Published in final edited form as:

Radiother Oncol. 2016 April ; 119(1): 117–122. doi:10.1016/j.radonc.2016.01.013.

Urinary bladder dose–response relationships for patient-reported genitourinary morbidity domains following prostate cancer radiotherapy

Maria Thor^{a,1,*}, Caroline Olsson^{b,1}, Jung Hun Oh^a, Stine Elleberg Petersen^c, David Alsadius^d, Lise Bentzen^c, Niclas Pettersson^e, Ludvig Paul Muren^c, Morten Høyer^c, Gunnar Steineck^d, and Joseph O. Deasy^a

^aDept of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, USA

^bRadiation Physics, University of Gothenburg, Sweden

^cDepts of Medical Physics of Oncology, Aarhus University Hospital, Denmark

^dDivision of Clinical Cancer Epidemiology, Department of Oncology, Institute of Clinical Sciences, The Sahlgrenska Academy at the University of Gothenburg

^eMedical Physics and Biomedical Engineering, Sahlgrenska University Hospital, Gothenburg, Sweden

Abstract

Background and purpose—Radiotherapy (RT) induced genitourinary (GU) morbidity is typically assessed by physicians as single symptoms or aggregated scores including symptoms from various domains. Here we apply a method to group patient-reported GU symptoms after RT for localized prostate cancer based on their interplay, and study how these relate to urinary bladder dose.

Materials and methods—Data were taken from two Scandinavian studies ($N = 207/276$) including men treated with external-beam RT (EBRT) to 78/70 Gy (2 Gy/fraction; median time-to-follow-up: 3.6–6.4 y). Within and across cohorts, bladder dose–volume parameters were tested as predictors for GU symptom domains identified from two study-specific questionnaires (35 questions on frequency, incontinence, obstruction, pain, urgency, and sensory symptoms) using univariate and multivariate logistic regression analysis (MVA) with 10-fold cross-validation. Performance was evaluated using Area Under the Receiver Operating Characteristic Curve (A_z).

Results—For the identified *Incontinence* (2–5 symptoms), *Obstruction* (3–5 symptoms), and *Urgency* (2–7 symptoms) domains, MVA demonstrated that bladder doses close to the prescription

*Corresponding author at: Department of Medical Physics, Memorial Sloan Kettering Cancer Center, 485 Lexington Avenue, New York, NY 10017, USA. thorm@mskcc.org (M. Thor).

¹Both authors contributed equally.

Conflict of interest

This work was supported by the Danish Cancer Society, CIRRO – the Lundbeck Foundation Centre for Research in Radiation Oncology, the Swedish Cancer Society, the King Gustav V Jubilee Clinic Cancer Foundation in Göteborg, the Swedish State under the ALF agreement in Göteborg and Stockholm, the Swedish Society for Medical Research, SSMF, and Varian Corporation. The Assar Gabrielsson Foundation, the Kamprad Family Foundation for Entrepreneurship Research & Charity are also gratefully acknowledged.

doses were the strongest predictors for *Obstruction* (A_Z : 0.53–0.57) and *Urgency* (A_Z : 0.60). For *Obstruction*, performance increased for the across cohort analysis (A_Z : 0.61–0.64).

Conclusions—Our identified patient-reported GU symptom domains suggest that high urinary bladder doses, and increased focus on both obstruction and urgency is likely to further add to the understanding of GU tract RT responses.

Keywords

Radiotherapy; Toxicity; Patient-reported outcome; Prostate cancer; Bladder; Dose–response

State-of-the-art planning and delivery of radiotherapy (RT) for prostate cancer offers considerable opportunities to spare critical segments of the gastrointestinal tract. However, possibilities to spare genitourinary (GU) structures remain limited due to their critical locations relative to the prostate. Symptoms of the GU tract are commonly multi-faceted [1,2], and it is currently not fully understood how they relate to underlying dose–volume characteristics [3,4].

Commonly used toxicity scoring systems, *e.g.* the Common Terminology Criteria for Adverse Events (CTCAE) [5] capture a selected subset of GU symptoms, and are typically assessed by physicians. Patient-reported outcomes (PROs), reflecting an individual's experience of a certain symptom, have been advocated to capture GU and other symptoms difficult for an observer to quantify [3,4,6]. Typically, PROs result in an extensive amount of data, making it challenging to identify the most central symptoms [6]. To use PROs for quantitative RT dose–response modelling, it is crucial to understand the interplay between symptoms and to test that identified relationships are generalizable across studies and cohorts [7].

The purpose of this study was to explore whether RT dose of the urinary bladder relates to the occurrence and severity of patient-reported GU-specific symptom domains. Data on bladder dose and patient-reported GU symptoms were taken from two Scandinavian prostate cancer studies ($N = 483$). We used factor analysis to identify symptom domains, and univariate (UVA) followed by multivariate logistic regression analysis (MVA) to assess relationships between identified domains and bladder dose. Best-performing regression results were also further explored in predictive modelling of normal tissue response within and across cohorts.

Materials and methods

This computational exercise was performed with already collected data from two studies in Denmark (DK) and in Sweden (SW) [8,9], and included patients who had been treated with primary EBRT for localized prostate cancer. Information on the investigated cohorts and the study-specific questionnaires is summarized below; details can be found in previous publications [8–10].

Original study design and treatment

The DK study consisted of 212 patients who were treated at Aarhus University Hospital, Aarhus, in 2005–2007 [8]. The patients completed the Danish study-specific questionnaire in 2010 (median time to follow-up (range): 3.6 (2.4–5.0) years; average age ($\pm$ SD): 70 ± 5.0 years; Table S1). The SW study consisted of 276 patients treated at the Sahlgrenska University Hospital, Gothenburg, in 1993–2006 [9,10]. The patients completed the Swedish study-specific questionnaire in 2008 (median time to follow-up: 6.4 (1.2–14) years; average age: 64 ± 5.0 years). In this work we focus on the 12 DK and 23 SW questions that directly reflected physical symptoms of potentially RT-related GU injuries: urinary frequency, incontinence, obstruction, pain, urgency, and sensory symptoms (Table S2). Methodological descriptions of the design (including validation) of the two PROs can be found in [11–13].

Primary EBRT had been planned based on CT imaging and was planned and delivered with the patient in supine position and prescribed according to the International Commission on Radiation Units and Measurements recommendations [14]. The majority of patients received conformal three- or five-field treatments with 15 MV photon beam quality and the total dose was 78 Gy in DK and 70 Gy in SW. The treatment had been delivered in 2 Gy fractions (five fractions/week). For DK patients, the planning target volume (PTV) margin was 7 mm in all directions, except craniocaudally where it was 9 mm, and the majority had been treated with a two-phase approach including the proximal seminal vesicles to 50 Gy in the first phase. For SW patients, the PTV margin was 20 mm in all directions, except posteriorly where the margin was the lesser of 15 mm or half of the rectal cross-sectional area. No bladder preparation protocol (including bladder filling instructions) was applied. All patients were treated according to the clinical routines in use at the respective hospital during the studied time period. Individual dose–volume histograms (DVHs) were electronically available and extracted from the planned 3D bladder dose distributions. The bladder had been consistently delineated from the apex to the fundus for each patient under supervision of a senior Radiation Oncologist. The following DVH-based parameters were studied as candidate predictors for the identified GU symptom domains (see preceding section below): the relative volume receiving x Gy, V_x (V_5 – V_{80} and V_5 – V_{75} for DK and SW, respectively, in steps of 5 Gy [%]), the minimum dose to the hottest $x\%$, D_x , (D_5 – D_{100} , in steps of 5% [Gy]), the mean dose of the hottest $x\%$ volume, MOH_x (MOH_5 – MOH_{100} , in steps of 5% [Gy]), and the maximum and the mean dose ($D_{\max}$ and D_{mean} , respectively).

Symptom domains and dose–response outcome variables

Given the level of detail in the two PROs and to avoid subjective grouping of symptoms from various GU-specific symptom domains, factor analysis was applied to the 12 and 23 questions of potentially RT-related GU injuries in DK and SW, respectively [15]. Factor analysis is a statistical method to investigate the relationship between items in a dataset (Appendix). Dose–response outcome variables for each symptom domain were then defined as the resulting binary response when addressing the presence of any individual symptom (Boolean ‘OR condition’ used when combining symptoms). To focus on clinically relevant and likely RT-induced symptoms, a moderate symptom severity (defined in dialogues with M.H and D.A, with at least weekly/50% of the times occurrence; Tables 1 and S2), and a symptom prevalence 5% were considered.

Statistics

To identify DVH-based predictors, logistic regression with UVA followed by MVA was applied. A candidate predictor was suggested by a two-sided p -value < 0.10 on UVA, and a Pearson's correlation coefficient (P_r) < 0.85 with any other selected candidate predictor. Best-performing domain-specific symptoms were then investigated in a normal tissue complication probability setting. To investigate model generalizability across cohorts, dose-response modelling was performed in the joint DK and SW dataset for the combination of symptoms of specific domains with the highest predictability within each cohort. All analyses were performed in MATLAB v.R2013a.

Regression analyses

In addition to the DVH-based parameters, seven patient-specific parameters were investigated: age at RT (continuous [y]), bladder volume (continuous [cm^3]), diabetes (binary; yes = 9%/12% in DK/SW), hormonal treatment (anti-androgens/gonadotropin-releasing hormone/orchiectomy; binary; yes = 91%/16% in DK/SW), intensity-modulated RT (binary; yes = 6% in DK), current (2)/former (1)/no (0) smoker (categorical; 2 = 69%/60% in DK/SW), and time to follow-up (continuous [y]; Table S2). The same criteria as used for the DVH-based candidate predictors regarding p -value < 0.10 and $P_r < 0.85$, was also applied to the patient-specific parameters. To investigate model generalizability, both the UVA and MVA were performed using 10-fold cross-validation by 50 iterations, resulting in a total of 500 generated models. In addition to a combined backward-stepwise MVA approach ($\text{MVA}_{\text{stepwise}}$), a Least Absolute Shrinkage and Selection Operator approach [16] ($\text{MVA}_{\text{LASSO}}$) was considered a Supplementary method to find the predictors from the set of UVA-suggested candidate predictors. MVA model performance was evaluated based on the area under the receiver-operating curve (A_z), assessed as the mean over the 500 generated models. Important DVH-based predictors were identified as occurring in at least 25 of the 500 generated models *i.e.* having a frequency $> 5\%$. Added model predictability, as measured from an increase in A_z , determined if any of the patient-specific parameters to be included into the final models.

Normal tissue complication probability modelling

The Lyman-Kutcher-Burman (LKB) model [17–19] was used for dose-response modelling. Data were fitted using a Maximum Likelihood method in a grid search approach (a range: 0.001:100 in 56 steps, D_{50} range: 50:150 in 101 steps, and m range: 0.01:1.1 in 55 steps) with the Profile Likelihood method to calculate 95% confidence intervals (CIs).

Results

Dose-response modelling within cohorts

The identified symptom domains (No. of symptoms) for DK consisted of *Incontinence* (3), *Obstruction* (5), and *Urgency* (7; Fig. S1), of which symptoms of the two latter domains qualified for dose-response modelling since the prevalence was $\geq 5\%$ for the majority of the included symptoms (Table 1). In SW, the same domains were identified, albeit with two separate domains for both *Incontinence* and *Obstruction*, including 2 and 5, 3 and 4, as well

as 2 symptoms, respectively. Symptoms of one *Incontinence* domain, both *Obstruction* domains, and the *Urgency* domain qualified for further analysis in SW.

On UVA, various individual dose/volume parameters of the high dose region ($D_{\max}$, D_5 , D_{20} , MOH_5 , and V_{80}) predicted *Obstruction* in both cohorts, and *Urgency* ($D_{\max}$, D_5 , MOH_5 , and V_{80}) in DK (Tables S3 and S4). A combination of parameters of the low to intermediate (D_{70} , and V_{40}), and the high (V_{65} , and V_{75}) dose region individually predicted *Incontinence* in SW (Table S4). The two MVA approaches generated the same dose/volume parameters with equal discriminative ability (Table 2), but since MVA_{LASSO} provided models with slightly increased discriminative ability/additional models, we hereafter focus on the MVA_{LASSO} -generated models. On MVA, three *Obstruction* models were identified in both DK (A_z : 0.51–0.53) and in SW (A_z : 0.51–0.57). In both cohorts, high doses predicted this domain (DK: MOH_5 , and $D_{\max}$; SW: D_{20}). The highest A_z for *Urgency* in DK (A_z : 0.60) was provided by the same two dose/volume parameters of the high-dose region (MOH_5 , and $D_{\max}$) as for *Obstruction* in DK. No models with $A_z > 0.50$ could be identified for *Incontinence* in SW. In SW, hormonal treatment was an individual predictor ($p = 0.01$) for *Obstruction* and, in DK, age ($p = 0.03$), hormonal treatment ($p = 0.01$), and time to follow-up ($p = 0.05$), were individual predictors for *Urgency*. The adjusted discriminative ability by including these clinical parameters to the final MVA models was modest: For *Obstruction*, the A_z increased at most 0.06 (SW), and for *Urgency*, it decreased at most 0.06 (DK).

The value for the best-fitting LKB model parameter a suggested a serial behaviour of the bladder for both *Obstruction* in DK and SW, and *Urgency* in DK (*Obstruction*: $a = 30$ and 70 in DK and $a = 100$ in SW; *Urgency*: $a = 100$ in DK; Table 3). The 95% CI of the a and the D_{50} values for both domains were, however, wide.

Dose–response modelling across cohorts

Given that both cohorts provided models for *Obstruction*, outcome variables for the combined cohorts were defined from the MVA results of this domain only. More specifically, either DK Q2Q4 or DK Q2Q3Q4 was joined with SW Q1 (Table 2; Fig. S1). The A_z increased from 0.53 in DK and 0.57 in SW to 0.61–0.64 for the joint analysis. Similarly as for the individual cohort analyses, high doses (V_{75}) predicted *Obstruction*. Bladder volume ($p = 0.01$), hormonal treatment ($p < 0.001$), smoking ($p = 0.08$), and time to follow-up ($p = 0.003$) were individual predictors for *Obstruction* but inclusion of these five candidate parameters did not increase the discriminative ability. The population averaged dose–volume histograms for patients with and without a moderate symptom severity used as input to these final *Obstruction* models are illustrated in Fig. 1. The increased discriminative ability was also reflected within the LKB modelling as 95% CIs for all fitted parameters were narrower in joint as compared to individual cohort analyses (Table 3).

Discussion

Using data from two Scandinavian prostate cancer studies, we found that urinary bladder dose and volume metrics in the upper range of the prescribed doses (70–78 Gy) consistently predicted the two factor-analysis-identified GU symptom domains, *Obstruction* and

Urgency, in men treated with primary EBRT for localized prostate cancer. Our results were stable across two investigated MVA methods, and across both cohorts for *Obstruction* with improved model performance for the joint dataset. Standard dose–volume response modelling also implied a serial response of the urinary bladder for both domains.

Previous efforts in urinary bladder dose–volume response modelling are summarized in the GU-dysfunction-specific QUANTEC report [4]. Although some of the included studies, which were typically derived from non-prostate cancer-related cohorts, points towards a dose–response relationship for GU morbidity in the near vicinity of the prescribed dose; the report was unable to recommend any reliable dose–volume constraints due to the considerable disagreement in findings across studies. Based on a large number of patient-reported GU symptoms, we found that high urinary bladder doses ($D_{\max}$, D_{20} , MOH₅, and V_{75}) predicted symptoms of both *Obstruction* and *Urgency*. The lack of an identified dose–volume response relationship for *Incontinence* may be caused by various factors: additional (or other) structures than the urinary bladder may be involved in the dose–response aetiology for patient-reported incontinence, or the investigated RT doses may be below/above the critical range where such dose–response relationships exist. Either way, the prevalence of symptoms of *Incontinence* were low in comparison to the prevalence of symptoms of *Obstruction* and *Urgency*, and the clinical relevance of identifying relationships for the latter two is, therefore, possibly of higher importance. For a complete explanation, a modelling approach addressing all relevant urinary structures (e.g. urinary bladder trigone [20] and prostatic urethra [4]) would probably shed further light on this.

Clinically used scoring systems of late normal tissue effects commonly combine many symptoms to form practical but simplified definitions of symptom groups and symptom severities. *Incontinence* and other GU symptoms are addressed in a number of such systems, e.g. CTCAE [5], EPIC [21], LENT-SOMA [22], and RTOG-EORTC [23]. The GU-dysfunction-specific QUANTEC report, however, recognizes that predictive modelling of the urinary bladder needs to be accompanied by “patient-based, rather than physician-derived, toxicity scoring to better reflect the true symptomatic incidence of bladder injury.” [4]. Particularly central symptoms for our *Obstruction* domain reflected the need to push to initiate urination (Q4 in DK/Q1 in SW); for the *Urgency* domain, the need to quickly find a toilet was central (Q8 in DK). It is somewhat puzzling to note that such symptoms have various attentions in accepted scoring systems. Obstruction is addressed in CTCAE (“*Asymptomatic*” to “*Requiring urgent intervention/Death*”), in EPIC (“*Weak stream/incomplete bladder emptying*”), and in LENT-SOMA (“*Decreased stream*”), whereas RTOG-EORTC does not even mention *obstruction*. *Urgency* is addressed only in CTCAE but either as ‘present’ (Grade 1) or as ‘limiting instrumental Activities of Daily Living; medical management indicated’ (Grade 2). Our findings suggest that the RT response of the urinary bladder with respect to both *obstruction* and *urgency* can be detected at an intermediate symptom level, typically not covered by the aforementioned systems, but potentially placed between their lowest grades.

The main strengths of this work relate to a large study population with 35 patient-reported GU symptoms from two study-specific questionnaires, which included symptoms that are not addressed in common toxicity scoring systems, where relationships between urinary

bladder dose and factor-analysis-identified GU symptom domains could be thoroughly investigated. We also applied two independent MVA methods to describe relationships between urinary bladder dose and symptoms (stepwise and LASSO) with both methods arriving at the same best-fitting models. The investigated two cohorts allowed for the testing of generalizability for *Obstruction* with respect to study- and treatment-specific symptom profiles as well as a robustness test towards a range of clinical parameters, which did not alter the final models substantially. Limitations of this work could be that our results were based on information from relatively homogeneous groups of patients in terms of age, ethnicity, and treatment technique. Generalizability of our generated symptom groups and identified high bladder dose-relationships, with respect to the presently investigated and other cohort-specific parameters, need to be further confirmed as the use of PROs steadily increases in the RT community. The temporal pattern of the symptom domains was not addressed. There is evidence, however, that the majority of the investigated symptoms remain stable over time [9,24] and, therefore, the grouping of symptoms is not expected to be strongly time-dependent. Finally, it has to be kept in mind that our overall approach assists in identifying the more central symptoms within a symptom domain and that the A_z of our final models ranged between 0.53 and 0.64. The clinical usefulness of the weaker models at this stage is limited as models having A_z near 0.50 are regarded as not being better than random chance. However, if domain-central symptoms can be avoided in RT, the occurrence of related symptoms can potentially be reduced.

In conclusion, our study has demonstrated that high urinary bladder doses relate to patient-reported urinary *obstruction* and *urgency*. To further untangle the complex dose–response of the entire GU tract, focusing on particular questions reflecting the aspect of needing to push to initiate urination and of urgently needing to get to a toilet may be useful to increase our understanding of the urinary bladder RT response. Furthermore, limiting urinary bladder doses in the upper range of therapeutic prostate cancer doses may prove important to reduce the number of survivors experiencing moderate to severe GU morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Budaus L, Bolla M, Bossi A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol*. 2012; 61:112–27. [PubMed: 22001105]
2. Zelefsky MJ, Kollmeier M, Cox B, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012; 84:125–9. [PubMed: 22330997]
3. Rosewall T, Catton C, Currie G, et al. The relationship between external beam radiotherapy dose and chronic urinary dysfunction – a methodological critique. *Radiother Oncol*. 2010; 97:40–7. [PubMed: 20817289]
4. Viswanathan AN, Yorke ED, Marks LB, et al. Radiation dose–volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys*. 2010; 76:S116–22. [PubMed: 20171505]
5. The National Cancer Institute. Common Terminology Criteria for Adverse Events v4.03 (NCI CTCAE v4.03). 2010.

6. Siddiqui F, Liu AK, Watkins-Bruner D, Movsas B. Patient-reported outcomes and survivorship in radiation oncology: overcoming the cons. *J Clin Oncol.* 2014; 32:2920–7. [PubMed: 25113760]
7. Deasy JO, Bentzen SM, Jackson A, et al. Improving normal tissue complication probability models: the need to adopt a “data-pooling” culture. *Int J Radiat Oncol Biol Phys.* 2010; 76:151–4.
8. Petersen SE, Bentzen L, Emmertsen KJ, et al. Development and validation of a scoring system for late anorectal side-effects in patients treated with radiotherapy for prostate cancer. *Radiother Oncol.* 2014; 111:94–9. [PubMed: 24630536]
9. Olsson CE, Pettersson N, Alsadius D, et al. Patient-reported genitourinary toxicity for long-term prostate cancer survivors treated with radiation therapy. *Br J Cancer.* 2013; 108:1964–70. [PubMed: 23632483]
10. Pettersson N, Johansson KA, Alsadius D, et al. A method to estimate composite doses for organs at risk in prostate cancer patients treated with EBRT in combination with HDR BT. *Acta Oncol.* 2014; 53:815–21. [PubMed: 24460070]
11. Steineck G, Bergmark K, Henningssohn L, al-Albany M, Dickman PW, Helgason A. Symptom documentation in cancer survivors as a basis for therapy modifications. *Acta Oncol.* 2002; 41:244–52. [PubMed: 12195743]
12. Omerov P, Steineck G, Runeson B, et al. Preparatory studies to a population-based survey of suicide-bereaved parents in Sweden. *Crisis.* 2013; 34:200–10. [PubMed: 23261907]
13. Emmertsen KJ, Laurberg S. Low anterior syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg.* 2012; 255:922–8. [PubMed: 22504191]
14. International Commissions on Radiation Units and Measurements (ICRU) I, (Supplement to ICRU Report 50). Prescribing, Recording and Reporting Photon Beam Therapy. 1999.
15. Thor M, Olsson CE, Oh J, et al. Relationships between dose to the gastrointestinal tract and patient-reported symptom domains after radiotherapy for prostate cancer. *Acta Oncol.* 2015; 54:1326–34. [PubMed: 26340136]
16. Tibshirani R. Regression shrinkage and selection via the Lasso. *J Roy Stat Soc.* 1996; 58:267.
17. Kutcher GJ, Burman C, Brewster L, Goitein M, Mohan R. Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. *Int J Radiat Oncol Biol Phys.* 1991; 21:137–46. [PubMed: 2032884]
18. Lyman JT. Complication probability as assessed from dose–volume histograms. *Radiat ResSuppl.* 1985; 8:13–9.
19. Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Med Phys.* 1997; 24:103–10. [PubMed: 9029544]
20. Ghadjar P, Zelefsky MJ, Spratt DE, et al. Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2014; 88:339–44. [PubMed: 24411606]
21. Chang P, Szymanski KM, Dunn RL, et al. Expanded prostate cancer index composite for clinical practice: development and validation of a practical health related quality of life instrument for use in the routine clinical care of patients with prostate cancer. *J Urol.* 2011; 186:865–72. [PubMed: 21788038]
22. LENT SOMA tables. *Radiother Oncol.* 1995; 35:17–60. [PubMed: 7569012]
23. Cox JD, Stetz J, 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; 31:1341–6. [PubMed: 7713792]
24. Schmid MP, Pötter R, Bombosch V, et al. Late gastrointestinal and urogenital side-effects after radiotherapy — incidence and prevalence. Subgroup-analysis within the prospective Austrian-German phase II multicenter trial for localized prostate cancer. *Radiother Oncol.* 2012; 104:114–8. [PubMed: 22727264]

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2016.01.013>.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1.

Population averaged dose–volume histograms for the highest-frequency models of *Obstruction* for the joint DK and SW cohort (error bars denote 95% CI) for patients with <moderate symptom severity (blue) and with moderate symptom severity (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

The studied symptom domains, symptom phrasing, moderate severity cut-off, and related proportions for both cohorts.

Cohort	Symptom domain	Symptom id	Question/symptom	Moderate severity	Proportion (N)	moderate
DK	Incontinence	Q9*	Pain/sting@urination?	Daily	0.03 (7)	
		Q11*	Urinary leakage assoc. with physical activity (coughing/sneezing/lifting)?	Daily	0.03 (7)	
		Q12*	Urinary leakage NOT assoc. with physical activity/urgency?	Daily	0.02 (5)	
	Obstruction	Q1	Wait long for urinary flow@urge to pass urine?	Daily	0.14 (28)	
		Q2	Quality of urine stream?	Weak	0.17 (36)	
		Q3	Sensation of complete emptying of bladder@urination?	Rarely	0.16 (34)	
	Urgency	Q4	Push to initiate/continue urination?	Daily	0.14 (30)	
		Q9*	Pain/sting@urination?	Daily	0.03 (7)	
		Q2	Quality of urine stream?	Weak	0.17 (36)	
		Q5	Max. time between two urinations/day?	1–2 h	0.19 (39)	
		Q6	No. of nocturnal urinations?	3–4 times	0.26 (54)	
		Q7	Strong urinary urgency?	Daily	0.36 (74)	
SW	Incontinence 1	Q8	Urgency demanding toilet visit?	Daily	0.10 (20)	
		Q10	Drip of urine after urination?	Some into clothing	0.36 (74)	
		Q12*	Leakage@no physical exercise/urgency?	Daily	0.02 (5)	
		Q16	Leakage > few drops?	1/w	0.23 (64)	
		Q17	Urgency@leakage?	50% of the times	0.13 (37)	
		Q21*	Estimated amount urine leaked@leakage?	Moderate amount	0.05 (14)	
	Incontinence 2	Q23a	Use of drip protection/sanitary pad?	Yes	0.11 (30)	
		Q23b	Use of diaper?	Yes	0.08 (23)	
		Q19*	Leakage@coughing/sneezing/laughing?	1/w	0.03 (9)	
		Q20*	Leakage@physical activity?	1/w	0.05 (13)	
		Q1	Bear down/push@start of urination?	50% of the times	0.09 (24)	
		Q2	Wait long for urinary flow?	50% of the times	0.08 (22)	
Obstruction 1	Q3	Sudden stops@urination?	50% of the times	0.09 (24)		
	Obstruction 2	Q4	Long time to urinate?	50% of the times	0.18 (50)	
		Q5	Incomplete emptying after urination?	50% of the times	0.21 (57)	

Cohort	Symptom domain	Symptom id	Question/symptom	Moderate severity	Proportion (N)	moderate
	Urgency	Q6	Bear down/push @end of urination?	50% of the times	0.18 (49)	
		Q8	Weak urinary flow @urination?	1/w	0.22 (60)	
		Q10	Urgency demanding toilet visit?	1/w	0.39 (109)	
		Q11	How long able to restrain urination @urgency?	<10 min	0.34 (95)	

* Not studied due to prevalence <5%.

Table 2

All MVA models with mean A_z 0.50 sorted by the highest A_z in each domain, and the dose/volume parameters with frequency >5% for the models with the best discriminativeability (denoted by *).

Cohort	Symptom domain	Symptom ids	A_z (SD) MVA _{stepwise}	Frequency >5%	Frequency (%)	A_z (SD) MVA _{LASSO}	Frequency >5%	Frequency (%)
DK $N = 207$	Obstruction 1	Q2Q4*	–	–	–	0.53 (0.03)	MOH ₅	47
							D_{max}	42
							MOH ₅	86
	Obstruction 2	Q2Q3Q4*	–	–	–	0.53 (0.03)	MOH ₅	73
		Q2Q3	–	–	–	0.51 (0.04)	D_{max}	7
							D_{max}	53
	Urgency	Q8*	0.60 (0.03)			0.60 (0.02)	MOH ₅	26
							D_5	10
							MOH ₁₀	10
		Q2Q5Q8	–	–	–	0.58 (0.02)	MOH ₅	99
		Q5Q8	0.53 (0.04)	D_5	45	0.57 (0.02)	D_5	56
				MOH ₅	26		MOH ₅	43
		Q6Q10	0.56 (0.02)	D_{75}	42	0.56 (0.02)	D_{70}	43
SW $N = 276$	Obstruction			D_{70}	41		D_{75}	43
				D_{65}	8		D_{65}	9
		Q2Q5	–	–	–	0.53 (0.03)	MOH ₅	91
		Q6Q8Q10	0.52 (0.04)	D_{75}	53	0.53 (0.03)	D_{75}	57
				D_{70}	20		D_{70}	23
							D_{65}	6
		Q2Q5Q6Q8	–	–	–	0.52 (0.03)	MOH ₅	81
		Q6	0.51 (0.03)	V_{50}	39	0.52 (0.03)	V_{50}	42
				V_{55}	20		V_{55}	20
				V_{45}	8		V_{45}	11
				V_{60}	6		V_{60}	6
		Q1*	0.57 (0.04)	D_{20}	84	0.57 (0.04)	D_{20}	93

Cohort	Symptom domain	Symptom ids	A_z (SD) MVA _{stepwise}	Frequency >5%	Frequency (%)	A_z (SD) MVA _{LASSO}	Frequency >5%	Frequency (%)
DK + SW $N=483$	Obstruction 1	Q4Q5	0.56 (0.02)	D ₂₀	81	0.56 (0.02)	D ₂₀	81
		Q4Q5Q8	–	–	–	0.51 (0.02)	V ₇₀	43
	Obstruction 2	DK Q2Q3Q4 SW Q1	0.64 (0.01)	V ₇₅	97	0.64 (0.01)	V ₇₅	97
		DK Q2Q4 SW Q1	0.61 (0.01)	V ₇₅	100	0.61 (0.01)	V ₇₅	100

Best-fitting LKB model parameters for each symptom domain in DK, and in SW, and the associated symptom combinations (denoted with * in Table 2).

Table 3

Cohort	Symptom domain	a (95% CI)	D_{50} (95% CI) Gy	m (95% CI)	Proportion (N)	moderate
DK	Obstruction 1	30 (1->100)	150 (118->150)	0.75 (0.57-1.03)	0.25 (52)	
	Obstruction 2	70 (1->100)	150 (11->150)	0.99 (0.71-> 1.1)	0.31 (65)	
	Urgency	100 (7->100)	150 (128->150)	0.37 (0.31-0.47)	0.10 (20)	
SW	Obstruction	100 (7->100)	150 (128->150)	0.39 (0.33-0.47)	0.09 (24)	
DK + SW	Obstruction 1	100 (50->100)	86 (83-88)	0.15 (0.13-0.19)	0.18 (89)	
	Obstruction 2	100 (40->100)	91 (88-95)	0.19 (0.15-0.23)	0.16 (76)	