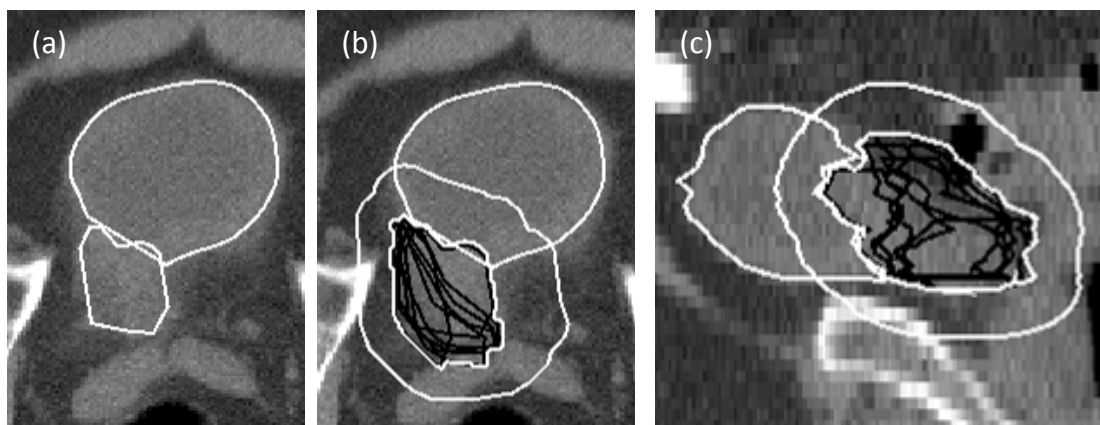


Figure 2.1: a: The GTV is delineated on the first CT-scan. b: The delineations of the GTVs of five repeat CTs are projected on the first CT and a summated GTV is drawn, surrounding all GTVs: GTV_{SUM} . The PTV is defined as a 1.0 cm margin around GTV_{SUM} . c: The sagittal point of view.

GTV_{SUM}-PTV margin of 10 mm. This is illustrated in figure 2.1. From now on, this PTV will be called PTV_{tumor}. For more details regarding this technique see Pos *et al* [25].

For IMRT planning a number of additional structures were delineated: pelvic lymph nodes, rectum, small intestines and a PTV for the 40 Gy field (PTV₄₀). The PTV₄₀ included the PTV_{tumor}, a margin of 5 mm around the lymph nodes and an anisotropic margin around the bladder. The margins around the bladder were 20 mm in the cranial and anterior direction and 10 mm in posterior, lateral and caudal direction. The rectum was delineated from the first slice above the anal verge to the slice below the recto-sigmoid flexure. The small intestines were delineated up to 5 slices above the upper slice where PTV₄₀ appears. All delineations were checked by the same experienced physician .

2.3.3 Conformal treatment planning and field set-up

All treatment plans were made with the planning system PLATO (Nucletron BV, Veenendaal, The Netherlands) using an energy of 10 MV. A conformal four-field technique was used for the elective field and the conformal concomitant boost was delivered by 2-4 beams [24]. A requirement of the plans was that 99% of the volume of the PTV_{tumor} received $\geq 95\%$ of the prescription dose.

The prescribed dose to the elective field was 40 Gy. The elective field included the whole bladder and the pelvic lymph nodes. The cranial limit was the L5-S1 inter space, the caudal limit was 5 mm caudal of the symphysis, the anterior and posterior limits were 15 mm beyond the bladder or tumor and the lateral margins were 10 mm beyond the maximum width of the bony pelvis. The field set-up is shown in figure 2.2. The prescribed dose to the PTV_{tumor} was 55 Gy or 60 Gy. Before the year 2006, 55 Gy was the standard treatment. From then on and up to the present, 60 Gy is the standard treatment. However, 55 Gy is prescribed if small intestines are in the boost field, because small intestines are the first organs at risk of severe complications. Ten patients in this study were treated with 55 Gy and ten patients were treated with 60 Gy.

If a dose of 55 Gy was prescribed, the patient received twenty fractions of 2.75 Gy: 2 Gy on the elective field and a concomitant boost of 0.75 Gy to the PTV_{tumor}. If a dose of 60 Gy was prescribed, the patient also received 2.75 Gy in the first twenty fractions as well as two additional fractions of 2.5 Gy to the PTV_{tumor}. A separate treatment plan was made for the last two fractions.

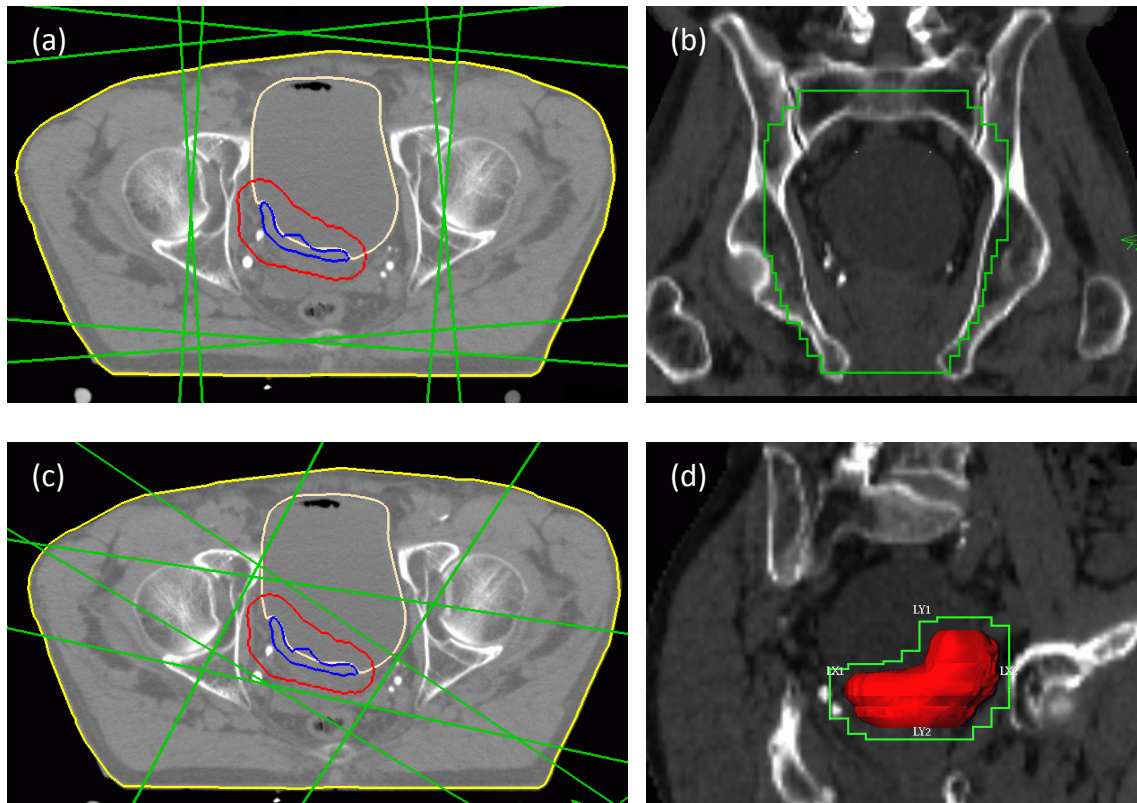


Figure 2.2: a: The beams of the elective part of the conformal treatment. b: The beams-eye-view of the AP beam. c: The beams of the boost part of the conformal treatment. d: The beams-eye-biew of one beam.

The dose was normalized in a point conform ICRU 62 in all plans [46]. For patients with an additional boost plan, the total dose was evaluated in PLATO's evaluation tool EVAL.

2.3.4 IMRT treatment planning

For the IMRT plans, the same fractionation schedule was maintained as in the original plans. All treatment plans were made with the same treatment planning system, with an energy of 10 MV.

For every patient, one IMRT plan was made with five beam angles (40° , 110° , 180° , 250° and 320°) and one was made with seven beam angles (30° , 80° , 130° , 180° , 230° , 280° and 330°). A requirement of the plans was that 99% of the volume of the PTV_{tumor} received $\geq 95\%$ of the prescription dose. Since the PTV_{40} had been delineated for IMRT, an additional requirement for the IMRT plans was that 99% of the volume of PTV_{40} received $\geq 95\%$ of 40 Gy.

IMRT was separated in two plans: a boost plan and a plan for the elective field. Both plans will be given each fraction, with the option to adjust the patient position between

irradiation of both plans. We used the same gantry angles for both plans. First we planned the boost field. While planning the elective field, the dose received due to the boost field was taken into account.

2.3.5 Analysis

For the small intestines, the volumes that received at least 25 Gy ($V_{25\text{Gy}}$), and 40 Gy ($V_{40\text{Gy}}$) were compared. For rectum and bladder, $V_{45\text{Gy}}$ and $V_{55\text{Gy}}$ were compared. For PTV_{40} , $V_{38\text{Gy}}$ was compared, because the requirement is that 99% of the volume receives 95% of the prescribed dose. Because IMRT usually creates a large area with a low dose, we also compared $V_{5\text{Gy}}$ of the body. We used the relative volume for the bladder, rectum and PTV_{40} . For small intestines the absolute volume was used, since that structure is only delineated in the area that receives dose. For the body, we also used the absolute volume. The results are displayed as: median (interquartile range (IQR) 25% - 75%)

Because the results did not have a normal distribution, they were compared with a Wilcoxon signed rank test. This paired test compares the IMRT results of a patient with the result of the original plan of that same patient. This way, the statistics are not influenced by the two different prescription doses. Bonferroni correction was applied, because eight variables were tested ($V_{25\text{Gy}}$ and $V_{40\text{Gy}}$ for small intestines, $V_{45\text{Gy}}$ and $V_{55\text{Gy}}$ for bladder and rectum, $V_{38\text{Gy}}$ for PTV_{40} and $V_{5\text{Gy}}$ for the body). To test with $\alpha = 0.05$, p-value after Bonferroni correction was 0.006. For the analysis, we have not made a distinction between the groups that were treated with 55 Gy and 60 Gy. The dose per fraction is the same in both situations. Therefore, the dose that is representative for complications is also the same for both groups.

The correlation between underdosage of PTV_{40} in the original treatment plan and the benefit that small intestines have with IMRT compared to the FiF technique, was calculated with Kendall's tau. For the statistical analysis, SPSS release 12.0.1 (SPSS Inc., Chicago, USA) was used.

2.4 Results

IMRT results in a different dose distribution than FiF. Compared to IMRT, FiF leads to a relatively rectangular dose distribution, for both boost field and elective field, see figures 2.3 a-d. The dose distribution of IMRT conforms more to the shape of the target, and because of that the small intestines, in particular, are spared. Note that PTV_{40} , pelvic

lymph nodes, small intestines and rectum were not delineated at the moment the FiF treatment planning was made.

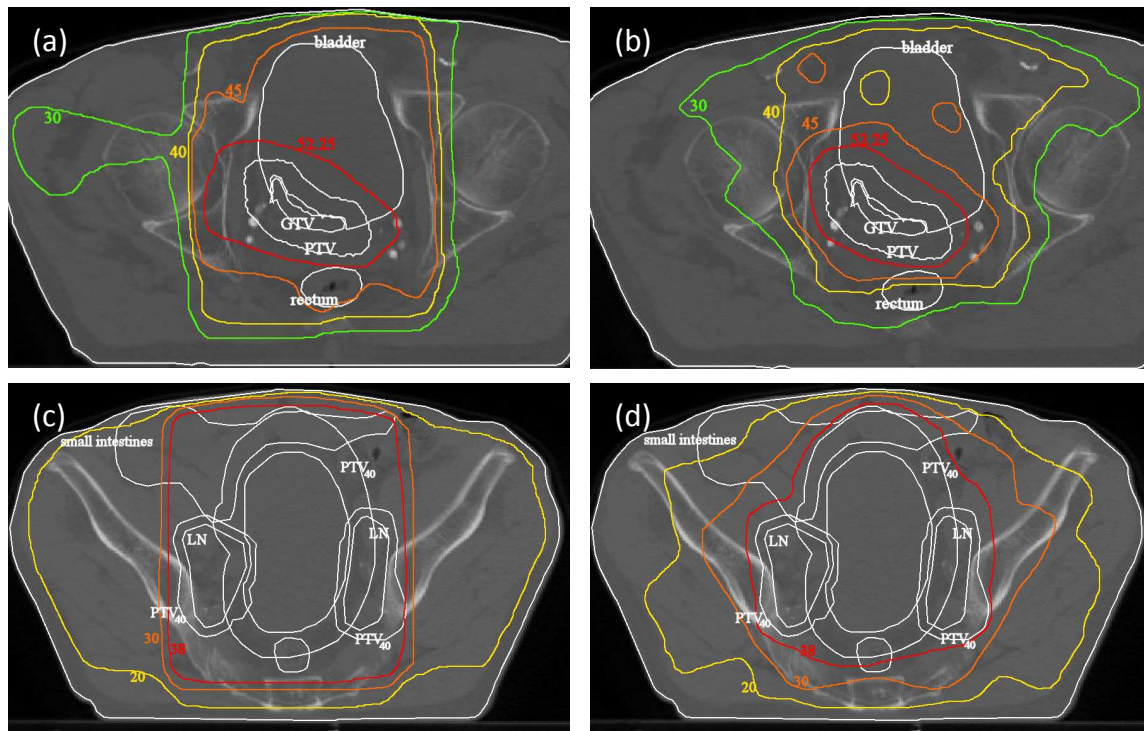


Figure 2.3: Dose distributions. Figure a shows the dose distribution of the boost with the FiF-technique and figure b with IMRT for a patient with a prescription dose of 55 Gy. Figure c shows the dose distribution of the elective field with the FiF-technique and figure d with IMRT.

Comparing dose-volume histograms (DVHs) for all patients for both the 5- and 7-beam IMRT plans shows that there is hardly any gain using seven over five beams. Figures 2.4 a-d show the DVHs of a typical patient with a prescribed dose of 60 Gy. They show that the DVHs of IMRT using five beams and IMRT using seven beams almost overlap. Furthermore, this example clearly shows that the dose in small intestines is lower with IMRT than with FiF. For the rectum and the bladder, the situation was slightly more complicated since the lines cross at 55 Gy and 59 Gy respectively. This means that for doses higher than 55 Gy for the rectum and 59 Gy for the bladder the conformal plan outperforms the IMRT plan. However, for lower doses it is the other way around. Also note that in this example the PTV_{40} is underdosed with the FiF-technique.

For the healthy bladder, there was no statistically significant difference between FiF and the IMRT plans, as can be seen in tables 2.1a and 2.1b. V_{40Gy} of the small intestines and V_{45Gy} of the rectum showed a significant decrease with IMRT. PTV_{40} is underdosed in almost all FiF plans. V_{5Gy} of the body did not show a statistical difference.

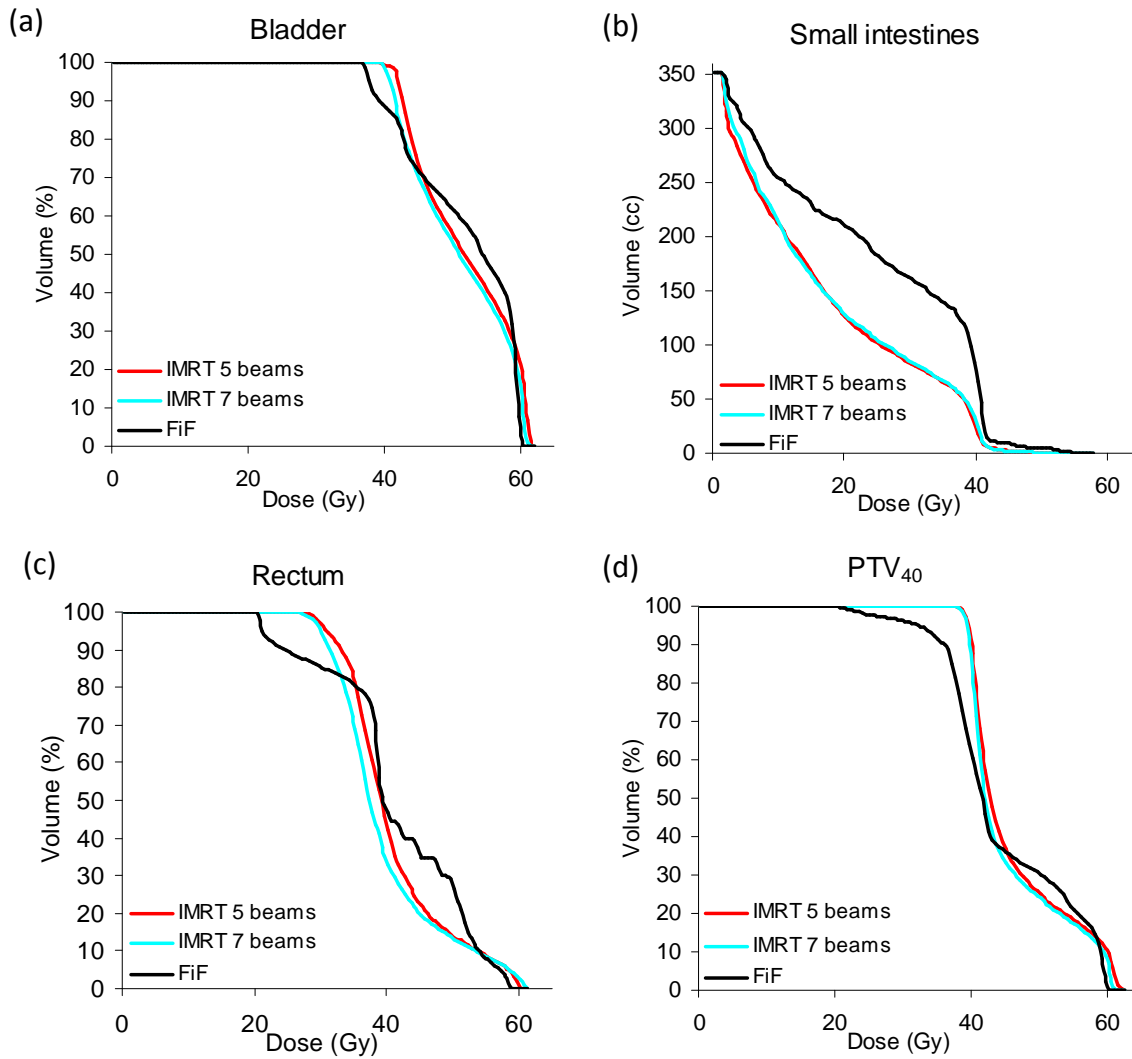


Figure 2.4: Cumulative dose-volume histograms from a patient with a prescribed dose of 60 Gy. a: The dose to the bladder is almost equal in all techniques. b: FiF gives a higher dose to more volume of the small intestines compared with IMRT. c: For the rectum, the lines cross at 35 Gy and 55 Gy. d: PTV₄₀ is underdosed with FiF.

Underdosing PTV₄₀ might spare small intestines in FiF plans. We therefore calculated the correlation between the underdosage of PTV₄₀ and the benefits that small intestines have from IMRT. Kendall's tau = -0.40 ($p = 0.008$), indicating that underdosage of PTV₄₀ with the FiF technique underestimates the improvement in dose reduction gained by IMRT. The correlation between underdosage of PTV₄₀ and small intestines is shown in figure 2.5.

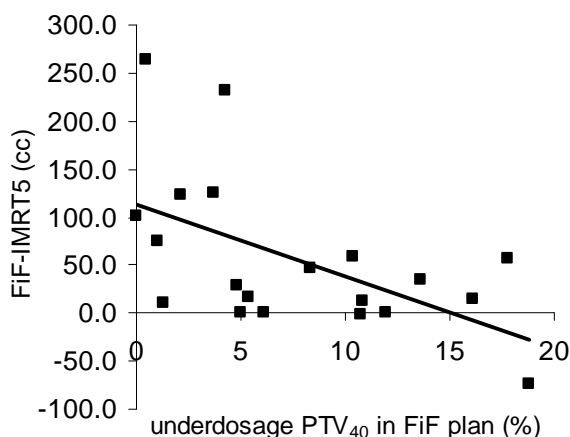


Figure 2.5: Relation between the underdosage of PTV₄₀ in the FiF plan and the difference in volume of small intestines that receives 40 Gy or more between FiF and 5-beam IMRT.

Table 2.1a: Results of the comparison of FiF with IMRT using five beams

	FiF Median (25%-75% quartile)	IMRT 5 beams Median (25%-75% Quartile)	p-value
Bladder V _{45Gy}	71.9 % (60.1 – 80.5)	75.3 % (46.8 – 83.6)	0.131
Bladder V _{55Gy}	30.2 % (3.4 – 52.7)	30.5 % (17.3 – 48.6)	0.104
Small intestines V _{25Gy}	252 cc (87 – 335)	221 cc (77 – 333)	0.052
Small intestines V _{40Gy}	114 cc (40-188)	66 cc (17 – 153)	0.001*
Rectum V _{45Gy}	34.2 % (20.7 – 51.9)	17.5 % (6.9 – 29.3)	0.004*
Rectum V _{55Gy}	3.7 % (0.0 – 8.5)	4.7 % (0.2 – 9.5)	0.932
PTV ₄₀ V _{38Gy}	93.3 % (87.4 - 96.5)	99.6 % (99.4 – 99.7)	< 0.001*
Body V _{5Gy}	8520 cc (6934 – 9344)	8257 cc (7483 – 10640)	0.057

*statistical significant p-values with Bonferroni correction.

Table 2.1b: Results of the comparison of FiF with IMRT using seven beams

	FiF Median (25%-75% quartile)	IMRT 7 beams Median (25%-75% Quartile)	p-value
Bladder V _{45Gy}	71.9 % (60.1 – 80.5)	72.5 % (51.2 – 78.1)	0.779
Bladder V _{55Gy}	30.2 % (3.4 – 52.7)	32.8 % (16.9 – 42.4)	0.370
Small intestines V _{25Gy}	252 cc (87 – 335)	211 cc (77 – 333)	0.033
Small intestines V _{40Gy}	114 cc (40-188)	55 cc (14 – 140)	0.001*
Rectum V _{45Gy}	34.2 % (20.7 – 51.9)	15.0 % (5.2 – 27.7)	0.003*
Rectum V _{55Gy}	3.7 % (0.0 – 8.5)	3.1 % (0.0 – 9.0)	0.816
PTV ₄₀ V _{38Gy}	93.3 % (87.4 - 96.5)	99.6 % (99.5 – 99.8)	< 0.001*
Body V _{5Gy}	8520 cc (6934 – 9344)	8311 cc (7365 – 10807)	0.048

*statistical significant p-values with Bonferroni correction.

2.5 Discussion

This study shows that the dose in small intestines can be decreased significantly with IMRT, while PTV_{tumor} meets the prescription dose in all IMRT and FiF plans. Reducing the dose in small intestines is very important, because of their sensitivity to radiation and the fact that they cause the majority of serious complications in the treatment of bladder cancer using irradiation. The risk of complications is related to the volume of small intestines that receives more than 45 Gy in 2 Gy fractions, which corresponds to 41 Gy in 2.75 Gy fractions, using biological modeling with L-Q modeling parameter $\alpha/\beta = 6$ Gy [47].

The healthy part of the bladder did not receive a lower dose with IMRT compared to the FiF technique, because, contrary to the other organs at risk, a minimum dose of 40 Gy is prescribed to the bladder. Also, there is always a part overlapping with PTV_{tumor} , which has a prescription dose of 55 Gy or 60 Gy.

$V_{45\text{Gy}}$ for rectum is significantly smaller with both IMRT plans than with FiF, but $V_{55\text{Gy}}$ is the same in both techniques. This is because the volume that receives 55 Gy or more is the volume that overlaps with PTV_{tumor} , and that volume is not reduced. However, the mean volume that receives more than 55 Gy is relatively small in all treatment planning techniques (see table 2.1a and 2.1b).

This study is partially biased because the small intestines and rectum were not delineated at the moment the original planning was made. The dose in these structures was determined retrospectively. If they would have been delineated and the DVHs were available, the planning could have been different. So a part of what is considered as benefits of IMRT may be benefits of delineating all these organs as well.

IMRT is usually associated with irradiation of a larger volume of the body to a low dose and with increased treatment time. In this study we found no significant difference in $V_{5\text{Gy}}$ for the body between FiF and the IMRT plans. The FiF technique uses 6 – 8 beams and usually some of them have wedges. Therefore, no large benefits or disadvantages were expected from IMRT on this point. The number of monitor units in the IMRT plan is on average 1.4 times higher than in the FiF plan (data not shown). Newer techniques such as VMAT and RAPID ARC might benefit on this point. Reducing the treatment time would be beneficial in the case of a bladder tumor, because the target is mobile and a shorter treatment time would also reduce the intrafraction motion. These techniques are still very new and they are not clinically available in our department.

The difference between IMRT plans with 5 and 7 beams is very small and is probably not clinically relevant. As IMRT with 5 beams is easier to implement clinically, we suggest using IMRT with 5 beams.

A number of additional structures had to be delineated for the IMRT plan that were not delineated for the original plan: the lymph nodes, PTV₄₀, rectum and small intestines. This was necessary to be able to steer the dose during IMRT optimization. We chose to delineate only the rectum and small intestines as additional OARs. The rectum is very close to the bladder and it overlaps with the PTV in a number of cases and the small intestines are the most radiosensitive structure in the pelvic area. Femoral heads and the colon were not delineated; they received a low dose in this treatment, typically below 30 Gy. The plans were visually checked for hotspots in these organs.

PTV₄₀ was significantly underdosed in the conformal treatment plan. This is mainly due to the fact that PTV₄₀ was not delineated for the original treatment plans. Wang-Chesebro *et al.* also found that a significant percentage (25%) of the lymph nodes will be missed if the elective field is based on bony landmarks [48]. The negative correlation between the underdosage of PTV₄₀ in the conformal treatment plan and the reduction in V_{40Gy} of the small intestines with IMRT suggests that if the PTV₄₀ would have been covered adequately in the conformal treatment plan, the difference in small bowel irradiation might have been in favor of IMRT even more.

When we compare our results to those of Sondergaard *et al.*, we notice that they find a statistically significant advantage of IMRT on more DVH-points than we do [44]. They showed that IMRT is better on V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{40Gy} and V_{50Gy} for the bowel, while we only found a difference on V_{40Gy}, but not on V_{25Gy}. A major difference is that they compared IMRT to a 3-field box technique. We used four beams for the elective field and chose the angles of the beams for the boost in such a way that the OARs were mostly spared. Therefore, the technique we compared IMRT with, might already give a lower dose in the OARs than their conventional technique.

Some other studies comparing IMRT with conformal RT including pelvic lymph nodes consider prostate cancer [49,50]. In the study of Ashman *et al.*, 3D conformal radiotherapy (3D-CRT) was compared with IMRT using five beams in prostate cancer patients with pelvic lymph node irradiation of 45 Gy. V_{40Gy} in small intestines decreased from 29.1% (\pm 15.1) with 3D-CRT to 21.4% (\pm 11.1) using IMRT and V_{25Gy} is the same in both techniques (59.1%). V_{45Gy} of the rectum decreased from 40.5% (\pm 9.7) using 3D-CRT to 2.8% (\pm 2.4) with IMRT, which is a larger decrease than what we have shown. This is probably due to the fact that only the elective phase of the treatment was taken into account in Ashman's study, whereas we considered the dose distribution as a whole. Muren *et al.* also

compared 3D-CRT to IMRT, using IMRT with 7 beams. The mean $V_{40\text{Gy}}$ of the small intestines decreased from 139 cc with CRT to 89 cc with IMRT, but $V_{20\text{Gy}}$ increased from 264 cc to 281 cc and they found no significant difference in $V_{30\text{Gy}}$. For rectum $V_{40\text{Gy}}$, $V_{50\text{Gy}}$ and $V_{60\text{Gy}}$ decreased statistically significant with IMRT compared to CRT. We cannot compare the decrease in dose to the bladder in both studies with our study, because the patients in those studies were prostate cancer patients.

In our department it is standard practice to include the pelvic lymph nodes in the 40 Gy elective field. The reason for this, is that pathology studies have shown that about 25% of the patients have lymph node metastases at the time of cystectomy and several radical cystectomy studies have shown that treatment outcome is positively correlated with the number of lymph nodes removed during the surgery [51-53]. Unfortunately, there has never been a randomized trial to study the effect of elective treatment of the lymph nodes with radiotherapy. For that reason, the indication for lymph node treatment is still a matter of debate. A negative side effect of irradiating the pelvic lymph nodes, is the increased risk of bowel complications, which we hope to reduce by implementing IMRT for this treatment. The results of this study are promising, but only a clinical study can show the real effects of introducing IMRT.

In general, IMRT with its steep dose gradients is beneficial for the OARs. However, the steep dose gradients also induce an increased risk of target miss. Therefore, we can't stress enough that the introduction of IMRT for irradiation of bladder tumors should be accompanied by IGRT. Considering the intrafraction motion for this organ, we should be careful with reducing the margin even when daily on-line position correction is being applied.

2.6 Conclusion

We have shown that IMRT improves the dose distribution in small intestines. A smaller part of the volume is in the high dose region, which reduces the risk of complications. This enables future dose escalation and, with that, hopefully an improved treatment outcome. We have also shown that we can separate the elective field and the boost in two separate IMRT plans without creating additional high dose regions. This enables on-line position correction of both plans separately and as a next step it might enable us to reduce margins, which will result in an even lower dose in the OARs.

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