Long term toxicity after radiotherapy for prostate cancer: generation of multivariable prediction models

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# Table of contents

Summary ........................................................................................................................................... 3
English ............................................................................................................................................... 3
Dutch ................................................................................................................................................ 3

Introduction ...................................................................................................................................... 4
The prostate ....................................................................................................................................... 4
Prostate cancer .................................................................................................................................. 4
Treatment options ............................................................................................................................. 4
Radiotherapy ...................................................................................................................................... 5
Normal tissue complication probability models .............................................................................. 5
Objective .......................................................................................................................................... 5

Materials and methods .................................................................................................................... 6
Study design ....................................................................................................................................... 6
Patient selection ................................................................................................................................. 6
Target delineation .............................................................................................................................. 7
Treatment characteristics .................................................................................................................. 7
Organ at risk definition ..................................................................................................................... 8
Endpoints .......................................................................................................................................... 8
Study parameters .............................................................................................................................. 9
Statistical analysis ............................................................................................................................. 10

Results ............................................................................................................................................ 11
Gastro-intestinal toxicity .................................................................................................................. 11
  Rectal blood loss .............................................................................................................................. 11
  Faecal incontinence CTCAE v3.0 grade 2+ ...................................................................................... 12
  Rectal pain during defecation .......................................................................................................... 14
Obstipation ......................................................................................................................................... 15
Genitourinary toxicity ....................................................................................................................... 15
  Bladder incontinence CTCAE v3.0 grade 2+ ................................................................................... 15
  Haematuria ...................................................................................................................................... 16

Discussion ....................................................................................................................................... 18
NTCP models ...................................................................................................................................... 18
  Rectal blood loss .............................................................................................................................. 18
  Faecal incontinence .......................................................................................................................... 18
  Rectal pain ...................................................................................................................................... 19
  Urinary incontinence ......................................................................................................................... 19
  Haematuria ...................................................................................................................................... 19
Proton therapy ................................................................................................................................... 20
Conclusion ......................................................................................................................................... 20

Bibliography ..................................................................................................................................... 21
Every year, 10,000 men in the Netherlands are diagnosed with prostate cancer, making it the most common cancer among men. Radiotherapy is commonly used as a curative treatment for localised prostate cancer. Normal tissue complication probability (NTCP) models predict the risk of toxicity after radiotherapy. These models are mostly based on patient characteristics, treatment characteristics and radiation dose/volume data within organs at risk (OAR’s). These are organs in or surrounding the treatment area. The purpose of this study is to develop NTCP-models for rectal and urinary toxicity, in order to reduce toxicity in the future.

A prospective study was carried out with 302 men, who were treated in the University Medical Centre Groningen (UMCG), with primary radiotherapy for localised, biopsy proven prostate cancer. After treatment, patients filled in questionnaires and visited their radiation oncologist annually to keep track of disease progression and treatment related toxicity. Using multivariable logistic regression analyses, NTCP models were developed.

Rectal bleeding is associated with rectal wall V70 (Vx is the relative volume of an OAR receiving at least x Gy), anal canal V30 and aspirin use. Fecal incontinence is associated with anal canal V10 and patient age. Rectal pain is associated with anorectum V70 and androgen deprivation therapy. Bladder incontinence is associated with bladder V76, α-blocker use, diabetes, age. Macroscopic haematuria is associated with bladder V76 and diabetes. These models could be used to limit long-term toxicity, by reducing the dose in the OAR’s.

Jaarlijks worden in Nederland 10.000 mannen gediagnostiseerd met prostaatkanker, waarmee prostaatkanker de meest voorkomende maligniteit onder mannen is. Prostaatkanker wordt vaak curatief behandeld met radiotherapie. Normal tissue complication probability (NTCP) modellen voorspellen de kans op toxiciteit na radiotherapie. Deze modellen kunnen gebaseerd zijn op patiënt- en behandelkarakteristieken en straling dosis/volume data in organs at risk (OAR’s). Dit zijn organen in of rondom het behandelgebied. Het doel van dit onderzoek is het ontwikkelen van NTCP-modellen voor rectale en urologische toxiciteit, zodat deze toxiciteit in de toekomst gereduceerd kan worden.

Een prospectieve studie is uitgevoerd met 302 mannen, die in het Universitair Medisch Centrum Groningen (UMCG) zijn behandeld voor gelokaliseerde prostaatkanker met primaire radiotherapie. Na de behandeling hebben patiënten periodiek vragenlijsten ingevuld en hadden periodieke controleafspraken bij hun radiotherapeut, voor controle van mogelijke ziekteprogressie, toxiciteit en gezondheid. Met behulp van multivariabele regressie analyses zijn NTCP modellen gemaakt.

Rectaal bloedverlies is geassocieerd met rectumwand V70 (Vx is het relatieve volume van een OAR dat minimaal x Gy ontvangt), anale kanaal V30 en aspirinegebruik. Fecale incontinentie is geassocieerd met anale kanaal V10 en leeftijd van de patiënt. Rectale pijn is geassocieerd met anorectum V70 en hormonale therapie. Urine-incontinentie is geassocieerd met blaas V76, α-blockergebruik, diabetes en leeftijd. Macroscopische hematurie is geassocieerd met blaas V76 en diabetes. Deze modellen kunnen worden gebruikt om de toxiciteit te beperken, door de dosis in kwetsbare organen te verminderen.
Introduction

The prostate
The prostate gland is situated below the bladder and surrounds a part of the urethra. The prostate weights 11 grams on average and has the size of a walnut (1). It is part of the male reproductive system and is homologous with the female Skene’s gland, which is often referred to as the female prostate (2). The prostate gland contracts during semen emission, secreting prostatic fluid which mixes with the semen. Prostatic fluid is an alkaline, milky fluid which contains several components that contribute to successful fertilisation, including prostate-specific antigen (PSA). PSA is a glycoprotein enzyme that liquefies semen, in order to increase the mobility of the spermatozoa (3). The fluid that is emitted from the vas deferens is acidic, as is the vaginal tract (pH is 3.5-4.0). However, spermatozoa are optimally mobile when the pH of their environment is 6.0-6.5. The semen achieves the right pH, due to the alkaline characteristic of the prostatic fluid. Without the addition of prostatic fluid to the semen, the spermatozoa would be less mobile, resulting in a smaller chance of fertilisation (4).

Prostate cancer
Approximately 10.000 men in the Netherlands received diagnoses of prostate cancer in 2014, making it the most common cancer among men in the Netherlands, followed by colon cancer and skin cancer respectively. In the same year, more than 2600 men in the Netherlands died as a result of prostate cancer, meaning that this cancer has a mortality rate of approximately 25% (5). Prostate cancer is predominantly a disease of the elderly, with 99,1% being ≥ 50 years of age and 88,6% being ≥ 60 years of age in 2014 (6). Almost all prostate cancers are adenocarcinomas, developing from prostate gland cells. Other cancer types, like sarcomas or small cell carcinomas, are rare (7). Crissmann et al. found that small prostatic adenocarcinomas can be revealed on autopsy in 64% of men aged 60 to 70 years old, while only a small percentage of these men was diagnosed with prostate cancer during their lives (8). It follows that most prostate cancers are not giving any symptoms. Due to the incidence and mortality rate, the global burden of this disease is high.

Treatment options
Multiple treatment options are available to curatively treat localised prostate cancer, including radical prostatectomy and radiotherapy (eventually combined with androgen deprivation therapy) (9). Each treatment differs in efficacy, side-effects and costs, which makes it not easy to compare different therapies. Furthermore, therapies are improved over time, which makes accurate comparisons between different therapies even more challenging. Treatment decisions are based on several patient and tumor related factors, such as cancer stage, age, comorbidities, chance of success and the patients preference. An elderly patient with low-risk prostate cancer and many comorbidities might benefit the most from watchful waiting. These patients are not treated, but only consult their doctor for regular medical check-ups, because the side-effects of treatment would outweigh the gain in quality of life or life expectancy (7).
Radiotherapy

External beam radiotherapy (EBRT) probably is the best known non-invasive treatment form and is the most common curative cancer therapy for localised prostate cancer in elderly patients (7,10,11). Radioactive beams are planned from different angles of the patient, in order to maximise the radiation dose in the tumour, and minimise the dose in the surrounding tissue. Radiation damages the cell DNA, which could result in cell death. The position of the beam in multiple angles around the patient is necessary, as this will spread out the dose received by organs at risk (OAR’s). These are normal tissue organs in or surrounding the treatment area. Radiation can be as harmful to healthy tissues as it is to malignant cells (12). Although cure rates are high, radiotherapy in the prostate area can be complicated by dermatologic, genitourinary (GU) and gastrointestinal (GI) toxicity, including incontinence for urine and/or faeces, rectal blood loss and an increased stool frequency (13,14). Especially GI toxicity has been studied extensively and most studies focus on the anorectum as a single OAR (15-18). However, it has been shown by multiple studies that dose-volume distributions in more specific anatomic substructures could refine prediction models of toxicity (13,19). Dose-volume distribution data are commonly used in radiation oncology studies and are measures for the relative volume of an OAR that has received a certain amount of radiation dose. For example, a bladder V30 of 50% means that 50% of the bladder volume has received at least 30 Gy. Most studies on GU toxicity focus on the bladder as a single OAR or are based on a small population size (20,21), asking for a study that includes the correlation between GU toxicity and dose-volume distributions on more specific anatomical substructures of the bladder.

Normal tissue complication probability models

Normal tissue complication probability (NTCP) models predict late toxicity in certain structures after radiotherapy treatment. For many structures, there is a positive relationship between the radiation dose on an organ and the risk of late toxicity (13,22-24). The radiation dose on a particular organ varies from one patient to another, since this dose depends on a patient’s anatomy, treatment plan and the delineated targets. NTCP models are important to decide which treatment dose distribution is the most appropriate for each patient and to estimate a patient’s individual risk on late toxicity and therefore feasibility of the treatment before start.

Objective

Since prostate cancer patients can experience a significant decline in quality of life due to late toxicity after radiotherapy (13), further improvement of radiotherapy techniques to lower dose in OAR’s is needed. The main objective of this project is to identify prognostic factors for toxicity by developing NTCP models for late GI and genitourinary GU toxicity in prostate cancer patients treated with radiotherapy. The purpose of these models is to investigate if further decrease in late toxicity and improvement of quality of life can be achieved by optimising the dose distribution in OAR’s of a treatment plan.
Materials and methods

Study design
A prospective cohort study was carried out with 302 men, who were diagnosed with biopsy-proven prostate cancer. All patients were treated in the University Medical Centre Groningen (UMCG) with external beam radiotherapy (EBRT) in the period of 2006 to 2010. The minimal follow-up period for each patient was 2 years after the end of radiotherapy.

Patient selection
To be included in this study, all patients have to meet the following eligibility criteria:

- Treated in the period 2006-2010;
- Biopsy proven prostate cancer;
- Tumour stage: low, intermediate or high risk prostate cancer;
- Treated with radiotherapy, with or without androgen deprivation therapy (ADT);
- Localised prostate cancer (N₀M₀);
- Treatment dose 78Gy, in 39 fractions of 2 Gy;
- Age: ≥18.

Patients were excluded if they had at least one of the following exclusion criteria:

- Prior pelvic irradiation;
- (Nodal) metastases present before radiotherapy treatment;
- Prior local treatment for prostate cancer;
- No clinical data available;
- No treatment data available;
- No clinical follow-up available;
- Concurrent chemotherapy;
- Elective pelvic node irradiation.

Clinical data was available for 1552 patients, of whom 428 patients have been treated between 2006 and 2010. 44 patients were excluded because their prostate cancer was already metastasised at the time of diagnosis. 63 patients were excluded because they underwent prostate salvage surgery before radiotherapy. 19 more patients were excluded because they were not treated with a dose of 78 Gy. In total, 302 patients were suitable for analyses (see figure 1).
**Target delineation**

The whole prostate is delineated as a clinical target volume (CTV). Due to movement of the prostate and other uncertainty factors, as couch position, it is necessary to create a planning target volume (PTV) which ensures daily irradiation of the whole CTV, despite movement of the prostate or other factors. Depending on multiple tumour characteristics, the CTV in low risk category patients was defined as the prostate solely without the seminal vesicles. The CTV in medium risk category patients was defined as the prostate including the first 2 centimetres of the seminal vesicles and the CTV in high risk category patients was defined as the prostate including the whole seminal vesicles.

**Treatment characteristics**

Patients were treated with linear accelerators, using 6 MV photons with intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). Patients received a total of 78 Gy on the prostate in 39 fractions of 2 Gy and were treated five times per week, with a minimum of 9 times per two weeks. Patients consulted their radiation oncologist at least biweekly during therapy. Radiation induced cystitis or proctitis complaints are expected side-effects of this radiotherapy treatment. Tamsulosine or solifenacine could be prescribed in case of obstructive urinary symptoms or irritative urinary symptoms respectively. If side-effects continued, prednisolone prescription was considered. Gastro intestinal side-effects, as faecal urge, incorporation of mucus in the stool and thinner consistency could be treated with loparemid oxide.

A selection of patients was treated with hormones as part of a randomised control trial. Patients undergoing androgen deprivation therapy (ADT) are more prone to erectile dysfunction, mood swings and hot flashes. Side-effects of ADT could be treated with cyproteron.

Blood tests were performed 7-8 weeks after the end of the radiotherapy to determine the patients’ PSA level. Three months after this consult, the urologist was consulted. After 6 months, the patients consulted their radiation oncologist, after which yearly follow-up consults were planned to a maximum of 5 years (or longer, based on individual considerations). The main task of the radiation oncologist during follow-up is to evaluate late...
toxicity that is related to radiotherapy or ADT and to monitor eventual tumour progression, with PSA levels (and testosterone levels, in case of ADT).

**Organ at risk definition**
The anorectum was defined as part of the bowel, ranging from the ischial tuberosities to the sigmoid flexure. The rectum was defined as the anorectum without the anal canal, which was defined as the 3 most distal centimetres of the anorectum. The sigmoid was defined as part of the bowel from the sigmoid flexure to the distal part of the descending colon. Rectal, anal, bladder and sigmoidal walls were defined as the most outer 3 mm of these organs and were calculated automatically from the delineated organs using the currently used delineation program at the department, namely *Philips Pinnacle*®. Furthermore, the femoral heads were delineated, but were not used for analysis in this study. For organ delineations, see figure 2.

![Fig. 2 Sagittal view of the prostate (red), bladder (green), rectum (yellow) and anal canal (blue).](image)

**Endpoints**
Toxicity was quantified using the EORTC QLQ-C30 (v3.0) and the EORTC QLQ PR-25 (both in the Dutch language). Questionnaires were filled out by all patients at the department of Radiation Oncology of the UMCG and have been used for previous studies (13,25-27). Data acquired using the questionnaires were retrospectively combined with additional data, acquired from patient files, such as medication use and comorbidities. However, toxicity data was solely prospectively scored and therefore not retrospectively acquired from patient files. Our main endpoint is the generation of NTCP models that describe the relationship between dose and the risk of toxicities. Toxicity is graded using the Common Terminology Criteria for Adverse Events version (CTCAE) 3.0 scoring system, with a division of toxicity in different grades.

According to this scoring system, genitourinary (GU) symptoms grade 1 or higher (1+) include occasional loss of urine, without the need for pads, increase in urine frequency or nycturia up to twice normal or limited urine retention occurring during the immediate postoperative period without the need for medication. GU grade 2 or higher (2+) symptoms include spontaneous urine loss asking for pad use, increase in urine frequency more than
twice normal, but less than hourly and urine retention indicating for medication. GU grade 3 of higher (3+) symptoms include urinary incontinence inferring with activities of daily living (ADL) in such a way that an intervention is needed, urinary frequency more than hourly, indicating a catheter and urinary retention needing more than daily catheterisation or an intervention such as a transurethral resection of the prostate (TURP).

Gastrointestinal (GI) 1+ symptoms include occasional constipation, occasional use of stool softeners, increase of less than four stools per day, occasional use of pads for stool loss, rectal discomfort due to proctitis. GI 2+ symptoms include persistent symptoms of constipations, asking for regular use of stool softeners or laxatives, increase of 4-6 stools per day or requiring intravenous (IV) fluids for less than one day, daily use of pads for stool loss, proctitis not interfering with ADL, but requiring medical intervention. GI 3+ symptoms include constipation interfering with ADL, requiring manual evacuation. Increase of 7 or more stools per day, the need for hospitalisation or IV fluids for more than one day and anal incontinence interfering with ADL, requiring an operative intervention. GI4+ symptoms include life-threatening situations such as a perforation, toxic megacolon and hemodynamic collapse due to fluid depletion.

**Study parameters**

Toxicity is patient rated using the EORTC QLQ PR25 and includes (but is not limited to):

- Rectal blood loss (CTCAE 3.0 grade 1+);
- Faecal incontinence requiring daily pad use (CTCAE 3.0 grade 2+);
- Obstipation requiring daily use of laxatives (CTCAE 3.0 grade 2+);
- Abdominal cramping or pain;
- Bladder incontinence requiring daily pad use (CTCAE 3.0 grade 2+);
- Haematuria.

Multiple parameters were collected for the purpose of this study. Parameters that were taken into account for this study are described in table 1.

Dose-volume data:

Volume of the OAR receiving dose (Vx: relative volume of OAR receiving ≥ x Gy (0-100%)).

Organs: bladder, bladder wall, anal canal, anal wall, rectum, rectal wall, anorectum, anorectal wall, sigmoid, sigmoidal wall, femoral heads.

Dose volume parameters: V5, V10, V20, V30, V40, V50, V60, V70, V74, V76, V78, V80, minimal dose, maximum dose and mean dose in any of the mentioned OAR’s.

Patient follow-up

- PSA blood levels;
- Biochemical failure (PSA: lowest concentration measured (nadir) +2ng/ml);
- Patient reported toxicity, using EORTC QLQ-PR25 questionnaire;
- Recurrence;
- Death, including cause of death (prostate cancer, other primary malignancy, other).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at treatment start</td>
<td>&lt;65</td>
<td>64 (21,2%)</td>
</tr>
<tr>
<td></td>
<td>65-&lt;75</td>
<td>173 (57,3%)</td>
</tr>
<tr>
<td></td>
<td>≥75</td>
<td>65 (21,5%)</td>
</tr>
<tr>
<td>Use of the following medications</td>
<td>α-blockers</td>
<td>35 (11,6%)</td>
</tr>
<tr>
<td></td>
<td>aspirin</td>
<td>56 (18,5%)</td>
</tr>
<tr>
<td></td>
<td>anticoagulants</td>
<td>42 (13,9%)</td>
</tr>
<tr>
<td></td>
<td>insulin</td>
<td>7 (2,3%)</td>
</tr>
<tr>
<td>TURP</td>
<td></td>
<td>35 (11,6%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>38 (12,6%)</td>
</tr>
<tr>
<td>Tumour stage</td>
<td>T1</td>
<td>99 (32,7%)</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>37 (12,3%)</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>17 (5,6%)</td>
</tr>
<tr>
<td></td>
<td>T2c</td>
<td>61 (20,2%)</td>
</tr>
<tr>
<td></td>
<td>T3-T4</td>
<td>56 (18,6%)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>≤6</td>
<td>95 (31,4%)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>135 (44,7%)</td>
</tr>
<tr>
<td></td>
<td>≥8</td>
<td>72 (23,9%)</td>
</tr>
<tr>
<td>PSA level</td>
<td>&lt;10</td>
<td>94 (31,1%)</td>
</tr>
<tr>
<td></td>
<td>10-&lt;20</td>
<td>115 (38,1%)</td>
</tr>
<tr>
<td></td>
<td>≥20</td>
<td>93 (30,8%)</td>
</tr>
<tr>
<td>Risk category</td>
<td>Low</td>
<td>17 (5,6%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>59 (19,5%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>226 (74,8%)</td>
</tr>
<tr>
<td>Prostate volume</td>
<td>&lt;20cc</td>
<td>64 (21,2%)</td>
</tr>
<tr>
<td></td>
<td>20-&lt;40cc</td>
<td>102 (33,8%)</td>
</tr>
<tr>
<td></td>
<td>≥40cc</td>
<td>101 (33,4%)</td>
</tr>
<tr>
<td></td>
<td>unknown</td>
<td>35 (11,6%)</td>
</tr>
<tr>
<td>Androgen deprivation therapy</td>
<td></td>
<td>162 (53,6%)</td>
</tr>
<tr>
<td>Seminal vesicles irradiation</td>
<td></td>
<td>251 (83,1%)</td>
</tr>
</tbody>
</table>

*tab. 1 Patient, tumour and treatment characteristics.*

**Statistical analysis**

Statistical analyses were performed using IBM SPSS Statistics version 23 in the UMCG, Groningen. Toxicities were scored binominal with no (0) or yes (1). Univariate analyses for toxicity outcomes were performed using a binary logistic regression. For all outcomes, all clinical parameters were taken into account. For rectal toxicity, correlations with dose volume distributions in the anal canal, rectum, anorectum, sigmoid and corresponding walls were investigated. For bladder toxicity, correlations with dose volume distributions in the bladder and bladder wall were investigated. A p-value of ≤0,05 was considered significant. Multivariate analyses were performed using a binary logistic regression with variables that appeared to be significantly correlated in univariate analysis or close-to significant variables (p<0,16), that appeared significantly correlated in other studies. Using the ‘correlation of estimates’ function, confounders among dose volume distribution variables were revealed. A correlation of >0,8 was considered significant. The variable with the highest p-value was then removed. This process was repeated until no significant correlations were left. The Hosmer-Lemeshow test was performed to validate the goodness of fit. The area under the curve was calculated in order to the model’s performance.
Results
24 out of 302 patients were excluded for statistical analysis due to limited follow up data. 12 patients had less than two years of follow-up, 2 patients developed another primary malignancy in the pelvic area during follow-up, so it was not possible to attribute toxicity to radiotherapy with certainty. 10 patients did not fill in the questionnaires. The median follow-up duration of our cohort (n=278) is 5.6 years (range: 2-10 years).

Gastro-intestinal toxicity
153 out of 302 patients (50.7%) reported at least one grade ≥1 gastrointestinal toxicity at some point in the follow-up. Obstipation was most often reported (n=75), followed by rectal pain (n=49), rectal bleeding (n=46) and faecal incontinence (n=18).

Rectal blood loss
46 out of 278 patients (16.5%) reported at least a single event of rectal blood loss, that could not be explained by haemorrhoids. Candidate variables for analyses were dose volume distributions in the anal canal, rectum, anorectum, sigmoid and corresponding walls. Pre-treatment variables that were taken into account are the patients’ age, aspirin use, prescription anticoagulant use, α-blocker use, diabetes, androgen deprivation therapy (ADT), risk category and prostate volume.

In the univariate analysis, significant relationships were found between rectal blood loss and aspirin use, α-blocker use and dose volume distributions as shown in table 2. All dose volume distributions variables except rectal wall V70 and anal canal V30 were dropped in the multivariate analysis due to confounding.

<table>
<thead>
<tr>
<th>Organ/variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value</td>
<td>Odds-ratio (CI-95%)</td>
</tr>
<tr>
<td>Pre-treatment aspirin use</td>
<td>0.010</td>
<td>2.470 (1.217-5.013)</td>
</tr>
<tr>
<td>Pre-treatment α-blocker use</td>
<td>0.020</td>
<td>3.000 (1.338-6.726)</td>
</tr>
<tr>
<td>Anal canal</td>
<td>Dmean</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>V5</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>V10</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>V30</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>V40</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>V50</td>
<td>0.029</td>
</tr>
<tr>
<td>Anal wall</td>
<td>Dmean</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>V5</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>V10</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>V30</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>V40</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>V50</td>
<td>0.040</td>
</tr>
<tr>
<td>Anorectum</td>
<td>V40</td>
<td>0.037</td>
</tr>
</tbody>
</table>
In the multivariate analysis, a prediction model was created, that includes pre-treatment aspirin use, rectal wall V70 and anal canal V30. For individuals, the risk of experiencing at least one event of rectal bleeding that could not be attributed to haemorrhoids, can be estimated using the following equation:

$$\text{NTCP} = \frac{1}{1 + e^{-S}}$$

Where S is defined as:

$$S = -4.211 + 1.168 \times \text{(aspirin use)} + 0.022 \times \text{(anal canal V30)} + 0.078 \times \text{(rectal wall V70)}$$

With anal canal V30 and rectal wall V70 in relative volume (0-100%) and pre-treatment aspirin use is 0 (no) or 1 (yes).

The area under the curve (AUC) of this prediction model is 0.70 (95% CI: 0.60-0.79). The Hosmer-Lemeshow test was not significant (chi square 8.0; df 8; p=0.43), indicating a good agreement between observed and expected outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>V50</th>
<th>V70</th>
<th>V70</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorectal wall</td>
<td>V70</td>
<td>0.015</td>
<td>1.094</td>
<td>(1.017-1.178)</td>
<td>0.719</td>
</tr>
<tr>
<td>Rectum</td>
<td>V70</td>
<td>0.027</td>
<td>1.068</td>
<td>(1.007-1.134)</td>
<td>0.985</td>
</tr>
<tr>
<td>Rectal wall</td>
<td>V70</td>
<td>0.037</td>
<td>1.065</td>
<td>(1.003-1.131)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Tab. 2 Univariate and multivariate analysis for rectal blood loss.

Fig. 3 Probability of developing rectal blood loss without aspirin use (left) or with aspirin use (right).

Faecal incontinence CTCAE v3.0 grade 2+
18 out of 276 patients (6.0%) experienced faecal incontinence, for which daily pad use was needed. Pad dependency is scored by the common terminology criteria for adverse events (CTCAE) v3.0 as a grade 2 event. Candidate variables for analyses were dose volume distributions in the anal canal, rectum, anorectum, sigmoid and corresponding walls. Pre-
treatment variables that were taken into account are the patients’ age, aspirin use, prescription anticoagulant use, α-blocker use, diabetes, ADT, risk category, pre-treatment trans urethral resection of the prostate (TURP) and prostate volume.

In the univariate analysis, significant relationships were found between faecal incontinence and the patients’ age, α-blocker use, TURP and dose volume distribution variables as shown in table 3.

<table>
<thead>
<tr>
<th>Organ/variabele</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>Odds-ratio (CI-95%)</td>
</tr>
<tr>
<td>Age</td>
<td>0.003</td>
<td>1.153 (1.147-1.269)</td>
</tr>
<tr>
<td>Pre-treatment α-blocker use</td>
<td>0.019</td>
<td>3.291 (1.089-9.943)</td>
</tr>
<tr>
<td>TURP</td>
<td>0.005</td>
<td>4.107 (1.429-11.803)</td>
</tr>
<tr>
<td>Anal Canal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V10</td>
<td>0.017</td>
<td>1.044 (1.007-1.084)</td>
</tr>
<tr>
<td>Anal Wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V10</td>
<td>0.027</td>
<td>1.038 (1.004-1.072)</td>
</tr>
</tbody>
</table>

In the multivariate analysis, a prediction model was created, that includes age and anal canal V10. The risk for developing CTCAE grade 2+ faecal incontinence can be estimated for individual patients using the following equitation:

\[ \text{NTCP} = \frac{1}{1+e^{-S}} \]

Where S is defined as:

\[ S = -15.118 + 0.131 \times \text{age} + 0.040 \times \text{anal canal V10} \]

With age in years and anal canal V10 in relative volume (0-100%).

The area under the curve (AUC) of this prediction model is 0.76 (95%-CI: 0.65-0.87). The Hosmer-Lemeshow test was not significant (chi square 4.6; df 8; p=0.80), indicating a good agreement between observed and expected outcomes.
Fig. 4 Probability of developing faecal incontinence grade 2+.

Rectal pain during defecation
49 out of 277 patients (17.7%) experienced at least one episode of rectal pain during defecation. Candidate variables for analyses were dose volume distributions in the anal canal, rectum, anorectum, sigmoid and corresponding walls. Pre-treatment variables that were taken into account are the patients’ age, aspirin use, prescription anticoagulant use, α-blocker use, diabetes, ADT, risk category and prostate volume.

In univariate analysis, significant relationships were found between rectal pain and pre-treatment ADT (p=0.036) and dose volume distribution variables as shown in table 4.

<table>
<thead>
<tr>
<th>Organ/variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>Odds-ratio (CI-95%)</td>
</tr>
<tr>
<td>ADT</td>
<td>0.108</td>
<td>1.694 (0.891-3.223)</td>
</tr>
<tr>
<td>Pre-treatment anticoagulant</td>
<td>0.064</td>
<td>0.251 (0.058-1.085)</td>
</tr>
<tr>
<td>Anal canal V10</td>
<td>0.047</td>
<td>1.021 (1.000-1.041)</td>
</tr>
<tr>
<td>V70</td>
<td>0.046</td>
<td>1.050 (0.998-1.105)</td>
</tr>
<tr>
<td>V74</td>
<td>0.044</td>
<td>1.567 (0.949-2.587)</td>
</tr>
<tr>
<td>Anal wall V10</td>
<td>0.041</td>
<td>1.021 (1.001-1.042)</td>
</tr>
<tr>
<td>V74</td>
<td>0.044</td>
<td>1.567 (0.949-2.587)</td>
</tr>
<tr>
<td>Anorectum V70</td>
<td>0.005</td>
<td>1.106 (1.031-1.187)</td>
</tr>
<tr>
<td>Anorectal wall V70</td>
<td>0.039</td>
<td>1.078 (1.003-1.158)</td>
</tr>
<tr>
<td>Rectum V70</td>
<td>0.018</td>
<td>1.073 (1.012-1.137)</td>
</tr>
</tbody>
</table>

**tab. 4 Univariate and multivariate analysis for rectal pain.**

In multivariate analysis, a prediction model was created, that includes ADT and anorectum V70. For individuals, the risk of experiencing at least one event of significant pain during defecation can be estimated using the following equitation:

$$\text{NTCP} = \frac{1}{1 + e^{-S}}$$

Where S is defined as:

$$S = -3.004 + 0.705 \times \text{(ADT)} + 0.099 \times \text{(anorectum V70)}.$$
The area under the curve (AUC) of this prediction model is 0.67 (95%-CI: 0.59-0.76). The Hosmer-Lemeshow test was not significant (chi square 10.6; df 8; p=0.21), indicating a good agreement between observed and expected outcomes.

![Graph showing probability of developing rectal pain.](image)

**Fig. 5 Probability of developing rectal pain.**

**Obstipation**
75 out of 277 (24.8%) reported obstipation, for which a regular use of laxatives was needed (CTCAE grade 2+). For this outcome, significant variables were found neither in univariate nor in multivariate analysis.

**Genitourinary toxicity**
56 out of 302 patients (18.5%) reported at least one genitourinary event. Bladder incontinence was most often reported (n=40), followed by haematuria (n=30).

**Bladder incontinence CTCAE v3.0 grade 2+**
40 out of 278 (14.4%) patients experienced bladder incontinence, for which daily pad use was needed. Pad dependency is scored by the common terminology criteria for adverse events (CTCAE) v3.0 as a grade 2 event. Candidate variables were dose volume distribution variables in the bladder and bladder wall. Pre-treatment variables that were taken into account are the patients’ age, aspirin use, prescription anticoagulant use, α-blocker use, pre-treatment TURP, diabetes, ADT, risk category and prostate volume.

In univariate analysis, significant correlations were found between bladder incontinence and the bladder V76, age, diabetes, α-blocker use and TURP, as can be seen in table 5.

<table>
<thead>
<tr>
<th>Organ/variabele</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>Odds-ratio (CI-95%)</td>
</tr>
<tr>
<td>Age</td>
<td>0.051</td>
<td>1.061 (1.000-1.126)</td>
</tr>
<tr>
<td>Pre-treatment diabetes</td>
<td>0.006</td>
<td>3.223 (1.395-7.448)</td>
</tr>
<tr>
<td>Pre-treatment α-blocker use</td>
<td>0.000</td>
<td>4.844 (2.134-10.997)</td>
</tr>
<tr>
<td>Pre-treatment TURP</td>
<td>0.000</td>
<td>4.364 (1.943-9.801)</td>
</tr>
<tr>
<td>Bladder V76</td>
<td>0.041</td>
<td>1.188 (1.007-1.401)</td>
</tr>
</tbody>
</table>

**tab. 5 Univariate and multivariate analysis for bladder incontinence grade 2+.**
In multivariate analysis, a prediction model was created that includes the bladder V76, patients’ age, diabetes and pre-treatment α-blocker use. The risk of developing bladder incontinence, requiring daily pad use, can be estimated by the following equitation:

\[
\text{NTCP}=\frac{1}{1+e^{-S}}
\]

Where S is defined as:

\[
S = -9,792 + 1,126*(\text{diabetes}) + 1,847*(\alpha\text{-blocker use}) + 0,101*(\text{age}) + 0,184*(\text{bladder V76})
\]

With diabetes 0 (no) or 1 (yes), α-blocker use 0 (no) or 1 (yes), age in years and bladder V76 in relative volume (0-100%).

The area under the curve (AUC) of this prediction model is 0,77 (95%-CI: 0,69-0,85). The Hosmer-Lemeshow test was not significant (chi square 8,5; df 8; p=0,39), indicating a good agreement between observed and expected outcomes.

![Fig. 6 Probability of developing bladder incontinence CTCAE grade 2+](image)

**Haematuria**

30 out of 277 patients (10,8%) experienced at least one event of macroscopic haematuria. Candidate variables were dose volume distribution variables in the bladder and bladder wall. Pre-treatment variables that were taken into account are the patients’ age, aspirin use, prescription anticoagulant use, α-blocker use, pre-treatment TURP, diabetes, ADT, risk category and prostate volume.

In univariate analysis, significant correlations were found between haematuria and pre-treatment diabetes and dose volume distributions in the bladder and bladder wall, as can be seen in table 6.
In multivariate analysis a prediction model was generated, including the bladder V76 and the presence of pre-treatment diabetes. The risk of experiencing at least one event of macroscopic haematuria, can be estimated by the following equation:

$$\text{NTCP} = \frac{1}{1 + e^{-s}}$$

Where $S$ is defined as:

$S = -2.959 + 1.287 \times \text{(diabetes)} + 0.268 \times \text{(bladder V76)}$

With diabetes 0 (no) or 1 (yes) and bladder V76 in relative volume (0-100%).

The area under the curve (AUC) of this prediction model is 0.64 (95% CI: 0.50-0.78). The Hosmer-Lemeshow test was not significant (chi square 5.7; df 8; p=0.679), indicating a good agreement between observed and expected outcomes.

<table>
<thead>
<tr>
<th>Organ/variable</th>
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<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>Odds-ratio (CI-95%)</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>0.047</td>
<td>2.587 (1.012-6.613)</td>
</tr>
<tr>
<td>diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder V74</td>
<td>0.010</td>
<td>1.123 (1.028-1.227)</td>
</tr>
<tr>
<td>V76</td>
<td>0.004</td>
<td>1.303 (1.088-1.561)</td>
</tr>
<tr>
<td>V78</td>
<td>0.012</td>
<td>6.166 (1.486-25.592)</td>
</tr>
<tr>
<td>Bladder wall V74</td>
<td>0.034</td>
<td>1.072 (1.003-1.145)</td>
</tr>
<tr>
<td>V76</td>
<td>0.019</td>
<td>1.118 (1.018-1.227)</td>
</tr>
<tr>
<td>V78</td>
<td>0.017</td>
<td>2.142 (1.145-4.009)</td>
</tr>
</tbody>
</table>

Tab. 6 Univariate and multivariate analysis for haematuria.
Discussion

NTCP models
Three prediction models for rectal toxicity and two prediction models for urinary toxicity were developed.
In most of the univariate and multivariate models, radiation dose >70 Gy (V70) appeared to be significantly correlated to the incidence of late toxicity. V70 appears to be a cut-off point above which cells are not able to repair the radiation induced damage of the DNA. Up to a certain dose level, irradiated or surrounding tissue appears to be capable of repairing the damage. This dose threshold has already been demonstrated in many previous studies (13,22).

Rectal blood loss
A model for rectal blood loss grade 1 was created. This model includes aspirin use, anorectal wall V70 and anal canal V30. Aspirin use and the V70 of a rectal substructure has been found in previous studies (13,22).
A model for rectal blood loss grade 2 could not have been created. This could be explained by two reasons. Firstly, our follow-up questionnaires did only question rectal blood loss, which is a grade 1 event and did not mention a minor cauterisation or any medical interventions, which are scored as a grade 2 events. Secondly, the doctor-reported GU en GI toxicity in the follow-up was limited or not reported when patients developed metastasised disease. It is unknown whether a correlation exists between rectal toxicity and disease progression. Therefore, it is possible that a follow-up bias is created by altering the follow-up for patients with metastasised disease. In order to develop a prediction model for grade 2 rectal blood loss, based on prospectively scored data, alternative questionnaires could be a solution.

Faecal incontinence
In this study, we found that the anal canal V10 is significantly correlated to the development of grade 2 faecal incontinence. However, the anal canal might be a surrogate for a substructure of the continence apparatus. Smeenk et al. (19) investigated the relationship between pelvic floor muscles and faecal incontinence and found significant relationships between faecal incontinence and minimum dose on the puborectal muscle and mean and maximum dose on the external anal sphincter. Schaaake et al. (13) found that grade 2 faecal incontinence is significantly correlated with the V15 of the external anal sphincter, which is part of the anal canal and with the V55 of the iliococcygeal muscle. These findings are in line with the fact that the external sphincter is responsible for voluntary control, while the internal sphincter is responsible for involuntary control (28). Altered sphincter tensions were broadly studied by Yeoh et al. (29) who found a decrease in external sphincter tensions using manometry in patients that have been treated with radiotherapy for prostate cancer. Decrease of external sphincter tension appeared to be significantly correlated with the development of faecal incontinence. Dobben et al. carried out a study in which a significant correlation between external anal sphincter atrophy and development of faecal incontinence was found (30). This study emphasises our findings on the correlation between anal canal damage and faecal incontinence.
**Rectal pain**

Rectal pain is correlated with anorectum V70 and ADT. However, pain is a difficult parameter to study, since it is a relatively subjective endpoint. Individual factors, including self-efficacy, could have an influence on pain experience (31). It is, however, an important outcome, since pain has a direct impact on quality of life (32). While many studies were not able to find predictors of rectal pain (24,33), we were able to create a NTCP model including anorectum V70 and hormonal therapy. Since our findings could not be confirmed by other studies, further investigation of this model is necessary to validate our findings.

**Urinary incontinence**

Correlations between urinary incontinence and bladder dose volume distributions were strong for the higher dose distribution V-values (V76). Cheung et al. (34) have found a correlation between GU toxicity and the V78 of the bladder, which is in line with our findings. The question is, if it is possible to reduce the bladder V76 due to anatomical position of the bladder, in relationship to the prostate. As can be seen of the planning CT of one of our patients, the bladder is situated against the prostate and is placed partly in de PTV. It is imminent that a small portion of the bladder will receive a high dose. It is doubtful if this dose could be brought back with any treatment plan, without lowering the dose in de PTV. We chose to exclude TURP from our multivariate analysis, since no NTCP model could be generated including both TURP and a dose volume distribution variable.

![Fig. 8 Bladder (green), PTV (yellow), prostate (red).](image)

**Haematuria**

We were able to create a prediction model for haematuria, including bladder V76 and diabetes. Haematuria in diabetic patients might me caused by a diabetic nephropathy or thin blood vessels that are prone to bleeding. The major limitation of this model, is the outcome; Haematuria is not a disease, but a symptom of multiple diseases, including cystitis, kidney disease or urethral damage. In order to make a model for a specific disease, the cause of haematuria should be known.

The bladder as organ at risk (OAR) appeared to be a better predictor of GU toxicity than the bladder wall. The bladder as OAR consists of bladder tissue, but predominantly of urine, which is not sensitive to radiation. Thus, theoretically the bladder wall is expected to be the
best predictor of bladder toxicity. This probably can be explained by the fact that the bladder wall is only 3 millimetres thick and therefore more sensitive to motion, since its volume changes with different filling states. The planned dose in the solid bladder appears to be more representative than the bladder wall for the actual dose. Also, setup accuracy was verified by matching bony anatomy or implanted golden markers, which are not representative for soft, surrounding tissues.

**Proton therapy**

Limiting the radiation dose in healthy tissues is one of the main challenges within the radiation oncology. Numerous radiation types and techniques have been studied to find the most profitable treatment option with the least toxicity. The majority of world’s cancer treatment institutions make use of photon therapy to treat their patients, but proton therapy (PT) is increasingly used around the globe. Although modern techniques in photon radiation are increasingly capable of sparing OAR’s, radiation doses are still high enough to cause late toxicity. Due to certain characteristics of the proton beam, PT delivers less dose to OAR’s as compared to photon therapy (35-37). Less dose in OAR’s may result in less radiation damage and toxicity. However, differences in outcome and toxicity between both therapies are currently not clear enough.

Currently, most NTCP-models for rectal and bladder toxicity are derived from patient cohorts treated with photon techniques, while limited data are available on NTCP-models derived from patient cohorts treated with protons. To create NTCP models with photon and proton therapy, data from the Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville (US) (protons) and the department of Radiation Oncology of the University Medical Center Groningen (photons) will be merged.

**Conclusion**

In this study, NTCP models were created for rectal bleeding, faecal incontinence, rectal pain, urinary incontinence and macroscopic haematuria. A concurrent finding in the calculated NTCP models, is that in particular high radiation doses (radiation dose >70 GY) in organs at risk (i.e. bladder and rectum) appear to be a reliable predictor of adverse events. Although our models showed a good performance and goodness of fit, external validation is warranted to support our findings. Radiation techniques that are able to lower the dose in normal tissue, while maintaining the high dose in the target (necessary for tumour control) are currently investigated, like the application of proton therapy.
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