Impact of changing rectal dose volume parameters over time on late rectal and urinary toxicity after high-dose intensity-modulated radiotherapy for prostate cancer: A 10-years single centre experience

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ABSTRACT

Background. External beam radiotherapy is an excellent treatment for patients with prostate cancer (PC). Assessing long-term radiotherapy-induced toxicity is important. We evaluated the impact of implementing different rectal dose volume constraints (DVC) on late rectal and urinary toxicity.

Material and methods. Six hundred and thirty-seven PC patients were treated with high-dose intensity-modulated radiotherapy (IMRT) in the primary (median dose of 78 Gy to the prostate) or postoperative setting [median dose of 74 (adjuvant) and 76 Gy (salvage) to the prostatic bed]. Three groups were defined according to different DVC applied over time. The incidence of late rectal and urinary toxicity was evaluated. Three-year actuarial risk estimations of grade 2–3 rectal and urinary toxicity were calculated (Kaplan-Meier statistics).

Results. Median follow-up was five years. Overall, the incidence of late grade 3 and 2 rectal toxicity was 1% and 11%. The calculated three-year actuarial risk of developing late grade ≥2 rectal toxicity decreased from 16% to 7% and 5% for patients in Group 1, Group 2 and Group 3, respectively (p < 0.001). Respectively, 17 (4%) and 98 (24%) patients developed grade 3 and 2 late urinary toxicity in the primary setting. In the postoperative setting, 15 (6%) and 62 (26%) patients developed grade 3 and 2 urinary toxicity, respectively. The three-year actuarial risk of developing late grade 2 urinary toxicity in primary- and postoperative-treated patients was 22% and 23%, respectively. This was not significantly different between the three groups.

Conclusion. The majority of patients developed no or only moderate rectal toxicity after high-dose IMRT for PC. Implementing different rectal DVC resulted in a significant decrease of late rectal toxicity without affecting urinary toxicity.

High-dose external beam radiotherapy (EBRT) has an important role in the treatment of patients with prostate cancer (PC) with excellent clinical outcome data as primary treatment for localised or locally advanced PC [1]. In the postoperative setting, adjuvant [2] or salvage [3] RT can be advocated to minimise the risk of biochemical and local failure [2]. Unfortunately, high-dose EBRT for PC is associated with a substantial risk of causing acute and late toxicity, certainly when conventional technologies are used [4]. Much research has been performed to identify the mechanisms responsible for developing toxicity. Several groups tried to define clinical parameters that are associated with late rectal toxicity [5,6]. A step forward in reducing the incidence of PC-induced toxicity was the implementation of new technologies [7]. Intensity-modulated radiotherapy (IMRT) creates a concave dose distribution that allows increasing the dose to the prostate with still sufficient sparing of the rectum. While the association of bladder dose volume parameters and urinary toxicity remains unclear, there is a well-known dose response relationship for rectal toxicity after three-dimensional conformal radiotherapy (3D-CRT) [8–10] and IMRT [11]. With time different rectal volume parameters have been proposed and consecutively implemented in the treatment planning of PC patients, overall resulting in lower rectal doses. In contrast, a reduction of the high-dose areas at the level of the rectum can come at the cost of the delivery of increased doses at the level of...
surrounding tissues, including the bladder. An increased spreading of intermediate- and low-dose regions is probably even more pronounced when techniques, such as IMRT, are applied. The aim of this study was to evaluate how the implementation of different rectal DVCs over time in the IMRT planning of PC patients affected the incidence of both rectal and urinary toxicity.

**Material and methods**

At Ghent University Hospital, anatomy-based segmental IMRT [12] is applied in the treatment planning of patients with PC in the primary and postoperative setting. Only patients with a minimal follow-up of 18 months were eligible for this analysis resulting in 637 patients: 405 patients treated for primary PC, 110 patients treated with adjuvant RT and 122 patients treated with salvage RT (Table I).

As there were no significant differences between rectal toxicity data of patients treated in the primary or postoperative setting (\(\chi^2\) and Fisher's exact test, \(p = 0.22\)), we pooled the toxicity data of all patients.

**Target definition**

In the primary setting, the clinical target volume (CTV) was defined as the prostate + seminal vesicles. If the probability of seminal vesicle invasion was <15% the latter were excluded from the CTV at 50 Gy. The planning target volume (PTV) was created by adding a 4 mm margin (positioning performed with ultrasound) and 7 mm [positioning performed with cone beam computed tomography (CT)] in all directions. In the postoperative setting, the CTV was defined as the prostate and seminal vesicular bed. The PTV was created by adding a 7 mm margin in all directions. No patient was irradiated to the pelvic lymph nodes.

**Delineation of organs at risk**

Prior to the planning CT a fleet enema was used to obtain an empty rectum. The rectum was thereafter defined as rectal wall (excluding remaining air and faeces) and delineated from the anal verge caudally up to the anatomic transition to the sigmoid colon cranially. Sigmoid colon, bladder, small bowel and femoral heads were delineated separately.

**Dose prescription, planning and delivery**

A median dose of 78 Gy, 76 Gy and 74 Gy was prescribed to the PTV in the primary, salvage and adjuvant setting, respectively. A maximal rectal dose of 76 Gy, 74 Gy and 72 Gy was used as planning dose. Table I. Patient’s characteristics for all patients and for the three groups separately.

| Characteristic | All patients (N = 637) | Group 1 (N = 193) | Group 2 (N = 212) | Group 3 (N = 232) | p-Value |
|----------------|------------------------|-------------------|-------------------|-------------------|---------|
| Age (years) median (range) | 66 (41–85) | 65 (41–79) | 65 (48–77) | 66 (49–85) | ns |
| Follow-up (months) median (range) | 60 (18–168) | 96 (24–168) | 60 (18–120) | 36 (18–72) | \(p < 0.001\) |
| Radiotherapy type | | | | | |
| Primary | 405 (64) | 145 (75) | 109 (52) | 151 (65) | \(p < 0.001\) |
| Adjuvant | 110 (17) | 21 (11) | 54 (25) | 35 (15) | |
| Salvage | 122 (19) | 27 (14) | 49 (23) | 46 (20) | |
| Crohn-colitis yes | 3 (1) | 0 | 0 | 3 (1) | ns |
| no | 634 (99) | 193 (100) | 212 (100) | 229 (99) | |
| Diabetes yes | 61 (10) | 16 (8) | 16 (8) | 29 (13) | ns |
| no | 576 (90) | 177 (92) | 196 (92) | 203 (87) | |
| Nicotine yes | 135 (21) | 39 (20) | 40 (19) | 56 (24) | ns |
| no | 502 (79) | 154 (80) | 172 (81) | 176 (76) | |
| Haemorrhoids yes | 157 (25) | 44 (23) | 60 (28) | 53 (23) | ns |
| no | 480 (75) | 149 (77) | 152 (72) | 179 (77) | |
| Abdominal surgery yes | 376 (59) | 114 (69) | 136 (64) | 126 (54) | ns |
| no | 261 (41) | 79 (31) | 76 (36) | 106 (46) | |
| IBS yes | 23 (4) | 8 (4) | 8 (4) | 7 (3) | ns |
| no | 614 (96) | 185 (96) | 204 (96) | 225 (97) | |

IBS, irritable bowel syndrome; ns, not significant.
objective in the primary, salvage and adjuvant setting. Over time three rectal DVC were applied. Table II summarises the different DVC that were applied over time resulting in three different patients groups: Group 1 (period 1998–2003): 193 patients, Group 2 (period 2004–2006): 212 patients [13] and Group 3 (period 2007–present): 232 patients [11]. Both maximal rectal dose and rectal DVC were implemented in the treatment planning. Maximal rectal dose was used as a hard constraint. The other rectal DVC were set as planning’s objectives.

In the primary setting a three-beam set-up was used for planning initially. Since the publication of Ost et al. [14], a seven-beam set-up was routinely applied for patients treated in the primary setting (20 patients). For postoperative planning a seven-beam set-up was used in all patients. Patient positioning was controlled daily by portal imaging, 3D ultrasound system (SonArray™ Zmed, Ashland, OR, USA) or cone beam CT. Patients were instructed to use a daily rectal suppository and to have a comfortably filled bladder.

**Evaluation of toxicity**

Before the start of IMRT, a standard questionnaire was used to assess the medical and surgical history (Crohn’s disease, colitis, irritable bowel disease, diabetes, nicotine abuse, haemorrhoids and previous non-prostate-related abdominal surgery) and pre-treatment rectal symptoms of each patient. Patients were seen following a fixed schedule: every three months for the first year, six-monthly from two to five years then yearly thereafter. Late rectal and urinary toxicity was defined as any increase of rectal or urinary toxicity lasting more than three months after the end of IMRT, or occurring for the first time later than three months after the end of IMRT. The grade of late rectal toxicity was scored according to the Radiation Therapy Oncology Group (RTOG) toxicity scale [15], combined with rectal urgency and incontinence as determined by Yeoh [16] and by an in-house developed scoring system [11]. Altogether, this was defined as radiotherapy-induced lower intestinal toxicity (RILIT) system. In total eight different lower intestinal symptoms were recorded: diarrhoea, rectal blood loss (RBL), mucus loss, incontinence, abdominal cramps, urgency, frequency and anal pain. For each symptom, the maximal toxicity score was registered. Urinary toxicity was scored according to an in-house developed scoring system based on the RTOG, SOMA/LENT and CTC urinary toxicity scorings system. In total six different symptoms were recorded: frequency, nocturia, incontinence, urgency, haematuria and dysuria.

**Statistical analysis**

For rectal toxicity the data of all patients were pooled (vide supra; N = 637). For urinary toxicity, patients treated in the primary setting (N = 402) and postoperative (both adjuvant and salvage; N = 235) setting were analysed separately. \( \chi^2 \) or Fisher’s exact test (categorical variables) and Kruskal-Wallis test (continuous variables) were used to compare the pre-treatment characteristics, doses delivered and rectal and urinary toxicity incidences between the three groups. In order to take into account the differences in follow-up time between the three groups, the differences in late rectal and urinary toxicity incidence were compared at 12, 24, 36, 48 and 60 months (\( \chi^2 \) or Fisher’s exact test) as well as calculated by log-rank analysis. Three-year actuarial risk estimations of developing grade 1–3 late rectal and GU toxicity were calculated with Kaplan-Meier statistics. Significance level was set at \( p = 0.05 \). Statistical analysis was performed with SPSS version 22.0 software (Chicago, IL, USA).

**Results**

Patient’s characteristics were comparable between the three groups except for median follow-up time, use of androgen deprivation, risk group and RT type (Table I). Significantly more patients were treated with primary RT in Groups 2 and 3 resulting in a slight dose increase to the target volumes in both groups compared to Group 1 (median dose to the PTV: 75.2 Gy ± 1.9 Gy, 76.4 Gy ± 2.5 Gy and 76.1

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**Table II. Rectal dose volume constraints per group.** For patients in Group 3, two separate sets of dose volume constraints were applied. One to prevent late grade ≥ 2 and one to prevent late grade 1 rectal toxicity, respectively. Following planning strategy was routinely used in the treatment planning of patients in Group 3: start of the planning with initial implementation of rectal volume constraints to prevent grade ≥ 2 late rectal toxicity. If these constraints were easily met, a second optimisation was performed in order to lower the rectal dose further and, if possible, to meet the criteria for preventing late grade 1 rectal toxicity.

| Rectal volume parameter | Group 1 N = 193 | Group 2 N = 212 | Constraints applied in first optimisation | Constraints applied in second optimisation |
|-------------------------|-----------------|-----------------|------------------------------------------|------------------------------------------|
| R40                     | /               | /               | <84%                                     | <64%                                     |
| R50                     | <100%           | <60%            | <69%                                     | <46%                                     |
| R60                     | <60%            | <50%            | <59%                                     | <35%                                     |
| R65                     | <50%            | <30%            | <48%                                     | <34%                                     |
| R70                     | <30%            | <30%            | /                                        | /                                        |

N, number of patients; R40, R50, R60, R65, R70, volume of the rectum receiving 40 Gray (Gy), 50 Gy, 60 Gy, 65 Gy and 70 Gy respectively.
Gy ± 2.1 Gy for Group 1, Group 2 and Group 3, respectively, p < 0.001). Despite the delivery of higher doses to the prostate, the volumes of the rectum receiving 40 Gy, 50 Gy, 60 Gy and 65 Gy were significantly lower (p < 0.01) in Groups 2 and 3 (Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.974826). The volume of the delineated rectal wall decreased with time (41.3 ± 20.7 cm³ vs. 38.4 ± 11.3 cm³ vs. 33.5 ± 14.9 cm³ for Group 1, Group 2 and Group 3, respectively, p < 0.01) in the primary setting a significant decrease for all bladder constraints, except for volume of the bladder receiving a dose of 40 Gy, was seen for Groups 2 and 3 compared to Group 1. In the postoperative setting none of the parameters was significantly different between the three groups besides volume of the bladder receiving a dose of 75 Gy (10.6 ± 8.4 cm³ for Group 1, Group 2 and Group 3, respectively, p < 0.001) and maximal dose (77.1 ± 7.8 cm³ vs. 77.0 ± 4.9 cm³ vs. 76.9 ± 5.2 cm³ for Group 1, Group 2 and Group 3, respectively, p < 0.001) to the bladder (Supplementary Table I to be found at online http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.974826).

With a median follow-up of five years, six (1%) patients and 68 patients (11%) developed grade 3 and grade 2 late rectal toxicity, respectively. Half of the patients (318 patients) experienced grade 1 late rectal toxicity.

The incidence of rectal toxicity at 12 months was significantly lower for Group 3 compared to Group 1. There also was a strong trend towards lower rectal toxicity for Group 3 at 36 months (Table III). The three-year actuarial risk of developing late ≥ grade 2 rectal toxicity was 16% for Group 1, 7% for Group 2 and 5% for patients in Group 3, respectively (p ≤ 0.001). Late ≥ grade 2 rectal toxicity was significantly higher in Group 1 than Group 2 (log-rank: p = 0.013) and Group 3 (log-rank: p < 0.001).

Most frequently reported late grade 2 rectal toxicities were rectal blood loss, diarrhoea, frequency and anal pain. The three-year actuarial risk of developing late grade 2 abdominal cramps, rectal blood loss, mucus loss and rectal incontinence was significantly lower in Group 3 compared to Group 1 (Table IV).

For urinary toxicity, respectively, 17 (4%), 98 (24%) and 155 (39%) patients had grade 3, 2 and 1 late urinary toxicity.

### Table III: Incidence of late grade 1–3 rectal toxicity for the three groups separately at different time points after the end of radiotherapy based on analysis of all patients. χ² statistics were calculated. Percentages are reported between brackets. Groups between which statistical significant differences at a certain time point were found are added.

| Time point | Group | Number of patients | Grade 1 | Grade 2 | Grade 3 | p-Value |
|------------|-------|--------------------|---------|---------|---------|---------|
| Month 12   | 1     | 193                | 47 (24) | 7 (4)   | 1 (1)   | 0.024 (G1-G3) |
|            | 2     | 212                | 37 (17) | 5 (2)   | 1 (1)   |         |
|            | 3     | 232                | 39 (17) | 2 (1)   | 0       |         |
| Month 24   | 1     | 193                | 40 (21) | 9 (5)   | 2 (1)   | 0.068 (G1-G3) |
|            | 2     | 209                | 33 (16) | 5 (2)   | 1 (1)   |         |
|            | 3     | 217                | 27 (12) | 6 (2)   | 1 (1)   |         |
| Month 36   | 1     | 185                | 32 (17) | 5 (3)   | 1 (1)   | ns      |
|            | 2     | 202                | 32 (16) | 4 (2)   | 0       |         |
|            | 3     | 164                | 25 (15) | 3 (2)   | 0       |         |
| Month 48   | 1     | 175                | 33 (19) | 4 (2)   | 1 (1)   | ns      |
|            | 2     | 184                | 23 (12) | 5 (3)   | 0       |         |
|            | 3     | 96                 | 15 (16) | 1 (1)   | 0       |         |
| Month 60   | 1     | 170                | 21 (12) | 7 (4)   | 0       | 0.028 (G1-G3) and 0.045 (G2-G3) |
|            | 2     | 153                | 20 (13) | 6 (4)   | 0       |         |
|            | 3     | 56                 | 15 (27) | 1 (2)   | 0       |         |

G, group; ns, not significant.
toxicity in the primary setting. In postoperative-treated patients, 15 (6%), 62 (26%) and 84 (35%) patients developed grade 3, grade 2 and grade 1 urinary toxicity, respectively.

Both in the primary and postoperative setting there was a significant increase in urinary toxicity at 36 months for patients treated in Group 3 when compared to Group 1 (Table V).

The three-year actuarial risk of developing late grade ≥ 2 urinary toxicity in primary-treated patients was 22% for patients in Group 1, 14% for patients in Group 2 and 24% for patients in Group 3, respectively (not significant). The three-year actuarial risk of developing late grade ≥ 2 urinary toxicity in postoperative-treated patients was 25% for patients in Group 1, 17% for patients in Group 2 and 15% for patients in Group 3, respectively (not significant).

The three-year actuarial risk of developing late grade ≥ 2 urinary toxicity did not increased by implementing new rectal DVC over time in the primary setting (Table VI). In the postoperative setting, the three-year actuarial risk of developing late grade 3 haematuria and grade 2 nocturia and urgency was significantly worse in Group 3 (Table VI).

### Discussion

In this study an overview on late toxicity after high-dose IMRT, in the primary or postoperative setting, for PC is presented. Over time three different rectal DVCs were applied in the treatment planning of our PC patients. The impact of changing rectal planning constraints on toxicity was evaluated.

Assessing long-term RT-induced toxicity is important as persisting treatment-related side effects, and more particularly bowel side effects, continue to have a negative impact on men’s quality of life even up to 10 years after diagnosis [17].

Based on patient data, several rectal DVC have been proposed in order to minimise the risk of developing late rectal toxicity [7–11]. In contrast, for the bladder, a clear dose-response relationship is lacking apart of avoiding hot spots [18]. Dosimetry studies have demonstrated the superiority of new radiation techniques, such as IMRT versus 3D-CRT, in rectum and bladder sparing without hampering the dose to the prostate. This dosimetric advantage has been translated in improved biochemical control and lower rectal toxicity [19]. For urinary toxicity, in contrast, the superiority of IMRT above 3D-CRT is less clear [19]. Also for postoperative RT the effectiveness of IMRT compared to 3D-CRT is doubtful as, in general lower doses, are administered when compared to primary RT [20]. Nevertheless there is evidence supporting the use of dose escalation in the postoperative setting too [21].

Spratt et al. reported the largest series with toxicity data on 1002 PC patients treated with high-dose

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**Table IV.** Three-year actuarial risk of developing late rectal toxicity per group. Data are presented as percentages. p-Values were calculated by log-rank analysis.

| Toxicity          | Grade | Group 1 N = 193 | Group 2 N = 212 | Group 3 N = 232 | p-Value  |
|-------------------|-------|-----------------|-----------------|-----------------|----------|
|                   |       | Group 1 vs Group 2 | Group 1 vs Group 3 | Group 2 vs Group 3 |         |
| Abdominal cramps  | 1     | 5               | 2               | 2               | NS       |
|                   | 2     | 3               | 1               | 0               | 0.075 NS |
| Rectal urgency    | 1     | 22              | 17              | 17              | NS       |
|                   | 2     | 2               | 3               | 3               | 0.069 NS |
| Frequency         | 1     | 22              | 17              | 16              | NS       |
|                   | 2     | 2               | 3               | 1               | NS       |
| RBL               | 1     | 19              | 12              | 10              | NS       |
|                   | 2     | 7               | 1               | 1               | 0.002 NS |
| Mucus loss        | 1     | 21              | 16              | 16              | NS       |
|                   | 2     | 3               | 0               | 0               | 0.046 NS |
| Incontinence      | 1     | 18              | 10              | 11              | 0.022 NS |
|                   | 2     | 3               | 1               | 0               | 0.082 NS |
| Diarrhoea         | 1     | 11              | 10              | 13              | NS       |
|                   | 2     | 2               | 3               | 3               | NS       |
| Anal pain         | 1     | 5               | 8               | 4               | 0.063 NS |
|                   | 2     | 3               | 1               | 1               | NS       |
| ns, not significant; RBL, rectal blood loss. Bold values represent significant differences (p<0.05). Italic values represent a trend although not significant difference.
Table V. Incidence of late grade 1–3 urinary toxicity for the three groups separately at different time points after the end of radiotherapy for patients treated in the primary and postoperative setting. χ² statistics were calculated. Percentages are reported between brackets. Groups between which statistical significant differences at a certain time point were found are added.

| Time point | Group | Number of patients | Grade 1 | Grade 2 | Grade 3 | p-Value | Number of patients | Grade 1 | Grade 2 | Grade 3 | p-Value |
|------------|-------|--------------------|---------|---------|---------|---------|--------------------|---------|---------|---------|---------|
| Month 12   | 1     | 145                | 49 (34) | 12 (8)  | 2 (1)   | ns      | 48                 | 19 (40) | 4 (8)   | 1 (2)   | ns      |
|            | 2     | 110                | 30 (27) | 6 (5)   | 2 (2)   |         | 102                | 41 (40) | 15 (14) | 0       |         |
|            | 3     | 147                | 46 (31) | 20 (14) | 2 (1)   |         | 85                 | 29 (35) | 8 (10)  | 0       |         |
| Month 24   | 1     | 145                | 34 (23) | 14 (10) | 2 (1)   | ns      | 48                 | 13 (27) | 7 (15)  | 1 (2)   | ns      |
|            | 2     | 110                | 33 (30) | 6 (5)   | 1 (1)   |         | 99                 | 34 (34) | 13 (13) | 0       |         |
|            | 3     | 145                | 48 (33) | 13 (10) | 3 (1)   |         | 72                 | 27 (38) | 3 (4)   | 0       |         |
| Month 36   | 1     | 140                | 31 (22) | 6 (4)   | 3 (2)   | 0.036   | 45                 | 8 (18)  | 7 (16)  | 1 (2)   | 0.02    |
|            | 2     | 109                | 27 (25) | 13 (12) | 1 (1)   |         | 93                 | 30 (32) | 11 (12) | 2 (2)   |         |
|            | 3     | 125                | 34 (26) | 17 (13) | 3 (2)   |         | 39                 | 17 (44) | 1 (3)   | 0       |         |
| Month 48   | 1     | 132                | 32 (24) | 8 (6)   | 5 (4)   | ns      | 43                 | 11 (26) | 8 (19)  | 1 (2)   | ns      |
|            | 2     | 107                | 25 (24) | 7 (7)   | 2 (1)   |         | 77                 | 21 (27) | 12 (16) | 1 (1)   |         |
|            | 3     | 83                 | 25 (30) | 7 (8)   | 2 (2)   |         | 13                 | 6 (46)  | 2 (16)  | 0       |         |
| Month 60   | 1     | 131                | 32 (24) | 9 (7)   | 5 (4)   | 0.056   | 39                 | 8 (21)  | 4 (10)  | 2 (5)   | ns      |
|            | 2     | 102                | 30 (29) | 10 (10) | 4 (4)   |         | 51                 | 19 (37) | 6 (12)  | 2 (3)   |         |
|            | 3     | 51                 | 23 (45) | 3 (6)   | 1 (2)   |         | 5                  | 2 (40)  | 1 (20)  | 0       |         |

G, group; ns, not significant.

IMRT. The actuarial seven years risk of developing grade ≥ 2 late rectal toxicity was 4.4% [22]. With a median follow-up of five years. The overall absolute incidence of severe grade ≥ 2 late rectal toxicity was 12% in our series. Our results illustrate that with the implementation of different rectal DVC over time a significant decrease in three-year actuarial risk of developing late grade ≥ 2 rectal toxicity from 16% (Group 1) to 5% (Group 3) was noted.

Apart from being a retrospective study, a shortcoming of this study is the differences in follow up length between the three different treatment groups.

Table VI. Three-year actuarial risk of developing late urinary toxicity per group both in the primary and postoperative setting. Data are presented as percentages. p-Values were calculated by log-rank analysis.

| Toxicity | Grade | Group 1: N = 48 | Group 2: N = 103 | Group 3: N = 84 | Group 1 versus Group 2 | Group 1 versus Group 3 | Group 2 versus Group 3 |
|----------|-------|----------------|------------------|-----------------|------------------------|------------------------|------------------------|
| Continence | 1     | 27             | 19               | 13              | NS                     | 0.07                   | NS                     |
|           | 2     | 4              | 11               | 7               | NS                     | NS                     | NS                     |
|           | 3     | 2              | 1                | 1               | NS                     | NS                     | NS                     |
| Dysuria   | 1     | 8              | 11               | 6               | NS                     | NS                     | NS                     |
|           | 2     | 0              | 1                | 0               | NS                     | NS                     | NS                     |
| Frequency | 1     | 25             | 5                | 5               | 0.009                  | NS                     | NS                     |
|           | 2     | 6              | 4                | 1               | NS                     | NS                     | NS                     |
| Haematuria | 1    | 2              | 1                | 0               | NS                     | NS                     | NS                     |
|           | 2     | 11             | 11               | 5               | NS                     | NS                     | NS                     |
| Nocturia  | 1     | 35             | 20               | 15              | 0.018                  | NS                     | NS                     |
|           | 2     | 10             | 3                | 6               | 0.044                  | NS                     | NS                     |
| Urgency   | 1     | 23             | 27               | 23              | NS                     | NS                     | NS                     |
|           | 2     | 2              | 2                | 0               | NS                     | NS                     | NS                     |

P value

| Toxicity | Group 1: N = 48 | Group 2: N = 103 | Group 3: N = 84 | Group 1 versus Group 2 | Group 1 versus Group 3 | Group 2 versus Group 3 |
|----------|----------------|------------------|-----------------|------------------------|------------------------|------------------------|
| Continence | 1     | 27             | 19               | 13             | NS                     | 0.01                   | <0.001                 |
|           | 2     | 4              | 11               | 7              | NS                     | NS                     | NS                     |
|           | 3     | 2              | 1                | 1              | NS                     | NS                     | NS                     |
| Dysuria   | 1     | 8              | 11               | 6              | NS                     | NS                     | NS                     |
|           | 2     | 0              | 1                | 0              | NS                     | NS                     | NS                     |
| Frequency | 1     | 25             | 5                | 5              | 0.009                  | NS                     | NS                     |
|           | 2     | 6              | 4                | 1              | NS                     | NS                     | NS                     |
| Haematuria | 1    | 2              | 1                | 0              | NS                     | NS                     | NS                     |
|           | 2     | 11             | 11               | 5              | NS                     | NS                     | NS                     |
| Nocturia  | 1     | 35             | 20               | 15             | 0.018                  | NS                     | NS                     |
|           | 2     | 10             | 3                | 6              | 0.044                  | NS                     | NS                     |
| Urgency   | 1     | 23             | 27               | 23             | NS                     | NS                     | NS                     |
|           | 2     | 2              | 2                | 0              | NS                     | NS                     | NS                     |

P value

ns, not significant.

Bold values represent significant differences (p<0.05). Italic values represent a trend although not significant difference.
which might explain the higher incidence in late rectal toxicity in Group 1. When looking at different time points the highest incidence of grade 2–3 rectal toxicity is seen within the first three years after the end of RT, which is the median follow-up time of the patients in Group 3. The largest benefit of applying new rectal DVC in our study was also noted within the first three years (Table III). According to the study of Fellin et al. [23], a follow-up of three years is representative for rectal toxicity as they demonstrated, based on data from a prospective cohort study, that long-term rectal symptoms are strongly correlated with moderate and severe events occurring during the first three years after treatment [23].

Although the constraints on R60 and R65 in Group 3, initially proposed to prevent grade ≥ 2 late rectal toxicity did not differ substantially from those used in Group 1, a further tightening of those constraints together with the introduction of R40 resulted in a reduction of all rectal volume parameters, with the largest advantage seen in the area of 40–50 Gy (Supplementary Table I to be found at online http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.974826). The most important decrease was seen in the incidence of late rectal bleeding, for which most DVC have been developed. Nevertheless, symptoms, such as rectal urgency and faecal incontinence, are quite common and relevant as they have a negative impact on quality of life. More than 20% of our patients presented with faecal urgency and/or incontinence. That the incidence of these symptoms remains rather high despite using stricter rectal DVC adds to the suggestion that other structures, such as anal sphincter, might be involved in late rectal toxicity [24].

Our analysis also showed that, with time, the volume of the rectal wall decreased. This probably reflects an increased effort to obtain an empty rectum on planning’s CT with time and could have influenced our results. The importance of an empty rectum both on toxicity profile as well as clinical outcome has been reported [25].

Since the already low incidence of severe rectal toxicity after IMRT, it is doubtful if a further decrease in toxicity can be expected by using even more stringent rectal DVC. Other, patient-related, factors also contribute to the development of rectal toxicity and deserve further attention [5,6].

The risk of developing late ≥ grade 2 urinary toxicity after high-dose EBRT for PC is substantial. In the study of Spratt et al., a seven-year actuarial risk of late ≥ grade 2 urinary toxicity of 22% was reported [22]. The three-year actuarial risk of developing late ≥ grade 2 urinary toxicity in our series climbed up to 25%, both in the primary and postoperative setting. Where the incidence of rectal toxicity was most prevalent within the first years after treatment, the incidence of urinary toxicity remained constant over the first years, but increased with time in our series. This is in agreement with what has been reported by others [26]. Our analysis illustrated that implementing more severe rectal DVCs was not at the cost of substantial higher doses to the bladder itself. Consequently we did not find a significant increase in urinary toxicity, except for urinary toxicity in Group 3 at three years (Table V). As approximately 40% up to half of the patients in the primary and postoperative setting develops some grade of urinary toxicity after IMRT further research to prevent urinary toxicity is mandatory certainly when focusing planning on rectal toxicity.

Based on the presented data we can conclude that high-dose IMRT for PC is feasible with low rates of severe late rectal toxicity. Nowadays, a majority of patients are free of late rectal toxicity or only develop moderate rectal toxicity. The implementation of different rectal DVC with time further decreased late rectal toxicity without significantly affecting the incidence of urinary toxicity.

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