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PHYSICS CONTRIBUTION

INFLUENCE OF ORGAN MOTION ON CONFORMAL VS. INTENSITY-MODULATED PELVIC RADIOTHERAPY FOR PROSTATE CANCER

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Purpose: To compare an intensity-modulated radiotherapy (IMRT) planning approach for prostate pelvic RT with a conformal RT (CRT) approach taking into account the influence of organ-at-risk (OAR) motion.
Methods and Materials: A total of 20 male patients, each with one planning computed tomography scan and five to eight treatment computed tomography scans, were used for simulation of IMRT and CRT for delivery of a prescribed dose of 50 Gy to the prostate, seminal vesicles, and pelvic lymph nodes. Planning was done in Eclipse without correcting for OAR motion. Evaluation was performed using the CRT and IMRT dose matrices and the planning and treatment OAR outlines. The generalized equivalent uniform dose (gEUD) was calculated for 894 OAR volumes using a volume–effect parameter of 4, 12, and 8 for bowel, rectum and bladder, respectively. For the bowel, the gEUD was normalized to a reference volume of 200 cm³. For each patient and each OAR, an average of the treatment gEUDs (gEUD_treat) was calculated for CRT and IMRT. The paired t test was used to compare IMRT with CRT and gEUD_treat with gEUD_plan.
Results: The mean gEUD_treat was reduced from 43 to 40 Gy, 47 to 46 Gy, and 48 to 45 Gy with IMRT for the bowel, rectum, and bladder, respectively ($p < 0.001$). Differences between the gEUD_plan and gEUD_treat were not significant ($p > 0.05$) for any OAR but was >6% for the bowel in 6 of 20 patients.
Conclusion: Intensity-modulated RT reduced the bowel, rectum, and bladder gEUDs also under influence of OAR motion. Neither CRT nor IMRT was robust against bowel motion, but IMRT was not less robust than CRT. © 2008 Elsevier Inc.

Intensity-modulated radiotherapy, Prostate cancer, Lymph nodes, Bowel, Organ motion.

INTRODUCTION

The motivation for introducing intensity-modulated radiotherapy (IMRT) for the treatment of pelvic lymph nodes in prostate cancer patients has been to reduce the incidence of gastrointestinal (GI) adverse effects and, if possible, to escalate the dose to the pelvic lymph nodes. Several planning studies have demonstrated the superiority of IMRT compared with conformal RT (CRT) to shape the dose distribution to the planning target volume (PTV), thereby reducing the dose to the main organs-at-risk (OARs) (*i.e.,* the bowel, rectum, and bladder) (1–13). Also, a few clinical studies have indicated a better outcome with IMRT (4, 6, 13, 14).

Although IMRT provides the possibility for improving treatment outcome, it is not straightforward to exploit this potential fully. First, knowledge about the radiobiologic mech-

anisms behind GI adverse effects is limited and influenced by the characteristic dose patterns of previous treatment approaches. Second, 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. Although a topic for planning and evaluation of three-dimensional CRT, these issues become even more pronounced with IMRT, because the dose distribution can be shaped more freely. In contrast to IMRT, three-dimensional CRT planning is target centric and does not need a planning OAR volume concept (15). Thus, CRT and IMRT dose distributions would show different characteristics in the presence of organ movements.

The aim of the present study was to understand these differences better. Because the examined IMRT approach applies

the OAR contours from one computed tomography (CT) scan as the basis for dose optimization, no attempt was made to correct for OAR motion during planning. We, therefore, hypothesized that IMRT would be less robust against OAR movement than would CRT. By robust, we mean that the dose metrics of the plan would be predictable to within a tolerable uncertainty of the metrics of the applied dose. In other words, does "better" in planning stay "better" in application, or is the planning advantage an illusion? Hence, a second aim of this study was to determine whether the IMRT approach actually is superior to CRT when also considering OAR movement. As a measure for evaluating the OAR doses, we used the generalized equivalent uniform dose (gEUD). The gEUD has not been frequently used for the bowel; therefore, we discuss how this parameter can be calculated for this organ.

METHODS AND MATERIALS

The patient data (16), as well as the procedure for the definition of targets and treatment planning and delivery (including patient setup), has been previously described in detail (13). A brief description of the materials and planning procedures is outlined.

Patient data

A group of 20 male patients with muscle-invasive transitional cell urinary bladder cancer was used. Of these 20 patients, 14 received RT at Haukeland University Hospital (HUH) during 2000 and 2001, and 6 were treated at Edinburgh Cancer Centre (ECC) in 2003. For the whole group, patient age was 58–87 years. Repeat CT scans were acquired once and twice weekly for the patients treated at HUH and ECC, respectively.

Repeat CT scanning and definition of normal tissues

Overall, one planning CT scan and five to eight treatment CT scans were acquired for each patient, giving a total of 149 scans, all covering the pelvic region up to the sacral promontory or above. All patients were scanned in the supine position with a 3- or 5-mm slice thickness. The treatment scans were registered to the planning scan using the bony anatomy.

In each of these scans, the bladder, rectum, and bowel were outlined. One of us (L.P.M.) did the outlining for the patients from HUH, and a physician from ECC did the outlining for the patients

treated at ECC, except for the bowel in the planning scans, which was outlined by another one of us (L.B.H.). The same instructions for outlining were followed by all three operators. The bowel volume included all parts of the small and large bowel located below the sacral promontory. For the rectum, we applied the first slice below the rectosigmoid flexure as the superior/cranial limit and the first slice above the anal verge as the inferior/caudal limit. All three organs were defined with their contents. All contours for the patients from ECC were reviewed by one of us (L.B.H.) to ensure the same definitions for outlining had been used for patients from ECC and HUH. The organ outlines in the treatment scans were transferred to the planning scan and saved as separate Digital Imaging and Communications in Medicine (DICOM) files. The planning outlines were actively used during optimization, and the treatment outlines were only used for evaluation.

Definition of target volumes

Using the Eclipse treatment planning system (Varian Oncology Systems, Palo Alto, CA), one radiation oncologist (S.I.H.) with delegated responsibility for prostate cancer contoured the prostate, seminal vesicles, and relevant lymph nodes on the planning CT scans. The lymph node volume encompassed the internal and external iliac vessels and a rim of about 2.5 cm along the pelvic wall between these vessels. The presacral nodes were not included. These volumes were then extended with margins to produce the PTV. Around the prostate and seminal vesicles, we applied a margin of 15 mm in all directions, except for posteriorly, where a 10-mm margin was used. The lymph node volume was included with an isotropic 10-mm margin.

Treatment planning

Following the planning procedures used at HUH, we created a three-dimensional CRT plan and an IMRT plan for simulation of the first treatment phase (prescribed dose, 50 Gy). The CRT plan consisted of two opposing anterior and posterior beams and two opposing lateral beams (gantry angles, 0°, 90°, 180°, and 270°), with all beams having a 15-MV beam quality. All beams were shaped with a MillenniumMLC-120 multileaf collimator (Varian Medical Systems) conformed to the PTV with a margin of approximately 10 mm superiorly and inferiorly and 6 mm laterally, except in the posterior direction, where the leaves were pulled closer toward/into the PTV to shield the rectum (Fig. 1). The collimator angle of the anterior and posterior beams was rotated to 90° and a few multileaf collimator leaves were positioned between the lobes of the
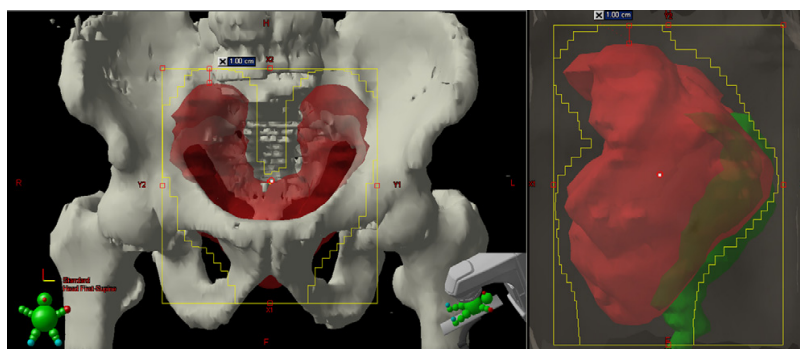

Fig. 1. Frontal and lateral beam's eye view of 1 patient showing the planning target volume (red), rectum (green), and the position of multileaf collimator leaves from the conformal radiotherapy plan.

PTV for 5 patients, in whom this was possible (Fig. 1). Although aiming for a dose of 95–107% of the prescribed dose to the PTV, a minimal point dose of 90% was accepted in the posterior part of the PTV to avoid an unacceptably high rectum dose (Fig. 2).

For the IMRT plan, we used a seven-field beam arrangement (gantry angles, 0°, 51°, 103°, 154°, 206°, 257°, and 309°) with the same beam quality as for the CRT plan (*i.e.,* 15 MV). The minimal dose criterion of 95% of the prescribed dose to the PTV was given the greatest priority during the optimization. For the OARs, we used objectives at 30, 40, and 50 Gy. These were defined relative to the dose–volume histogram (DVH) obtained from the CRT plan. For the bowel, rectum, and bladder, the DVH objectives were set to 50%, 75%, and 75%, respectively, of the CRT DVH. In addition, hot spots in the unspecified normal tissue were avoided by applying a maximal dose objective (95% of the prescribed dose) to the tissue surrounding the PTV with a distance of ≥3–5 mm from the PTV. One radiation oncologist (S.I.H.) reviewed all treatment plans.

Definitions and gEUD calculation

For all patients, both dose distributions were calculated on the planning CT scan using a 2.5×2.5-mm^2 grid size and exported from Eclipse as DICOM files. For each patient, the structure files from the CT scans were sorted chronologically with $j = 0$ for the planning CT, and $j \, \epsilon [1, N]$ for the treatment CT scans (with N being the number of treatment CT scans). Dose matrices and organ outlines (regions of interest [ROIs]) were then imported into VerA (an in-house created software program written in Interactive Data Language) as DICOM RT and DICOM structure files. The CT coordinates of the ROIs (given in the DICOM structure files) were approximated by the closest pixel coordinates of the dose matrix, and the DVH for the ROI was calculated from all pixels within the ROI.

The Interactive Data Language was also used for calculating the gEUD from each of the 894 OAR DVHs (using a resolution of 1

Gy). Because less than the whole bowel volume was contoured, we extended the gEUD concept of Niemierko (17, 18) to calculate the gEUD relative to an absolute reference volume (V_{ref}):

$$gEUD = \left(\frac{1}{V_{ref}} \sum_i v_i D_i^k \right)^{\frac{1}{k}} \qquad (1)$$

where (v_i, D_i) denotes the ith bin of the differential DVH, and k is associated with the volume effect of the organ considered. A V_{ref} of 200 cm^3 was used for bowel, and the gEUD for the rectum and bladder was calculated relative to the whole organ volume. For the k parameter we used 4, 12, and 8 for the bowel, rectum, and bladder, respectively (19, 20). A DVH reduction with k = 12 practically only considers the volume elements receiving ≥80% of the maximal OAR dose, while a reduction with k = 4 would also consider the volumes receiving intermediate doses (>50%) but would weigh these against greater dose volumes. For each patient and each organ, we also calculated the average value of the gEUDs obtained from the N treatment CT scans:

$$gEUD_{treat} = \frac{1}{N} \sum_{j=1}^{N} gEUD_j \qquad (2)$$

as well as its standard deviation:

$$SD_{treat} = \sqrt{ \frac{1}{N-1} \sum_{j=1}^{N} \left(gEUD_j - gEUD_{treat} \right)^2 } \qquad (3)$$

In analogy to gEUD$_{treat}$, gEUD$_{j=0}$ was denoted gEUD$_{plan}$.

We also compared the OAR volumes receiving doses greater than x ε {25, 30, 35, 40, 45, 50}Gy. Vx will henceforth be referred to as the volume (absolute or relative) receiving more than xGy, Vx$_{treat}$ as the average of Vx obtained from the treatment DVHs, and Vx$_{plan}$ as Vx obtained from the planning DVH.
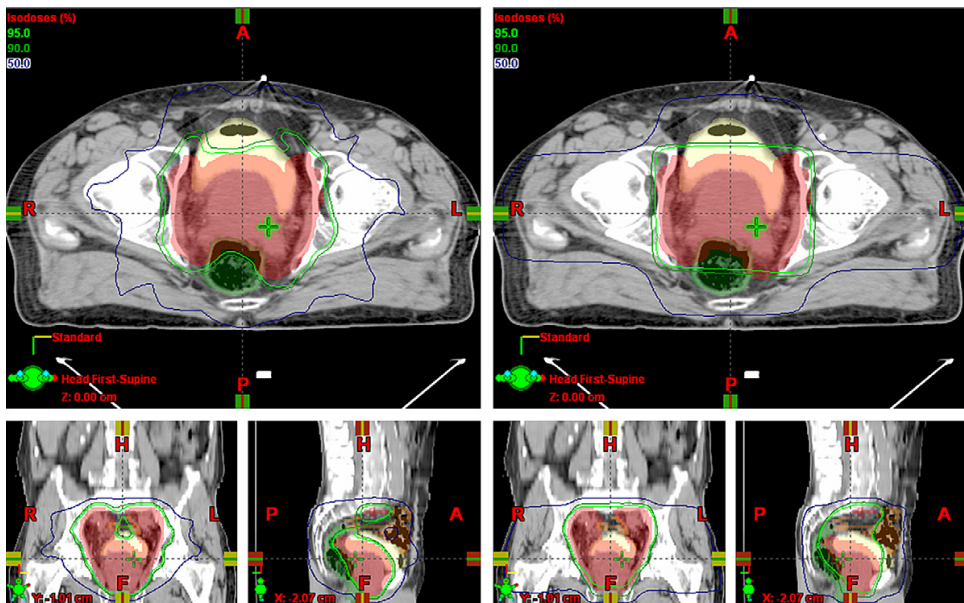

Fig. 2. Illustration of improved target coverage obtained with (Left) intensity-modulated radiotherapy compared with (Right) conformal radiotherapy.

After confirming the presence of normality by plotting histograms and performing the one-sample Kolmogorov-Smirnov test on the test variables (the paired differences), the paired *t* test was used for comparison of the gEUD$_{treat}$, SD$_{treat}$, and Vx$_{treat}$ values obtained with CRT with the values obtained with IMRT. We also compared gEUD$_{plan}$ with gEUD$_{treat}$ (and Vx$_{plan}$ with Vx$_{treat}$) for both CRT and IMRT. All statistical tests were performed using Statistical Package for Social Sciences, version 13.0 (SPSS, Chicago, IL).

RESULTS

The mean values of the bowel, rectum, and bladder gEUD$_{treat}$ and V$_{treat}$ across the group of patients are listed in Tables 1 and 2, respectively. Overall, reduced doses to the OARs were obtained using IMRT compared with those using CRT.

Figure 3 shows the absolute bowel volumes receiving doses >20–50 Gy. As expected, IMRT shifts the dose for the parts of the bowel outside the PTV that would have received 40–50 Gy using CRT toward 30 Gy. Consequently, a greater volume (*p* < 0.001) of the bowel would receive doses ≥30 Gy with IMRT compared with CRT (Fig. 3). The CRT dose distribution consists mainly of two dose levels (*i.e.,* 25 and 45–50 Gy), resulting from the contribution from two or four treatment fields, and hence only a small fraction of the bowel would receive exactly 30 Gy with CRT. In the case of IMRT, V$_{treat}$ was significantly greater than V$_{plan}$ (*p* = 0.003–0.03) for all intermediate dose levels investigated (*i.e.,* 25–40 Gy); such a difference was found for V$_{25}$, V$_{45}$, and V$_{50}$ for CRT (*p* = 0.001–0.04).

For the bowel, an average reduction in gEUD$_{treat}$ of 7% relative to CRT was obtained with IMRT (Fig. 4 and Table 1). While 8 of 20 patients would have received a bowel gEUD of >45 Gy with CRT, only 1 patient had a gEUD$_{treat}$ >45 Gy with IMRT (Fig. 4). However, 4 patients did not benefit from IMRT with respect to a reduced bowel gEUD (Fig. 4; Patients 2, 6, 7, and 13). These were among the 5 patients who had a conformal plan setup with a rotated collimator (as shown in Fig. 1), producing a more conformed dose distribution compared with the standard CRT plan.

The differences between the patients were large, and the bowel gEUD$_{treat}$ ranged from 28 to 51 Gy with CRT and 25 to 48 Gy with IMRT (Fig. 4). Also the intrapatient variation (SD$_{treat}$) was considerable for this organ (Table 3). The same pattern was seen for both techniques in the differences

Table 1. Mean and standard deviation of gEUD$_{treat}$ for all patients

OAR	gEUD$_{treat}$ (Gy)		
	CRT	IMRT	*p*
Bowel	42.6 ± 6.7	39.5 ± 4.9	<0.001
Rectum	47.0 ± 1.1	46.2 ± 1.1	<0.001
Bladder	48.1 ± 1.3	45.1 ± 1.6	<0.001

Abbreviations: gEUD$_{treat}$ = average of treatment generalized equivalent uniform doses; OAR = organ at risk; CRT = conformal radiotherapy; IMRT = intensity-modulated radiotherapy.

Table 2. Mean V$_{treat}$ for all patients

	V$_{treat}$		
	CRT	IMRT	*p*
Bowel volume (cm^3)			
≥25 Gy	258 (123–440)	237 (126–402)	0.003
≥30 Gy	140 (52–250)	170 (82–302)	<0.001
≥35 Gy	119 (27–222)	113 (38–213)	0.097
≥40 Gy	108 (19–207)	75 (16–159)	<0.001
≥45 Gy	98 (12–193)	44 (4–112)	<0.001
≥50 Gy	59 (1–143)	6 (0–15)	<0.001
Rectum (%)			
≥25 Gy	97 (86–100)	94 (84–99)	<0.001
≥30 Gy	90 (77–99)	89 (74–97)	0.120
≥35 Gy	82 (66–97)	79 (59–92)	0.116
≥40 Gy	75 (57–92)	67 (39–84)	0.001
≥45 Gy	64 (43–80)	51 (28–70)	<0.001
≥50 Gy	9 (0–40)	3 (0–8)	0.008
Bladder (%)			
≥25 Gy	99 (92–100)	98 (88–100)	0.051
≥30 Gy	93 (75–100)	89 (71–100)	0.003
≥35 Gy	87 (65–100)	76 (46–98)	<0.001
≥40 Gy	83 (60–99)	62 (34–90)	<0.001
≥45 Gy	78 (53–96)	46 (23–70)	<0.001
≥50 Gy	25 (6–72)	9 (3–20)	<0.001

Abbreviations: V$_{treat}$ = average cutoff volume from treatment dose-volume histogram; other abbreviations as in Table 1.
Data in parentheses are ranges.

between the planning and treatment bowel gEUDs (Fig. 4 and Table 3). In 6 of the 20 patients, the difference between the gEUD$_{plan}$ and gEUD$_{treat}$ was >6% relative to the gEUD$_{plan}$ (Fig. 4). A difference >20% was observed in 2 patients
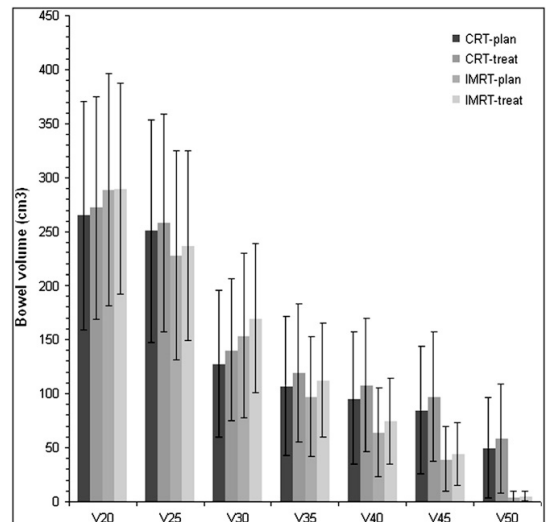

Fig. 3. Mean and standard deviation of bowel volume receiving more than xGy obtained from planning dose–volume histogram (Vx$_{plan}$) and average Vx obtained from treatment dose–volume histograms (Vx$_{treat}$) for all patients for conformal radiotherapy (CRT) and intensity-modulated radiotherapy (IMRT).
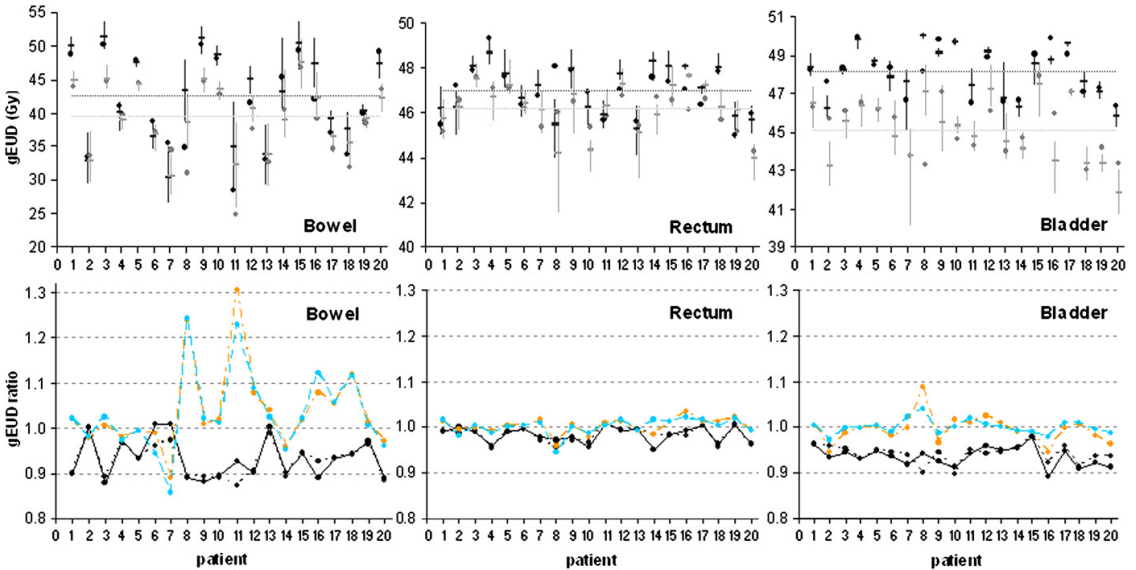
Fig. 4. (Upper) Generalized equivalent uniform dose (gEUD) from planning dose-volume histogram (gEUD$_{plan}$) (points) and average of treatment gEUDs (gEUD$_{treat}$) (streaks), with ranges marked by vertical lines in the case of conformal radiotherapy (CRT) (black) and intensity-modulated radiotherapy (IMRT) (gray) for each patient and for organs at risk considered. Horizontal dotted black and gray lines mark mean of gEUD$_{treat}$ across group in case of CRT and IMRT, respectively. (Lower) gEUD ratios between IMRT and CRT shown in black; dotted black line represents ratio between planning gEUDs (IMRT$_{plan}$/CRT$_{plan}$), and solid black line indicates ratio between treatment gEUDs (IMRT$_{treat}$/CRT$_{treat}$). Also, gEUD$_{treat}$/gEUD$_{plan}$ ratios shown. Dashed blue line indicates gEUD$_{treat}$/gEUD$_{plan}$ for CRT, and dash-dotted orange line indicates gEUD$_{treat}$/gEUD$_{plan}$ for IMRT.

(Patients 8 and 11); however, Patient 8 was obese and Patient 11 had an abnormal bladder shape (*i.e.*, a bifurcation). Excluding these 2 patients, gEUD$_{treat}$ was, on average, 1% greater than the gEUD$_{plan}$ for both techniques. However, the difference between the bowel gEUD$_{plan}$ and gEUD$_{treat}$ was not significant for either IMRT (38.4 Gy vs. 39.5 Gy, $p = 0.08$) or CRT (41.4 Gy vs. 42.6 Gy, $p = 0.13$).

For the rectum, an average reduction in gEUD$_{treat}$ of 2% relative to CRT was obtained with IMRT (Fig. 4 and Table 1). Of the 20 patients, 6 did not benefit from IMRT with respect to a reduced rectum gEUD (Fig. 4; Patients 2, 6, 11, 13, 17, and 19); that is, gEUD$_{treat}$/gEUD$_{plan}$ ≥1.00. Less inter- and intrapatient variations were observed for the rectum than for bowel (Fig. 4 and Table 3). For all patients except

2, the difference between gEUD$_{plan}$ and gEUD$_{treat}$ was within 2% of the gEUD$_{plan}$ and, on average, gEUD$_{treat}$ was equal to gEUD$_{plan}$ for both techniques (Fig. 4 and Table 3).

For the bladder, gEUD$_{treat}$ was again reduced using IMRT 6% on average (Fig. 4). All patients benefited from IMRT with respect to a reduced bladder gEUD$_{treat}$ (Fig. 4). The heterogeneity of the IMRT dose distribution across the bladder volume was reflected in a larger SD$_{treat}$ with IMRT than with CRT (Table 3). On average, gEUD$_{treat}$ was also equal to gEUD$_{plan}$ for the bladder (Fig. 4).

We accepted poorer geometric PTV coverage for CRT than for IMRT, and this was reflected in the minimal point doses to the PTV, which increased from 37–46 Gy using CRT to 44–47 Gy using IMRT ($p < 0.001$).

Table 3. Mean ratio between gEUD$_{treat}$ and gEUD$_{plan}$ and mean of individual standard deviations (SD$_{treat}$) in gEUD$_{treat}$

	gEUD$_{treat}$/gEUD$_{plan}$		SD$_{treat}$ (Gy)		
OAR	CRT	IMRT	CRT	IMRT	p^*
Bowel	1.03 (0.86–1.24)	1.04 (0.89–1.31)	2.2 (0.5–5.0)	2.1 (0.8–5.2)	0.09
Rectum	1.00 (0.98–1.02)	1.00 (0.98–1.03)	0.5 (0.2–1.1)	0.7 (0.1–2.1)	0.05
Bladder	1.00 (0.98–1.04)	1.00 (0.95–1.09)	0.4 (0.1–1.2)	0.8 (0.2–1.7)	<0.001

Abbreviations: gEUD = generalized equivalent uniform dose; gEUD$_{plan}$ = gEUD from planning dose-volume histogram; SD$_{treat}$ = standard deviations from gEUD$_{treat}$; other abbreviations as in Table 1.

Data in parentheses are ranges.

* p Values from comparison of SD$_{treat}$ between CRT and IMRT.

DISCUSSION

Several planning studies of pelvic RT for prostate cancer have emphasized the superiority of IMRT compared with CRT (1–13). The large mobility of the relevant OARs for this treatment approach could, however, jeopardize normal tissue sparing. From the present study, we can conclude that the examined IMRT approach still allows for reduced doses to the OARs and better target coverage, also when taking internal organ motion into account.

Evaluating the doses delivered to the bowel is difficult, because knowledge about the correlation between dose–volume parameters and the risk of GI adverse effects, especially diarrhea, is unclear. Although many clinical studies have recognized small bowel complications, only a few studies have reported a correlation with bowel dose–volume data (20–25). Furthermore, the findings from these studies have been ambiguous. Although Roeske *et al.* (20) found the absolute small bowel volume receiving the prescription dose of ≥45 Gy (*i.e.*, V_{45}) to be the solitary cutoff volume to predict for acute diarrhea in gynecologic patients undergoing IMRT, others have reported correlations for lower dose cutoff volumes (*e.g.*, V_5–V_{30}), particularly for V_{15} (21, 22, 25). However, that the latter studies were of chemoradiotherapy for rectal cancer predominantly performed with three-field CRT to a prescription dose of 45 Gy explains in part why V_{15} gave such a strong correlation. As noted by Tho *et al.* (22) and Baglan *et al.* (21), the effect of low-dose RT is impossible to isolate in these studies, because these volumes correlate highly to high-dose volumes owing to limited DVH variability. In addition, various combination schemes of RT with pelvic surgery and chemotherapy could alter the bowel's response to RT.

It is, therefore, uncertain whether the reduction we saw in V_{45} from IMRT in the present study would result in a lower incidence of diarrhea in this group of patients, because IMRT redistributed the dose such that the reduction in V_{45} had to be repaid by a greater V_{30}. Nevertheless, Ashman *et al.* (4) observed a similar redistribution with IMRT and yet their patients experienced an improved GI toxicity profile after IMRT compared with after CRT. Also, the initial clinical results from HUH have been promising (13, 26).

However, the volumes receiving intermediate doses might have an effect and should therefore not be neglected but somehow be weighted against the high-dose volumes. One efficient method of doing this is to reduce the DVH by the formalism of the gEUD. However, this relies on a proper estimation of k. For the rectum, the volume effect is fairly well known (19), but for bowel and bladder parameter sets are sparse and provisional. For the small bowel, Roeske *et al.* (20) found k = 3.2 ± 1.1 to provide the best fit between the incidence of Grade 2 acute diarrhea and V_{45}. They further suggested a threshold of 195 cm^3 for this volume (20). On the basis of these results, we chose k = 4 and V_{ref} = 200 cm^3 for the bowel. For the bladder, k was derived from the clinical experience of EUD-based optimization of IMRT at the University Clinic in Tübingen (Germany).

A lack of correlation between the dose–volume parameters for the bowel and the incidence of diarrhea could partly be explained by the snapshot provided by a single CT scan, which cannot represent the real treatment situation, because it pictures a mobile organ in an arbitrary shape and position (16, 27, 28). Consequently, depending on the heterogeneity of the dose distribution, the planned DVH will not provide a good estimate of the true bowel DVH. Kvinnsland and Muren (28) quantified large uncertainties in bowel DVHs from CRT for bladder cancer due to organ motion and recommended careful interpretation and use of dose–volume constraints for this organ, especially for use in IMRT optimization.

Because of our planning procedure, we suspected IMRT would be less robust against bowel motion than CRT. However, in terms of systematic ($gEUD_{plan}$ vs. $gEUD_{treat}$) and random (SD_{treat}) bowel gEUD variation, the same trend was seen for both techniques (Table 3 and Fig. 4), although different dose cutoff volumes contributed to the change in gEUD with IMRT compared with CRT (Fig. 3). IMRT conformed the dose better to the PTV, and the whole-body V_{45} was, therefore, considerably smaller with IMRT than with CRT (*i.e.*, 1.2 ± 0.2 dm^3 vs. 1.5 ± 0.2 dm^3, $p < 0.001$). Combined with a shrinkage in bladder volume (from V_{plan} = 183 ± 127 cm^3 to V_{treat} = 150 ± 95 cm^3, $p = 0.04$), this led to a significantly larger bowel $V45_{treat}$ than $V45_{plan}$ in the case of CRT ($p = 0.04$) but not in the case of IMRT ($p = 0.06$). Because of this, and because a change in V_{45} would alter the gEUD more than a comparable change in lower dose cutoff volumes, IMRT did not turn out to be less robust than CRT. The present study was performed on patients who had been instructed to have an empty bladder during treatment, although these patients are normally instructed not to void during the last hour before treatment.

To circumvent the uncertainties connected to the planning bowel DVH, some investigators (3, 7, 11, 29) outline all the space that could possibly be occupied by bowel and apply objectives/constraints to this volume. Alternatively, one could use margins around the bowel (16). However, because these approaches are nonspecific (16), they would unduly restrict the degrees of freedom. This would have to be repaid through either relaxation of the OAR constraints or by allowing a more inhomogeneous PTV dose distribution to remain within the space of physically obtainable solutions to the optimization problem. Nevertheless, these methods are believed to produce dose distributions that are more robust against bowel motion. However, they might not necessarily be more robust for the target, which was not observed in the present study. Another option would be to include information about bowel motion into the optimization by using coverage probabilities or similar approaches (30).

For the rectum, we found no change in the gEUD from planning to treatment. However, this result should not be transferred to treatments in which the presacral and/or perirectal lymphatics are included in the target volume, because a dose distribution with high doses surrounding the rectum (see Fig. 4 in the report by Price *et al.* [12]) would probably be less robust against rectal motion.

The limited reduction in rectal gEUD with IMRT in the present study was partially a result of the better PTV coverage with IMRT compared with CRT, but also because of the large margins around the prostate and seminal vesicles (10–15 mm).

In the present study, we used OAR contours from the treatment CT scans and the dose matrix calculated from the planning CT scan to obtain the treatment DVHs and gEUDs (*i.e.,* the dose was not recomputed on the repeat CT scans). This assumption of dose invariance is not entirely valid, because the shape of the patient, as well as the presence of air cavities within the pelvis, changes during the treatment period. Furthermore, setup uncertainties were not considered but were accounted for through the CTV to PTV margin. Depending on the method chosen for setting up the patient, the true delivered gEUD for the OARs would differ from the gEUD$_{treat}$. However, as long as the systematic setup errors of the bony anatomy are minimized, these uncertainties are believed to be minor sources of errors compared with the internal organ movements considered.

gEUD$_{treat}$ is a surrogate for the real accumulated gEUD, because it is calculated as the average value of a limited number of treatment gEUDs (whose distribution is not necessarily gaussian) and under the above-mentioned assumptions. Estimating the accumulated gEUD would require deformable registration algorithms. Such algorithms are currently available for the rectum and bladder (31, 32), but not for the bowel. Because of the chaotic pattern of the large amplitude movements of the bowel, and the complete absence of landmarks, tracking bowel doses would be immensely difficult and probably not feasible. Still, it might be possible to find surrogates that provide a better estimate for the real accumulated bowel gEUD than gEUD$_{treat}$.

CONCLUSION

Intensity-modulated RT was better than CRT for the planned dose. Internal organ motion made all metrics (gEUDs and volume parameters) worse, sometimes significantly so. However, IMRT remained better than CRT, also under the influence of internal organ motion. The gEUD was less sensitive toward bowel motion than were the volume parameters. For the bowel, gEUD should preferably be calculated relative to an absolute reference volume. The examined IMRT planning approach (of one contour only) is reasonably robust and therefore considered clinically acceptable.

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