Chapter 4

Acute and Late Complications after Radiotherapy for Prostate Cancer: Results of a Multicenter Randomized Trial comparing 68 Gy to 78 Gy

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* Both authors contributed equally to this work

ABSTRACT

**Purpose:** To compare acute and late gastrointestinal (GI) and genitourinary (GU) side effects in prostate cancer patients randomized to receive 68 Gy or 78 Gy.

**Patients and methods:** Between June 1997 and February 2003, 669 prostate cancer patients were randomized between radiotherapy with a dose of 68 Gy and 78 Gy, in 2 Gy per fraction and using three-dimensional conformal radiotherapy. All T-stages with a PSA < 60 μg/L were included, except any T1a and well-differentiated T1b-c tumors with a PSA ≤ 4 μg/L. Stratification was done for four treatment groups (according to the risk of seminal vesicles (SV) involvement), age, hormonal treatment (HT) and hospital. The clinical target volume (CTV) consisted of the prostate with or without the SV, depending on the estimated risk of SV invasion. The CTV to planning target volume margin was 1 cm for the first 68 Gy and was reduced to 0.5 cm (0 cm towards the rectum) for the last 10 Gy in the 78 Gy arm. Four Dutch hospitals participated in this Phase III trial. Evaluation of acute and late toxicity was based on 658 and 643 patients, respectively. For acute toxicity (< 120 days) the RTOG scoring system was used and the maximum score was reported. Late toxicity (> 120 days) was scored according to the slightly adapted RTOG/EORTC criteria.

**Results:** The median follow-up time was 31 months. For acute toxicity, no significant differences were seen between the two randomization arms. GI toxicity Grade 2 and 3 was reported as the maximum acute toxicity in 44 % and 5 % of the patients, respectively. For acute GU toxicity these figures were 41 % and 13 %. No significant differences between both randomization arms were seen for late GI and GU toxicity, except for rectal bleeding requiring laser treatment or transfusion ($p = 0.007$) and nocturia ($p = 0.05$). The 3-year cumulative risk of late RTOG/EORTC GI toxicity Grade ≥ 2 was 23.2 % for 68 Gy, and 26.5 % for 78 Gy ($p = 0.3$). The 3-year risks of late RTOG/EORTC GU toxicity Grade ≥ 2 were 28.5 % and 30.2 % for 68 Gy and 78 Gy, respectively ($p = 0.3$). Factors related to acute GI toxicity were HT ($p < 0.001$), a higher treatment group ($p = 0.01$) and pretreatment GI symptoms ($p = 0.04$). For acute GU toxicity prognostic factors were: pretreatment GU symptoms ($p < 0.001$), HT ($p = 0.003$) and prior transurethral resection of the prostate (TURP) ($p = 0.02$). A history of abdominal surgery ($p < 0.001$) and pretreatment GI symptoms ($p = 0.001$) were associated with a higher incidence of late GI Grade ≥ 2 toxicity,
whereas HT ($p < 0.001$), pretreatment GU symptoms ($p < 0.001$) and prior TURP ($p = 0.006$) were prognostic factors for late GU Grade $\geq 2$.

**Conclusions:** Raising the dose to the prostate from 68 Gy to 78 Gy resulted in higher incidences of acute and late GI and GU toxicity, but these differences were not significant, except for late rectal bleeding requiring treatment and late nocturia. Other factors than the studied dose levels appeared to be important in predicting toxicity after radiotherapy, especially previous surgical interventions (abdominal surgery or TURP), hormonal therapy and the presence of pretreatment symptoms.

**Introduction**

In the last decade, considerable attention has been paid to dose escalation for radiotherapy of prostate cancer because of unsatisfactory local control and survival results with the past treatment doses. [1,2] In this attempt to improve outcome in prostate cancer, other approaches regarding radiotherapy have been examined, such as the use of neoadjuvant, concomitant and/or adjuvant hormonal treatment (HT) combined with external beam irradiation [3-5], brachytherapy of the prostate in monotherapy [6] or as a boost [7], or boosting with proton [8,9] or neutron beams. [10]

Encouraging results of improved outcome with higher radiation doses have already been reported in several non-randomized [7,11-13] and randomized studies (8,14). Many studies tried to identify the patient group that would benefit most from a higher radiation dose to the prostate. In the M.D. Anderson Cancer Center (MDACC) randomized trial, intermediate-risk, and to lesser extent high-risk patients, benefited from higher doses [14], whereas low-risk patients showed a dose response when going from doses of 64-66 Gy to 68-70 Gy, but not beyond that dose level. [15] Others also reported improved outcome in intermediate-risk [11,13,16] or high-risk patients. [8,11] Less frequently, even low-risk patients have been reported to show a dose response. [17,18] Most studies, however, do not show a dose response effect in low-risk patients, but one can argue that a longer follow-up may be necessary to observe any benefit in these favorable patients. In contrast, some authors advocate watchful waiting (or deferred therapy) as initial management in selected low-risk patients. [19] We also have to keep in mind that the definitions of risk groups are different in many studies. Classifications into two or three risk groups are based on PSA alone, or more frequently on combinations of two or three of the following factors:
PSA, Gleason score and T-stage. Together with the rather frequent modifications of the TNM-staging, this can hamper outcome comparison of risk groups between different studies.

In 1997, we initiated a multi-institutional, randomized, Phase III trial to investigate if an additional boost of 10 Gy improves biochemical no evidence of disease (bNED) and overall survival. Moreover we wanted to explore which patient group in particular might benefit from higher radiation doses. However, an increase of the radiation dose to the tumor implicates an increase of the dose to the surrounding normal tissue, which is the dose-limiting factor. As prostate cancer patients have a potentially long survival, assessment of late toxicity is of major importance. Like others [12,20-22], we first performed a Phase I dose escalation trial to demonstrate the feasibility of irradiating the prostate to 78 Gy [23]. Few Phase III trials comparing higher doses with conventional doses using external beam radiotherapy have been performed or are under way [14,24] (Radiation Therapy Oncology Group (RTOG) P-0126, Medical Research Council (MRC) trial RT01). In our Phase III randomized trial we compared radiation doses of 68 Gy and 78 Gy. This first analysis was performed to compare both randomization arms concerning acute and late toxicity in relation to general treatment factors and patient-related factors.

**Patients and methods**

*Protocol entry criteria and stratification*

Between June 1997 and February 2003, 669 patients with a localized adenocarcinoma of the prostate were entered in this Phase III trial, randomizing patients between 68 Gy and 78 Gy. Four different centers in the Netherlands participated. Pretreatment evaluations included clinical history, physical examination, trans-rectal ultrasound of the prostate, laboratory studies (full blood count, creatinine, alkaline phosphates, gamma-glutamyl transferase and PSA), a bone scan, and optionally a pelvic CT-scan. The initial total PSA of each patient was determined, before digital rectal examination (DRE) and/or 10 days after biopsy or transurethral resection of the prostate (TURP), and use of Abbott IMx assay was recommended. TNM staging was scored according to the American Joint Committee on Cancer 1997 guidelines. At histological evaluation Gleason score and/or differentiation grade were assigned, and patients were divided into three groups: well-differentiated or Gleason score 2-4, moderately differentiated or Gleason score 5-7, poorly differentiated or Gleason score 8-10. All T-stages with a PSA < 60 μg/L were eligible, except any T1a prostate tumor and well-
differentiated (grade 1 or Gleason score < 5) T1b–c tumors with PSA levels ≤ 4 μg/L. Patients with positive regional lymph nodes, with distant metastases, on anticoagulant therapy, with a Karnofsky index below 80, with a previous radical prostatectomy or pelvic irradiation were excluded. Hormonal therapy (HT) was allowed and was (commonly) prescribed to high-risk patients. In hospital A, HT was started approximately 0-7 months before radiotherapy and was prescribed for 3 years. In hospital B, HT was administered 0-5 months before radiotherapy and was continued for a total period of 6 months. Generally, a luteinizing hormone-releasing hormone agonist preceded by an anti-androgen was prescribed. In hospital C and D no HT was given, except for one patient.

Patients were stratified for hospital, HT, age (≤ 70 vs. > 70 years) and treatment groups. Four treatment groups were defined according to the estimated risk of SV involvement (Table 1), according to Partin et al. (25). Group I included T1b, T1c and T2a patients with an estimated risk of SV involvement of less than 10 %. Group II included T1b, T1c and T2a patients with an estimated risk between 10 % and 25 %, whereas group III contained T1b, T1c and T2a patients with a risk larger than 25 %, and all T2b and T3a patients. Group IV finally, comprised all T3b and T4 patients. For patients of treatment groups II, III and IV, lymph node evaluation was obligatory by diagnostic pelvic CT-scan or ultrasound, and/or surgical or cytological sampling.

T3a patients were initially included into treatment group IV, but we changed policy during the study (since February 1998) by classifying them into group III. We estimated that a boost on the SV was not indicated for these patients, as invasion of the SV was not proven, although classification as a T3a implies a high risk of SV invasion. Fourteen patients with a T3a prostate cancer, treated before this date, were treated following the directions of group IV instead of group III. Eight of them were randomized in the high-dose arm. Approval of the Ethical Committee of each institution was obtained and every patient gave an informed consent.

Dose schemes and contouring
For each treatment group (Table 1), specific planning target volumes (PTV) were defined. Until 68 Gy, margins of 10 mm were added to the clinical target volume (CTV) to obtain the PTV. For patients included in the high-dose arm, the margins were reduced to 5 mm to obtain the PTV for the last 10 Gy, except for the interface between CTV and rectal wall where no margin was taken to spare the rectum. CTV1 and CTV2 were defined as the prostate only and the prostate with SV, respectively. In treatment group I, the PTV was based on CTV1 during the whole treatment and in both
randomization arms. In treatment group II, the PTV was based on CTV2 for the first 50 Gy, on CTV1 for the following 18 Gy, and for patients in the 78 Gy arm on CTV1 for the last 10 Gy. In treatment group III, the PTV was based on CTV2 until 68 Gy, and for those included in the high-dose arm on CTV1 for the last 10 Gy. Finally, for treatment group IV, the PTV was based on CTV2 for the whole treatment in both randomization arms.

Table 1. Grouping criteria and identification of the four corresponding defined patient ‘treatment groups’, according to the estimated risk of SV involvement.

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>T1b, T1c, T2a*</th>
<th>T2b*</th>
<th>T3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPSA (μg/l)</td>
<td></td>
<td>T3a</td>
<td>T4</td>
</tr>
<tr>
<td>Differentiation</td>
<td>0-4</td>
<td>4-10</td>
<td>10-20</td>
</tr>
<tr>
<td>2-4 Good</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>5-7 Moderate</td>
<td>I</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>8-10 Poor</td>
<td>II</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>

Abbreviation: iPSA, initial prostate-specific antigen.
*According to American Joint Committee on Cancer 1997 guidelines.

The rectum was delineated from the level of the tuberosities until the level of the inferior border of the sacro-iliacal joints, or when the rectum is no longer adjacent to the sacrum. This definition results from a quality control study performed at the beginning of the trial. [26] For some patients, the anal canal was drawn separately if the anal canal was not already included in the rectum delineated according to the definition. If the rectum volume including filling exceeded 150 cm³, rescanning was advised. In view of a future analysis with dose-volume parameters, the coordinating center (hospital B) reviewed all delineated structures, including CTV, PTV and organs at risk for consistency with the protocol, in order to achieve a more homogeneous delineation and reduce inter-observer variability. When a deviation was found for the organs at risk, the delineated structure was adapted according to the guidelines.

Radiotherapy techniques
All patients were scanned in treatment position (supine), with a slice thickness of 3 to 5 mm, and were treated with three-dimensional conformal therapy (3D-CRT) using a multileaf collimator. Patients were instructed to urinate about 1 hour before the CT-scan and every treatment fraction, then to drink 250 ml liquid and not to urinate till after CT-scan or radiotherapy. Treatment planning was done after random assignment. The treatment technique was left to the discretion of the participating institution. The
techniques used were a four-field technique (hospital C), three-field techniques using one anterior and two lateral (hospitals B and D), or two posterior oblique, wedged fields (hospital A). For the boost of 10 Gy in the high-dose arm, similar techniques were used. The boost was given sequentially with 3D-CRT, except for 41 patients in institution B, where a simultaneous integrated boost was given using intensity-modulated radiation therapy (IMRT). [27] Dose was specified to the ICRU (International Commission on Radiation Units and Measurements) reference point [28] and was delivered at 2 Gy per fraction per day with a megavoltage linear accelerator with ≥ 6 MV photons. Each participating center used its own method for tissue inhomogeneity correction. According to ICRU, the dose to the PTV was within –5 % and +7 % to the prescribed dose. At least 99 % of the PTV was treated to at least 95 % of the prescribed dose in the ICRU reference point.

Treatment plan and treatment evaluation
The dose constraint for the rectum stipulated that the percentage of rectum receiving ≥ 74 Gy should not exceed 40 %, similar to the constraint reported in the Memorial Sloan-Kettering Cancer Centre (30 % of the rectal wall to a maximum dose of 75.6 Gy). [11] The dose to the small bowel should not be higher than 68 Gy. This constraint was chosen on the basis of former clinical experience with treatment doses of 68 Gy to the prostate. In the low-dose arm all patients received the prescribed 68 Gy whereas in the high-dose arm, 37 patients received a dose lower than 78 Gy. One patient died after 16 Gy from a disease-unrelated cause, the other 36 patients received a total dose ranging from 68 to 76 Gy. Nineteen of these patients were planned with a lower dose because of small bowel (11 patients) or rectal (8 patients) dose constraints. In 17 patients the dose was lowered during radiotherapy because of toxicity, on patient’s request, or because of a technical problem. Only three of these patients had a maximal acute toxicity Grade 3 (GU). The analyses presented here are based on the intention to treat.

Multiple portal images or portal films of each field were obtained in the first week. In the subsequent weeks, orthogonal views were obtained weekly, and compared with corresponding digitally reconstructed radiographs or simulation images. A verification procedure with decision rules for setup corrections was specified by each institution according to the guidelines published by a collaborative study in the Netherlands. [29] By using this protocol, systematic errors did not exceed 5 mm.
Follow-up schedule
All patients were evaluated once a week during radiotherapy and had a follow-up every 3 months in the first year, every 4 months in the second year, biannually in the following 3 years and yearly thereafter. At each follow-up visit a physical examination, including a DRE, full blood count, PSA, alkaline phosphates and creatinine levels were determined (before DRE). At PSA relapse, defined according to the American Society for Therapeutic Radiology and Oncology (ASTRO) definition [30], a bone scan, a CT-scan of the abdomen and a prostate biopsy were advised. In case of a PSA > 1 μg/L at 2 years of follow-up without PSA relapse a transrectal ultrasound of the prostate was advised to obtain random biopsies.

Toxicity scoring
To determine the incidence and severity of the gastrointestinal (GI), and genitourinary (GU) complaints, patients completed a detailed self-assessment questionnaire, concerning these GI and GU complaints, at the start of the therapy, weekly during therapy and at each follow-up visit. This patient self-assessment questionnaire included 22 questions, and was comparable to the questionnaires used by Tait et al. [31] Together with the physician’s notes, including the use of medication, they were used to classify the GI and GU symptoms according to a modified RTOG scoring system (Radiation Therapy Oncology Group) for the acute radiation morbidity (Appendix Table A1), and to the RTOG/EORTC (European Organization for Research and Treatment of Cancer) (Appendix Table A2) [32] and SOMA/LENT (Subjective, Objective, Management and Analytic/Late Effects of Normal Tissue) scoring systems for the late radiation morbidity. The RTOG/EORTC and SOMA/LENT scales were both slightly adapted according to the scales used in the dose-escalation study preceding this randomized study. [23] In this analysis we only reported the RTOG/EORTC scores. The pretreatment score is defined as the RTOG score obtained before radiotherapy. Side effects occurring within 120 days from start of radiotherapy were considered acute toxicity. Late toxicity was scored from 120 days after start of the treatment.

For the evaluation of late toxicity we also analyzed more detailed GI and GU symptoms, called ‘indicators’, in order to be able to analyze the origin of high scores and differences between the various scoring systems. Scoring for an indicator results in a grade ≥ 2 in one or both scoring systems. Seven indicators were defined for the GU symptoms, and five for GI toxicity (Appendix Table A3). When patients were diagnosed with a loco-regional recurrence, further assessment of complications was omitted from that moment on, as distinction between treatment-related or recurrence-
related symptoms can be difficult. Patients with biochemical relapses or distant metastases were not censored from the analysis.

**Endpoints and statistical analyses**

Factors analyzed for their possible relationship with the endpoints were: randomization arm, treatment group, TURP before radiotherapy, HT, pretreatment symptoms, age at diagnosis (continuous variable), diabetes mellitus, cardiovascular history, a history of abdominal surgery, smoking, and use of acetylsalicylic acid (= covariates). The maximal acute toxicity was not included as a covariate in the analysis of late toxicity because it represents an effect of treatment, and not an independent variable.

Primary endpoints for acute toxicity were the maximum score on the RTOG toxicity scales for GI and GU adverse events. Possible interaction of the covariates and their joint effect on maximal acute toxicity were analyzed with ordered logistic regression. All covariates were first analyzed in a baseline model including the randomization arm, hospital of treatment, and the treatment group. After that, a multivariate (MV) ordered logistic regression analysis was performed including all covariates that appeared to be associated with the endpoint in the first analysis. The odds ratio was used to express the strength of the association of a parameter with the incidence of maximal acute toxicity.

Primary endpoints for late toxicity were the GI and GU RTOG / EORTC toxicity Grade ≥ 2 and ≥ 3. Secondary endpoints for late toxicity were the GI and GU indicators (Appendix Table A3). The Kaplan-Meier method was used to calculate cumulative incidences of late side effects by randomization arms and subgroups, and the Log Rank test was applied to compare the incidences by arms and subgroups. The Kaplan-Meier curves were cutoff at 4 years, but the Log Rank values were calculated on the total number of events.

The Cox proportional hazards regression (PHR) model was used to determine the independent effect of the covariates on each studied endpoint of late toxicity. The results of the regression analyses are presented in the form of relative hazard rates. All covariates were first analyzed in a Cox PHR baseline model including the randomization arm, hospital of treatment and the treatment group in order to adjust for these factors. Subsequently, a MV Cox regression analysis was performed to test whether significant covariates remained significant. In this MV analysis, all covariates were included that appeared to be associated ($p < 0.1$) with the endpoint in the former analysis, together with the covariates of the baseline model. Two-tailed tests were used. A $p$ value ≤ 0.05 was considered statistically significant. No adjustment was done for the multiple endpoints and multiple testing. When
pretreatment data were missing, the evaluation on Day 7 was considered as the pretreatment toxicity score, or if this form was missing too, these values were treated as missing and included separately in the MV analysis.

**Results**

*Patient data*
Five of the 669 randomized patients were excluded from the analysis because they were ineligible (three patients) or because they were not irradiated (two patients). **Table 2** shows a well-balanced distribution of the patient characteristics for both randomization arms.

Small differences between both arms were seen for differentiation grade and initial PSA. The high-dose arm had more grade II prostate cancers, whereas the 68 Gy arm included more grade I and grade III, and slightly more patients with a PSA levels > 20 μg/L. The mean age at diagnosis was 68.7 years. The median follow-up time was 31 months (range 2–71 months) in both randomization arms. The mean initial PSA amounted to 16.1 μg/L (range 0.4-59.0) for all patients. PSA was determined in all patients, and in 432 cases the Abbott IMx assay was used. Abdominal surgery included appendectomy (42 %), repair of inguinal hernia (32 %), cholecystectomy (10 %), surgery to the stomach (7 %), iliacal lymph node dissection (5 %) and other abdominal surgery (15 %). Hormonal therapy (HT) was administered to 78 patients of hospital A, to 64 patients of hospital B, and to one patient of hospital D. For acute toxicity, 658 patients were assessable for analysis, because 6 patients had no acute toxicity evaluation form. Due to lacking follow-up data, late toxicity analysis was based on 643 patients (68 Gy: 320 patients; 78 Gy: 323 patients). Seventy-nine of the analyzed patients (12 %) had a follow-up of less than 1 year.

*Acute toxicity*
The GI and GU scores gradually increased during treatment, leveling off after 5 weeks, and reaching a maximum at 7 weeks (**Fig. 1**). No significant differences were seen between the two dose levels when comparing for maximum acute GI ($p = 0.5$) and GU toxicity ($p = 0.5$). In the 68 Gy arm the incidence of Grade 2 and Grade 3 acute GI toxicity was 41 % and 6 %, respectively. For the 78 Gy arm these figures were 47 % and 4 %. For acute GU toxicity in the low-dose arm, Grade 2 and Grade 3 were reported as the maximum toxicity in 40 % and 13 % of the patients, respectively. In the high-dose arm these incidences of GU toxicity were 42 % and 13 %. No Grade 4 or Grade 5 toxicity occurred.
Table 2. Distribution of patients (n, %) by randomization arm and pretreatment characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>68 Gy arm (n=331)</th>
<th>78 Gy arm (n=333)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean age (Range)</td>
<td>68.6 (50.3-82.9)</td>
<td>68.8 (48.7-83.6)</td>
</tr>
<tr>
<td>Treatment groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>54 16 %</td>
<td>52 16 %</td>
</tr>
<tr>
<td>Group II</td>
<td>65 20 %</td>
<td>67 20 %</td>
</tr>
<tr>
<td>Group III</td>
<td>157 47 %</td>
<td>163 49 %</td>
</tr>
<tr>
<td>Group IV</td>
<td>55 17 %</td>
<td>51 15 %</td>
</tr>
<tr>
<td>T-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>3 1 %</td>
<td>5 2 %</td>
</tr>
<tr>
<td>T1c</td>
<td>54 16 %</td>
<td>62 19 %</td>
</tr>
<tr>
<td>T2a</td>
<td>87 26 %</td>
<td>77 23 %</td>
</tr>
<tr>
<td>T2b</td>
<td>64 19 %</td>
<td>64 19 %</td>
</tr>
<tr>
<td>T3a</td>
<td>71 22.5</td>
<td>81 24 %</td>
</tr>
<tr>
<td>T3b</td>
<td>45 14 %</td>
<td>42 13 %</td>
</tr>
<tr>
<td>T4</td>
<td>7 2 %</td>
<td>2 1 %</td>
</tr>
<tr>
<td>Differentiation grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (or Gleason score 2-4)</td>
<td>106 32 %</td>
<td>93 28 %</td>
</tr>
<tr>
<td>II (or Gleason 5-7)</td>
<td>170 51 %</td>
<td>194 58 %</td>
</tr>
<tr>
<td>III (or Gleason 8-10)</td>
<td>56 17 %</td>
<td>45 14 %</td>
</tr>
<tr>
<td>Initial PSA Mean (μg/L); SD</td>
<td>17.0; 12.8</td>
<td>15.3; 10.7</td>
</tr>
<tr>
<td>Range (μg/L)</td>
<td>1.7-59.0</td>
<td>0.4-57.0</td>
</tr>
<tr>
<td>&lt; 4 μg/L</td>
<td>25 8 %</td>
<td>19 6 %</td>
</tr>
<tr>
<td>4-10 μg/L</td>
<td>95 29 %</td>
<td>119 36 %</td>
</tr>
<tr>
<td>10-20 μg/L</td>
<td>125 38 %</td>
<td>125 38 %</td>
</tr>
<tr>
<td>&gt; 20 μg/L</td>
<td>86 26 %</td>
<td>70 21 %</td>
</tr>
<tr>
<td>Hormonal Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TURP</td>
<td>73 22 %</td>
<td>70 21 %</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>41 12 %</td>
<td>34 10 %</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>91 27 %</td>
<td>92 28 %</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>20 6 %</td>
<td>18 5 %</td>
</tr>
<tr>
<td>Smoking</td>
<td>105 32 %</td>
<td>113 34 %</td>
</tr>
<tr>
<td>Use of acetylsalicylic acid</td>
<td>51 15 %</td>
<td>57 17.5</td>
</tr>
<tr>
<td>Hospital A</td>
<td>201 61 %</td>
<td>203 61 %</td>
</tr>
<tr>
<td>B</td>
<td>86 26 %</td>
<td>85 26 %</td>
</tr>
<tr>
<td>C</td>
<td>35 11 %</td>
<td>35 11 %</td>
</tr>
<tr>
<td>D</td>
<td>9 3 %</td>
<td>10 3 %</td>
</tr>
</tbody>
</table>
Overall, 51\% of the patients experienced no or mild GI symptoms (Grade 0/1) during radiotherapy, while Grade 2 and Grade 3 was recorded as the maximum acute GI toxicity in 44\% and 5\% of the patients, respectively. At ordered logistic regression analysis, using the baseline model, pretreatment GI symptoms, HT and the treatment group were significant prognostic factors for acute GI toxicity (Table 3). The pretreatment score was significantly related to acute GI symptoms, but only 2\% of the patients scored a pretreatment GI grade \( \geq 2 \) (Fig. 1). When comparing treatment groups II, III or IV with group I (as categorical variable), no difference was seen for group II. Groups III and IV on the contrary showed significantly more acute toxicity compared with group I with an odds ratio of 1.8 and 1.7, respectively. Finally, patients receiving HT experienced less acute GI toxicity. Other analyzed factors, such as prior TURP, age, diabetes mellitus, cardiovascular history, history of abdominal surgery, smoking and use of acetylsalicylic acid were not associated with acute GU toxicity.

Table 3. Ordered logistic regression analysis for acute GI and GU toxicity. Estimates are based on ordered regression analysis using the baseline model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ordered logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GI</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td>Randomization Arm (78Gy vs. 68Gy)</td>
<td>0.5</td>
</tr>
<tr>
<td>Treatment group (continuous)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Hormonal treatment (yes vs. no)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pretreatment score (( \geq ) grade 2 vs. &lt; 2)†</td>
<td>0.04*</td>
</tr>
<tr>
<td>TURP (yes vs. no)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Abbreviations: OR = Odds Ratio; GI = Gastrointestinal; GU = Genitourinary
*p-values considered significant; †: Pretreatment GI score for acute GI, and pretreatment GU score for acute GU toxicity.

Overall, 46\% of the patients experienced no or mild GU complaints (Grade 0/1) during radiotherapy, 41\% had a Grade 2 and 13\% had a Grade 3 as maximum acute GU score. Prognostic factors for acute GU toxicity at ordered logistic regression, using the baseline model, were: the pretreatment GU score, prior TURP, and HT (Table 3). A higher pretreatment GU score and use of HT were associated with more acute GU complications, whereas a TURP before radiotherapy was associated with less acute toxicity. Eight percent of the patients scored a GU Grade \( \geq 2 \) before radiotherapy (Fig. 1), and 94\% of them also scored a Grade \( \geq 2 \) as maximal acute GU toxicity. Treatment group, age, diabetes mellitus, cardiovascular history, history of abdominal surgery, smoking, and use of acetylsalicylic acid were not associated with acute GI toxicity. In the multivariate ordered logistic
Acute and late complications

regression analysis, all the covariates significantly associated with acute GI and GU toxicity remained statistically significant.

![Graph showing the evolution in time of acute RTOG gastrointestinal (GI) and genitourinary (GU) toxicity Grade ≥ 2 and Grade ≥ 3.](image)

**Fig. 1.** Evolution in time of acute RTOG gastrointestinal (GI) and genitourinary (GU) toxicity Grade ≥ 2 and Grade ≥ 3.

**Late GI toxicity**

When comparing both randomization arms, the incidences of late GI symptoms were higher in the high-dose arm for the overall scores (Fig. 2A) and for the GI indicators (Fig. 3). However, these differences were not significant, except for the indicator ‘Rectal bleeding requiring laser/transfusion’ \( (p = 0.007) \) (Fig. 2C). Twenty-three patients (68 Gy: 5 patients; 78 Gy: 18 patients) required at least one blood transfusion and/or laser treatment because of rectal bleeding. The cumulative incidences of RTOG/EORTC GI Grade ≥ 2 at 3 years were 23.2 \% in the standard dose arm, and 26.5 \% in the high-dose arm. For RTOG/EORTC GI Grade ≥ 3 these figures were 2.3 \% and 4.7 \%, respectively.

Two patients experienced a late GI toxicity Grade 4, one in each randomization arm. One patient (68 Gy) had a laparoscopic lymph node dissection and was subsequently planned for a prostatectomy. During this procedure the patient turned out to be technically inoperable. Radiotherapy started 2 months later, and 5 months after completion of this treatment he had a perforated sigmoid and required urgent surgery. The second patient (78 Gy), with a history of appendectomy and gastric hemorrhage, had a
temporary bowel diversion because of severe radiation proctitis and sigmoiditis. An exacerbation of the symptoms by a diverticulitis could not be excluded.

The data also show an increase of GI toxicity during the first 3 years, followed by stabilization (Fig. 2). However, the number of patients at risk after 3 years is too small to draw definite conclusions, although results are consistent with data in literature.

Prognostic factors for late RTOG/EORTC GI toxicity in the Cox PHR baseline model were: history of abdominal surgery and the pretreatment GI score (Table 4). Patients with a history of abdominal surgery scored significantly more GI toxicity grade ≥ 2 (Fig. 2B) as well as grade ≥ 3. The higher incidences of GI toxicity in patients with previous surgery concurred with significantly higher incidences of three indicators: ‘Bleeding requiring laser/transfusion’ ($p = 0.002$), ‘Use of incontinence pads because of rectal loss of blood, mucus or stools’ ($p = 0.008$) and ‘Proctitis and use of steroids’ ($p = 0.05$). A higher pretreatment GI toxicity was also predictive for more late GI toxicity grade ≥ 2. The association with GI toxicity grade ≥ 3 was only borderline significant ($p = 0.05$). The higher GI toxicity in patients with a higher pretreatment score concurred with a higher incidence of two indicators, namely ‘Pain/cramps/tenesmus requiring medication’ ($p < 0.001$) and ‘Use of incontinence pads because of blood/mucus/stool loss’ ($p = 0.02$). However, only 14 patients had pretreatment GI symptoms Grade ≥ 2, and six of them have developed a late GI Grade ≥ 2 so far. Also patients with diabetes mellitus needed more frequently ‘Incontinence pads for rectal discharge’ ($p = 0.02$). Finally, the dose-volume group had a significant impact on the stool frequency ($p = 0.02$), with higher incidences of risen stool frequency in patients of treatment groups III and IV (Fig 2D). In the multivariate Cox PHR analysis, all the covariates associated with GI endpoints remained statistically significant. HT, age, cardiovascular history, smoking, use of acetylsalicylic acid and prior TURP were not predictive for late GI toxicity.
Fig. 2. Kaplan-Meier plots of late GI toxicity. A: Comparison of both randomization arms for RTOG/EORTC Grade ≥ 2. B: Comparison of patients with and without a history of abdominal (abd) surgery for RTOG/EORTC grade ≥ 2. C: Comparison of both randomization arms for 'Rectal bleeding requiring laser treatment or transfusion'. D: Comparison of the four treatment groups for 'High stool frequency'. The numbers of patients at risk are mentioned at the foot of each graph. N = total number of patients; F = number of events.
Table 4. Cox proportional hazards analysis showing the prognostic factors for the endpoints late GI and GU RTOG/EORTC Grade ≥ 2 and Grade ≥ 3. Estimates are based on the baseline Cox PHR analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value grade ≥ 2</th>
<th>HR</th>
<th>p value grade ≥ 3</th>
<th>HR</th>
</tr>
</thead>
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<tr>
<td><strong>Gastrointestinal (GI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm (78 Gy vs. 68 Gy)</td>
<td>0.3</td>
<td>1.2</td>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Treatment group (continuous)</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Previous surgery (yes vs. no)</td>
<td>&lt;0.001*</td>
<td>1.9</td>
<td>0.01*</td>
<td>4.2</td>
</tr>
<tr>
<td>Pretreatment GI symptoms (≥ vs. &lt; g2)</td>
<td>0.001*</td>
<td>4.1</td>
<td>0.05*</td>
<td>8.4</td>
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<tr>
<td><strong>Genitourinary (GU)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm (78 Gy vs. 68 Gy)</td>
<td>0.3</td>
<td>1.2</td>
<td>0.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Treatment group (continuous)</td>
<td>0.6</td>
<td>1.0</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Prior TURP (yes vs. no)</td>
<td>0.006*</td>
<td>1.7</td>
<td>0.001*</td>
<td>3.1</td>
</tr>
<tr>
<td>Hormonal treatment (yes vs. no)</td>
<td>&lt;0.001*</td>
<td>2.2</td>
<td>0.03*</td>
<td>2.3</td>
</tr>
<tr>
<td>Pretreatment GU symptoms (≥ vs. &lt; g2)</td>
<td>&lt;0.001*</td>
<td>2.2</td>
<td>0.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Abbreviations: HR = Hazard Ratio; g = grade; * p-values considered significant.

Fig. 3. Late GI toxicity: cumulative incidences of the indicators at 1, 2 and 3 years from start of radiotherapy, in both randomization arms. The error bars indicate the standard error. The p values compare both randomization arms and are obtained from the Cox PHR analysis using the baseline model.
Late genitourinary toxicity
When comparing both randomization arms for late RTOG/EORTC GU toxicity, no significant differences were seen for the overall toxicity scores, although the incidence of late GU toxicity was slightly higher in the 78 Gy arm (Fig. 4A). With regard to the GU indicators, only the incidence of ‘Nocturia’ was significantly higher in the high-dose arm (p = 0.05) (Fig. 5).

Fig. 5 shows that the overall late RTOG/EORTC GU toxicity is mainly due to ‘Nocturia’, and to a lesser extent to ‘Dysuria requiring drugs’. The 3-year cumulative risks for RTOG/EORTC GU Grade ≥ 2 were 28.5% and 30.2% for the 68 Gy and the 78 Gy arm, respectively. For GU Grade ≥ 3, these risks were 5.1 % and 6.9 %, respectively. Grade 4 RTOG/EORTC GU toxicity occurred in 1 patient, randomized to receive 68 Gy. This patient had a Bricker urinary diversion because of a severely reduced bladder capacity. The time course of toxicity in Fig. 4 suggests a further increase of toxicity after 3 years. More mature analysis with a longer follow-up is necessary to confirm this trend, as the number of patients at risk after 3 years becomes small.

Testing all potential prognostic factors in a Cox PHR baseline model with the defined GU toxicity endpoints, several significant associations were found. Prognostic factors for late RTOG/EORTC GU toxicity Grade ≥ 2 were: HT, prior TURP and pretreatment GU score (Table 4). HT and prior TURP also affected late GU grade ≥ 3. The use of HT resulted in higher RTOG/EORTC GU scores (Fig. 4B). This toxicity was mainly due to a significantly higher incidence of ‘nocturia’ (p < 0.001) in patients treated with HT. Patients who had a TURP before radiotherapy also experienced more late GU symptoms (Fig. 4C), and more specifically, a significantly higher incidence of ‘Urinary obstruction’ (p < 0.001) and ‘Dysuria requiring drugs’ (p = 0.05). A pretreatment GU score grade ≥ 2 was significantly associated with late GU toxicity (Fig. 4D). These patients had a significantly higher incidence of three indicators: ‘Nocturia’ (p < 0.001), ‘Urinary frequency during the day’ (p = 0.02) and ‘Urinary obstruction requiring treatment’ (p = 0.02). Finally patients with diabetes mellitus had significantly more ‘Nocturia’ (p = 0.01). Surprisingly, smoking was associated with more ‘Dysuria requiring drugs’ (p = 0.02). In the multivariate Cox PHR analysis, all the covariates associated with GU endpoints remained significant. Age, treatment group, history of abdominal surgery, a cardiovascular history and use of acetylsalicylic acid were not associated with late GU toxicity.
Fig. 4. Kaplan-Meier plots of late GU toxicity. Comparison of both randomization arms (A), of hormonal status (B), of TURP before radiotherapy (C) and of the pretreatment RTOG GU score (D) for RTOG/EORTC grade $\geq 2$. The numbers of patients at risk are mentioned at the foot of each graph. N = total number of patients; F = number of events.
Fig. 5. Late GU toxicity: cumulative incidences of the indicators at 1, 2 and 3 years from start of radiotherapy, in both randomization arms. The error bars indicate the standard error. The \( p \) values compare both randomization arms and are obtained from the Cox PHR analysis using the baseline model.

**Discussion**

This multi-institutional Phase III trial, randomizing prostate cancer patients between 68 Gy and 78 Gy, showed a significantly higher incidence of late rectal bleeding and late nocturia in patients included in the high-dose arm. For the other endpoints, incidences of acute and late toxicity were generally slightly higher in the 78 Gy arm, but these differences were not significant. Before discussing the toxicity results, we briefly want to review some considerations about scoring of toxicity.

**Scoring of toxicity**

Comparison of late toxicity between different trials is complicated, because the variety of adapted toxicity scales is large. The toxicity scoring systems widely used for rectal and bladder radiation complications are the RTOG/EORTC and SOMA/LENT scoring systems, often modified in one way or another. [33] We recorded the toxicity according to both (adapted)
scoring scales to compare them, but in this analysis we focused on the RTOG/EORTC results. Briefly, the GI toxicity scored by RTOG/EORTC or SOMA/LENT gave almost identical results. Actually, this means that the applied adaptations made them equivalent. However, for the SOMA/LENT GU toxicity, the score was shifted toward more severe complications compared with the RTOG/EORTC score due to the higher weight of urinary frequency in the SOMA/LENT score, as previously shown by Boersma et al. [23]

In our study, late toxicity scores were based on both the physician’s report and the patient’s self-assessment questionnaire through the use of extensive checklists. As showed by Goldner et al., this is a more consistent and reliable way to record toxicity, than based on the physician’s report only. [34] Especially for GU toxicity Goldner et al. found an underestimation of the GU symptoms by the physician. Thus, the use of both self-assessment questionnaires and the physician’s notes, but also our adapted scoring system with numerical details can explain the relatively high rate of late grade ≥ 2 complications.

Acute toxicity and prognostic factors

No significant differences were seen in acute GI and GU toxicity when comparing both dose levels. This corresponds to the results found in the MDACC trial, randomizing patients between 70 Gy and 78 Gy [35], and the French trial, randomizing patients between 70 Gy and 80 Gy [24], where also no significant differences were seen between the low-dose and high-dose arms. Our crude incidences of maximal acute GI and GU toxicity are comparable with those two trials, although slightly higher for both randomization arms, especially when comparing with the MDACC trial. This difference may partially be due to the somewhat different and less severe RTOG toxicity scales used in the MDACC trial compared with our scales (e.g. mild rectal bleeding, infrequent gross hematuria or the need for sanitary pads for mucous discharge were scored as Grade 2, whereas we score these items as Grade 3).

The use of hormonal treatment (HT) was a prognostic factor for acute GI toxicity and resulted in an improved GI tolerance. Reduction of the prostate volume by HT with subsequently smaller field sizes can explain this finding, but further investigation with dose volume parameters will be performed to clear up this point. Other studies reported no impact of neo-adjuvant and concomitant HT on acute GI toxicity. [36,37] Acute GU toxicity, on the other hand, was increased in our patients who received HT. In the RTOG 94-06 dose escalation trial, a significantly increased acute GU toxicity was seen in patients receiving HT compared with RT alone [38], but further
Acute and late complications

Analysis showed this was only true in men with poor pretreatment urinary function. [37]

In our study, the presence of pretreatment GI and GU symptoms (Grade ≥ 2) was associated with more acute GI and GU toxicity respectively, but the patient group with pretreatment GI symptoms was very small, accounting for only 14 patients, and significance level was only borderline. Therefore, no conclusions can be drawn from this result about pretreatment GI toxicity. For GU toxicity, on the other hand, our results clearly showed that having GU symptoms before starting RT is a strong predictor for acute GU toxicity, as 94% of the patients with a Grade ≥ 2 before radiotherapy also scored a Grade ≥ 2 as maximal acute GU score. However, we cannot deduce from this RTOG scale whether these symptoms before and during treatment were of the same kind. The treatment group was also a significant prognostic factor for acute GI toxicity, but not for acute GU toxicity. Patients of treatment groups III and IV had more GI symptoms compared with group I. These were the patients receiving a higher dose on the SV, resulting in more rectum volume irradiated to high doses. Further analysis of toxicity with dose-volume parameters will have to confirm this explanation.

As previously reported by Schultheiss et al., a TURP before RT was associated with significantly less acute GU complications. [39] This is probably due to the fact that patients have already attained relief from some GU symptoms and are also less subject to, for example, radiation-induced edema.

Late toxicity & prognostic factors

Increasing the dose to the prostate from 68 Gy to 78 Gy resulted in significantly more rectal bleeding requiring a laser treatment or transfusion, and in more nocturia. A significantly higher incidence of late rectal bleeding in the high-dose arm was not unexpected, as in the dose-escalation study, performed previously in one of the participating hospitals [23], a trend was found that a total radiation dose of ≥ 74 Gy resulted in a higher incidence of severe rectal bleeding. Others also reported a significant association of late rectal bleeding and a higher treatment dose. [40-42] Patients with a history of abdominal surgery in particular were prone to develop late rectal bleeding, and this resulted in a significantly higher overall late RTOG/EORTC score. These patients, with previous surgery, also needed significantly more incontinence pads, probably because of rectal blood loss, and experienced more proctitis. Abdominal surgery included not only lymph node dissection, but also disease-unrelated abdominal surgery, such as appendectomy or surgical repair of an inguinal hernia. The incidence of late GI complications in patients with a history of abdominal surgery excluding iliac lymph node
dissection was also significantly higher, although this correlation was slightly less pronounced (results not shown). Smit et al. previously described a significantly higher risk of late GI toxicity in patients with previous bowel disease or surgery compared with those with no preexistent disease. [43] Liu et al., conversely, did not find a statistically significant correlation between abdominal surgery and late toxicity. [44]

To the best of our knowledge, the association of frequent nocturia with a higher treatment dose has not been described earlier. Not only the treatment dose, but also diabetes mellitus, a higher pretreatment GU score and HT were found to be predictive for developing frequent nocturia. This difference for nocturia between the two randomization arms was only borderline significant and so the question arises if this result could be a fortuitous finding resulting from the multiple comparisons. The same remark can be made about the surprising association of smoking and dysuria requiring drugs.

The presence of pretreatment GI and GU symptoms was associated with more late GI and GU toxicity, respectively. This is consistent with previous findings. [45] For GI toxicity, only 14 patients reported GI symptoms grade ≥ 2 before starting radiotherapy, and this number of patients is too small to rely on. The presence of pretreatment GU symptoms was associated with late GI toxicity Grade ≥ 2, but not with Grade ≥ 3. This indicates that these patients are indeed more likely to complain about late toxicity, but not about severe late toxicity.

Overall, HT did not significantly influence late GI toxicity in our study, whereas late GU toxicity was significantly higher in patients who received HT. In this study, 22 % of the patients were treated with HT. Roughly half of these received neoadjuvant and concomitant HT for a total duration of 6 months, whereas the other half had neoadjuvant and concomitant HT, followed by adjuvant HT during 3 years. We analyzed them as one group although in the literature the use of neoadjuvant HT seems to have a different impact on late GI treatment toxicity compared with those receiving (also) adjuvant HT. Long-term adjuvant HT seemed to result in more late GI toxicity compared with neoadjuvant HT alone. [46,47] The reason for this difference between short-term and long-term HT is still unclear, but a plausible explanation is that the luteinizing hormone-releasing hormone agonists may have an influence on the reparative process of the irradiated normal tissue, possibly through an inhibitory effect on epidermal growth factor receptor on these normal tissues. [48] But even when we compare the impact of neo-adjuvant HT between different studies, the results are conflicting. The RTOG 94-06 trial reported no effect of neo-adjuvant HT on late GI or GU toxicity [37], whereas Schultheiss et al. described an increased
late GI and GU toxicity. [39] Liu et al. also found a higher incidence of late GI toxicity, but only in patients who received ≤ 2 months of neo-adjuvant HT. [44] How can we explain all these conflicting results? HT causes shrinkage of the prostate [49], resulting in reduced radiation field sizes. If this shrinkage is not taken into account in the treatment planning, this can result in a higher incidence of complications. [39] On the other hand, the results of Lilleby et al. suggested a further volume decrease until 9 months of HT, although the largest changes occurred during the first 3 months of HT. [50] This finding demonstrates the impact of the duration of neo-adjuvant HT on toxicity. We plan to analyze the effect on toxicity of the two treatment modalities (short-term versus long-term HT) separately, taking into account the dose-volume parameters and the exact interval between start of HT and planning CT-scan.

In this study, a TURP before RT was associated with significantly more late GU complications, compared with patients who never underwent this procedure. More specifically, urinary incontinence and urethral strictures were more frequently seen in patients with a prior TURP. This is consistent with the findings of Sandhu et al., where in addition no significant difference in late GU toxicity was found between TURP patients treated with high-dose (≥ 75.6 Gy) conformal radiotherapy compared with lower doses. [51]

Patients with diabetes mellitus were also found to have an increased risk of needing incontinence pads for rectal discharge and of having more nocturia, but this did not result in a significantly higher RTOG/EORTC GI or GU score, contrary to the results of Herold et al. [52] However, only 38 (6%) patients had diabetes mellitus, and this is a small group for statistical analysis. Age had no influence on late toxicity. Contrary to acute GI toxicity, the different treatment groups did not show a differential effect on overall late GI and GU toxicity, except for the stool frequency, where a higher cumulative incidence was seen in group III and group IV. An analysis with dose-volume parameters will be performed to study the differences in dose-volume parameters of the exposed normal tissues between the different treatment groups.

**Other considerations**

Despite the higher radiation doses, our results show an acceptable complication rate. Probably the small margins used for the boost, especially toward the rectum where no margin was taken, contributed to this result. We are aware that a longer follow-up is needed to confirm these data, especially because prostate cancer patients have a potentially long survival. Boersma et al. also described that the more severe complications often occurred later. [23] Furthermore, the incidences of toxicity are globally higher in the high-
dose arm. In the MDACC trial, for example, a first report did not show significant differences in toxicity, while with an extended follow-up the Grade 2-3 rectal complication rate was twice as high in the high-dose arm compared with the conventional low-dose arm. [15] The difference in bladder complications, on the contrary, was still not significant in their study, but there we have to be cautious too, because bladder complications may develop later than rectal toxicity. On the other hand, comparison with the MDACC trial is not completely fair, as they used conventional treatment till 46 Gy, followed by 3D conformal technique for the rest of the treatment, whereas we used 3D conformal during the whole treatment. Furthermore, HT was an exclusion criterion in their study, whereas we found that HT significantly improved acute GI tolerance and reduced acute and late GU tolerance.

In general, besides the treatment techniques used, and the inclusion or exclusion of HT, we have to keep in mind that several other factors may hamper comparisons between different studies concerning this topic, such as different definitions of CTV margins, adapted toxicity scales, method of collecting toxicity data (based on physician’s report and/or patients’ self-assessment questionnaires), dose specification or variable dose constraints.

Finally, we want to mention that IMRT allows for greater sparing of the surrounding normal tissue and it may therefore play a role in further reducing toxicity. In our study, a small group of 41 patients in the high-dose arm (12 %) was treated with simultaneous integrated boost technique using IMRT [26], but because this technique was introduced during the trial, these patients have a shorter follow-up and we did not analyze them separately yet.

**Conclusions**

Although the incidences of toxicity were slightly higher in the high-dose arm, no significant differences in toxicity were seen between 68 Gy and 78 Gy, except for late rectal bleeding and nocturia. Thus, RT of the prostate to 78 Gy resulted in an acceptable complication rate, but a longer follow-up is needed to confirm these data. In addition, this study shows that other factors than the radiation dose may be important in predicting toxicity from RT. A history of abdominal surgery was a poor prognostic factor for late GI toxicity. A TURP before RT resulted in less acute GU, but more late GU toxicity. Higher doses to the SV lead to more acute GI toxicity. Patients receiving HT experienced less acute GI symptoms, but more acute and late GU toxicity. The presence of pretreatment symptoms was associated with more acute and late toxicity. The use of indicators, which score more specific symptoms,
is of paramount importance, because it allows us to trace the reason for a higher overall GI or GU toxicity score. In addition, a significantly higher incidence of such an indicator did not always result in a significantly higher score on the global GI or GU toxicity scale, and by omitting of scoring these separate symptoms, differences in toxicity can be missed.
References


Acute and late complications


32. Cox JD, Stetz JA and Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341-1346


Appendix

Table A1. Acute GI complications according to the RTOG morbidity scale (adaptations with regard to the original RTOG scale in italics)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI</strong></td>
<td>Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics</td>
<td>Diarrhea requiring parasympatholytic drugs/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics</td>
<td>Obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion</td>
</tr>
<tr>
<td><strong>GU</strong></td>
<td>Frequency of urination or nocturia twice pretreatment habit/dysuria or urgency not requiring medication</td>
<td>Frequency of urination is less frequent than every hour (day: 12-16 times; nocturia 5-8 times)/dysuria, urgency, bladder spasm requiring local anaesthetic</td>
<td>Frequency of urination is more frequent than every hour (day: &gt;16 times; nocturia: &gt;8 times)/dysuria, bladder spasm, urgency requiring frequent regular narcotic/gross hematuria/complaints requiring permanent or suprapubic catheter</td>
</tr>
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</table>
### Table A2. Late GI and GU complications according to the RTOG/EORTC morbidity scale (adaptations with regard to the original RTOG/EORTC scale in italics).

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI</strong></td>
<td><strong>Grade 2</strong></td>
<td><strong>Grade 3</strong></td>
<td><strong>Grade 4</strong></td>
</tr>
<tr>
<td>Mild diarrhea; mild cramping; bowel movements 2-5 per day; slight rectal discharge or bleeding</td>
<td>Moderate diarrhea; intermittent, severe cramping; bowel movements &gt; 5 per day; moderate excessive, rectal discharge; intermittent, frequent bleeding → single laser treatment and/or transfusion</td>
<td>Watery diarrhea; obstruction requiring surgery; bleeding requiring surgery or ≥ 2 laser treatments and/or transfusions</td>
<td>Necrosis; perforation; fistula; abdominal pain or tenesmus requiring tube decompression or bowel diversion</td>
</tr>
<tr>
<td><strong>GU</strong></td>
<td><strong>Frequency during day 1/1-2 hrs; nocturia 2-3/night; slight dysuria or microscopic hematuria requiring no medication; slight epithelial atrophy, minor telangiectasia; bladder capacity &gt; 300 cc</strong></td>
<td><strong>Frequency during day 1/½-1 hrs; nocturia 4-6/night; moderate dysuria or intermittent (mild, moderate) hematuria requiring medication†; moderate telangiectasia; bladder capacity: 150-300 cc</strong></td>
<td><strong>Frequency during day &gt;1/½ hrs; nocturia &gt;6/night; severe dysuria; frequent (severe) hematuria; severe telangiectasia; bladder capacity: 100-150 cc; benign urethral strictures, requiring a TURP, dilation, suprapubic or permanent catheter</strong></td>
</tr>
</tbody>
</table>

*The difference between Grade 1 and Grade 2 GI pain, mucosal loss or bleeding is most easily made, when Grade 2 is defined as morbidity requiring specific medication: Grade 1 = stool softener, diet modification, occasional (< 2/week) non-narcotic drug, occasional antidiarrheal agent (= 2/week), occasional use of incontinence pads (1-2 days / week); Grade 2 = regular (> 2/week) use of (non)-narcotic drugs for pain, regular (> 2/week) antidiarrheals, steroid suppositories, 1 laser; † with the exception of antibiotics.

### Table A3. Some indicators for RTOG/EORTC and/or SOMA/LENT ≥ grade 2 (infrequently encountered symptoms not included in this list)

**GI Indicators**
1. Pain/cramps/ tenesmus requiring medication
2. Proctitis requiring use of steroids
3. Rectal bleeding requiring laser treatment or transfusion
4. Use of incontinence pads for rectal discharge blood/mucus/stools (pads >2 days/ week)
5. High stool frequency (≥ 6)

**GU Indicators**
1. Nocturia (≥ 4)
2. High urinary frequency during the day (≥ 16)
3. High urinary frequency during 24 h (≥ 9)
4. Use of incontinence pads for urinary incontinence (pads >2 days a week)
5. Dysuria requiring medication
6. Urinary obstruction requiring treatment (at least catheterization )
7. Hematuria requiring laser treatment or transfusion