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Factors associated with current and severe physical side-effects after prostate cancer treatment, what men report

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Preface

In front of you lies my thesis ‘Factors associated with current and severe physical side-effects after prostate cancer treatment, what men report’. I have executed my thesis in Belfast, Northern Ireland in the N. Ireland Cancer Registry in four months’ time. I would like to thank Anna Gavin and David Donnelly for all their help during my stay in Belfast. In addition, I would like to thank all my colleagues in the Registry for making my time there a pleasant one.

Last, I would like to thank Sabine Siesling, Jeannette van Manen, Linda Sharp and Frances Drummond for their support and comments, which made it possible for me to have the best result possible!

I wish everyone a great deal of fun reading my thesis!

Laura Steentjes
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Abstract

Background: Prostate cancer (PCa) is the second most common cancer in the developed world and numbers are increasing. 75% of PCa survivors report ongoing side-effects 2-18 years after treatment in a population based research. Part of the PiCTure study, we aim to identify patient and disease characteristics associated with 'current' physical side-effects of any severity and severe side-effects 'ever' experienced, to support decision-making processes for men and clinicians.

Methods: In 2012, 6,937 men diagnosed with PCa (C61) 2-18 years ago, identified through cancer registries in Northern Ireland (NI) and Republic of Ireland (RoI), were invited to participate in a survey on symptoms at diagnosis, primary treatments and physical side-effects; urinary incontinence, reduced libido, impotence, bowel problems, breast changes, hot flushes and fatigue. Men were grouped according to early (localized) and late (locally advanced and advanced) disease at diagnosis. Univariate and multivariate logistic regression analysis were performed to identify the factors associated with side-effects, such as age at diagnosis, pre-treatment function, comorbidities, treatment, education, living alone, jurisdiction (RoI/NI), TURPs, complications after biopsy (bleeding into bladder/rectum or infection) and time since diagnosis.

Results: Radical prostatectomy, was a factor associated with most side-effects both 'current' and 'severe'. In early disease, brachytherapy was associated with a lower risk of 'current' fatigue and 'severe/very severe' impotence. Active surveillance/watchful-waiting demonstrated lower risk of several 'current' side-effects in early disease. Pre-treatment symptom were also associated with a higher risk of side-effects. Complications post-biopsy were associated with a higher risk of libido loss, impotence, bowel problems and breast changes. No complications post-biopsy was also associated with a higher risk of 'current' impotence in both early and late disease.

Conclusion: Treatment is the most important factor associated with side-effects. Tailored information on these side-effects and specific monitoring should be available to patients/clinicians to make the best decision on treatment.

Keywords: prostate cancer, side-effects, physical effects, decision making process, PiCture study

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer among men worldwide and mortality rates have been decreasing in most western countries. That, with increased incidence has resulted in a prevalence increase and more patients coping with treatment-related side-effects (1, 2) .

Recommended clinical strategies for early (localised) PCa are radical prostatectomy (RP) and external beam radiotherapy (EBRT). For selected men, brachytherapy (BT), active surveillance (AS) and watchful waiting (WW) are suitable. AS can be used for men who are identified as those who will not benefit from definitive treatment (3). Appropriate strategies for late (locally advanced/advanced) disease are hormone therapy (HT), EBRT and WW. However, EBRT is unsuitable for advanced disease and RP is appropriate for a highly selected group of men with locally advanced disease. WW is an option for older men, in both early and late disease (3).

Few randomised controlled trials have been conducted, and none of the above described treatments in the subgroups of patients have a survival benefit over the other (4-6). The PCa treatment decision is based on the consultation between the patient and the physician, aiming to find the best fit to the patient's personal and clinical characteristics. For instance, disease extent at diagnosis, which has been shown to have an influence on both treatment decision and patient outcomes (5, 7). Moreover, patient preferences play a large role in shared decision making. Also, all treatments for PCa carry a significant risk of side-effects. For example, in one recent study of more than 3,300 PCa survivors, with at least a two years post-diagnosis, 90% of men reported 'ever' experiencing at least one physical side-effect of treatment. In addition, 75% of men reported at least one 'current' physical symptom (8). The most common side-effects after PCa treatment are urinary incontinence, sexual dysfunction and bowel problems (4, 9-11).

With the knowledge that treatment-related side-effects or symptoms affect the Health-related Quality of Life of PCa patients and survivors, it is necessary to investigate and identify what factors, if any, are associated with these side-effects. These factors could then support treatment decision making, to better prepare patients for what they can expect after their treatment. Furthermore, determine if the patient needs specific support or interventions to alleviate the expected and experienced side-effects. Several factors associated with side-effects have been identified; treatment modality, age, comorbidities, pre-treatment function (e.g. already experiencing urinary incontinence) and the D'Amico risk groups (7, 10-16).

The majority of studies focus on one specific side-effect with most of the data limited to urinary incontinence, sexual dysfunction and bowel problems. Little is known about other physical effects, such as hot flushes and fatigue, and their associated factors. Moreover, little is known about what factors are associated with either higher or lower risk of treatment-related side-effects. Also, when reported by men, what factors affects severe side-effects. Additionally, little information is available on the severity of side-effects, though reporting on severity is important for the decision making process. As men are

probably more likely to make decisions about treatment, based on severe side-effects and not based on mild ones (4).

Therefore, the aim of this study was to identify patient-related factors and disease-related characteristics that are associated with a range of physical side-effects among early and late disease PCa survivors.

Methods

Survivors

The study took place in the two countries on the island of Ireland – the Republic of Ireland (RoI) and Northern Ireland (NI). In both countries men were recruited with the same approach; full details are reported elsewhere (17). In brief, all men diagnosed with invasive PCa, between 1st January 1995 and 31st March 2010, were identified from the National Cancer Registry Ireland (NCRI) in RoI (*n*=17,304) and the Northern Ireland Cancer Registry (NICR; *n*=5,519), NI in November 2011. In both jurisdictions a stratified random sample of 54% of all survivors (*n*=12,322) was selected to ensure approximately equal numbers of survivors at <5 and >5 years post-diagnosis. Eligible men had to be: (I) alive, (II) aware of their PCa diagnosis, (III) well enough to complete a survey, (IV) usually a resident of RoI/NI and (V) able to understand English. Subsequently, 6,559 PCa survivors were considered eligible to be sent a survey of whom 3,348 men participated by completing the survey.

Survey

The focus of this study was on men's self-reported physical side-effects after treatment 'current' of any severity (i.e. at time of survey completion) and the measure of severity 'ever' experienced. Survivors were asked to provide information about the experience of seven potential or treatment-related side-effects. The side-effects that were included were urinary incontinence, impotence, loss of libido, bowel problems, breast changes, hot flushes, and fatigue. In addition, they had to indicate how severe the symptoms were at its worst from 1 (very mild) up to 5 (very severe). Additionally, men were asked to indicate all treatments received, including dates of commencement and completion for each treatment. Information on socio-demographic characteristics was also collected. Men were asked to indicate whether they had pre-treatment symptoms regarding urinary (increased frequency, pain urinating, blood in urine), bowel (diarrhoea, constipation) and/or sexual (impotence/erectile dysfunction) function. Additionally, they had to signify which comorbidities, if any, were present at diagnosis from a list of conditions (heart or lung disease, stroke, diabetes, high blood pressure, diverticular disease, bowel problems (e.g. constipation/diarrhoea), other cancer, depression or other).

Surveys were posted to eligible men between April and September 2012. Up to two written reminders at two weekly intervals, with a second copy of the survey in the second reminder were sent to non-responders.

Cancer registry data

For respondents, information on date of diagnosis, stage at diagnosis (TNM classification) and Gleason Grade (GG) was extracted from the cancer registries. The NCRI collected GG as a categorical variable; low (GG 2-4), medium (GG 5-7) or high grade (GG 8-10). Data of survivors in NI, diagnosed in early years, had a low completeness of staging. Therefore, for these respondents supplementary staging information was abstracted from medical records.

Statistical analysis

Early disease consisted of survivors with stage I/II and GG 2-7 at diagnosis i.e. broadly consistent with localised disease (n=1,700). Late disease survivors had stage III/IV and any GG at diagnosis i.e. locally advanced or advanced disease (n=689). Survivors with other combinations of stage and GG, or unknown stage or GG, were excluded from analysis (n=959) leading to a population of 2,389 PCa survivors.

Outcome variables were: urinary incontinence, loss of libido, impotence/erectile dysfunction, bowel problems, swelling/tenderness in the upper chest area, sweats/hot flushes and fatigue. Potential explanatory variables were; patient-related factors (age at diagnosis (0-59/60-69/≥70 years), comorbidities (no/1-2/≥3), educational (primary/secondary/≥tertiary), jurisdiction (RoI/NI), living alone (living alone/living with others), time since diagnosis (2-5/5-10/>10 years)), pre-treatment function (urinating more frequently, pain while urinating, blood in urine, impotence/erectile dysfunction, loss of interest in sex and back pain (all no/yes)), previous interventions (complications after biopsy (bleeding into bladder/rectum/infection (no biopsy/yes/no), TURPs, no complications after biopsy (no biopsy/yes/no)) and treatment (RP, EBRT, HT, BT, AS/WW). HT was coded as having the treatment 'previously', 'current' and 'never', other treatments were coded as received 'yes' or 'no'.

Univariate and multivariate analyses were performed in the form of logistic regression. First, to identify the factors associated with 'current' side-effects of any severity after PCa treatment. Second, the same analyses were performed to identify the variables associated with 'ever' experienced side-effects categorized as severe/very severe as reported by survivors.

Multivariate analysis was performed and included the variables in case p-value ($p \leq 0.10$) in univariate analysis. Subsequently, backward selection was used to determine the definitive predictors, with the p-value (≤ 0.05) as criterion to include the variable in the model. Missing data was handled with fully conditional specification multiple imputation method with five imputations and weighted for PCa survivors in the population (n=22,823). All explanatory variables with missing data were included. Missing data in outcome variables were coded as 'never had the side-effect'.

In addition, sensitivity analysis was performed for two 'current' side-effects in early and late disease. In order to show the difference in association between explanatory and outcome variables in the original dataset and the pooled dataset. Also, the goodness-of-fit of the different models were investigated with help of the Nagelkerke R^2 and the Hosmer-Lemeshow test. Correlation between the

variables included in the model was also addressed. The statistical analysis was carried out in SPSS version 20.

Results

Survivors

Characteristics of the survivors and differences between early disease (localised) and late disease (locally advanced/advanced) are shown in table 1. Time since diagnosis, age at diagnosis, living alone, and highest educational level achieved were equally distributed in early and late disease groups. In terms of treatment, men could obtain more than one treatment. HT (66% vs. 33%) and EBRT (70% vs. 53%) were more common in the late disease group and BT (7% vs. 2%) and AS/WW (6% vs. 1%) were more common in the early disease group.

Prevalence of side-effects

Percentages of prevalence of side-effects are shown in figure 1a and 1b. The prevalence of both 'current' and severe/very severe' side-effects were higher in the late disease group. For 'current' the most difference was in the following; loss of libido (42.4% vs. 57%), hot flushes (8.8% vs. 27.9%) and fatigue (18.8% vs. 30.5%). Loss of libido (25.8% vs. 41%), impotence (39.6% vs. 52.7%) and fatigue (16.1% vs. 29.1%) showed the most difference in the occurrence of 'severe/very severe' side-effects.

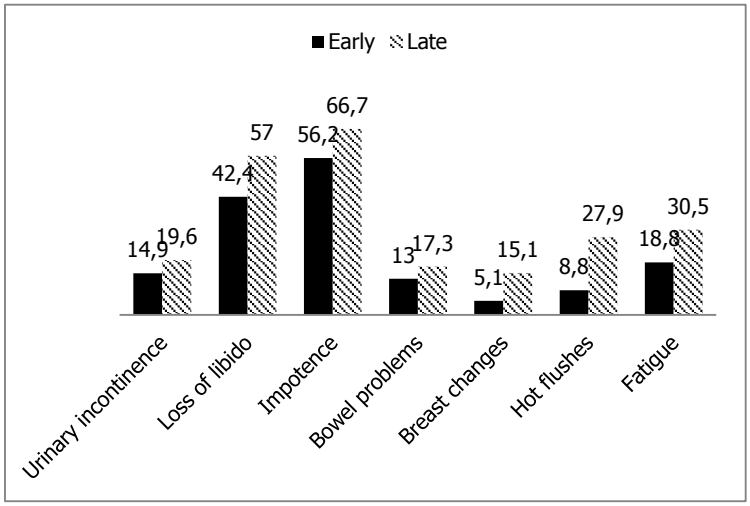

Figure 1a: 'Current' side-effects in early and late disease

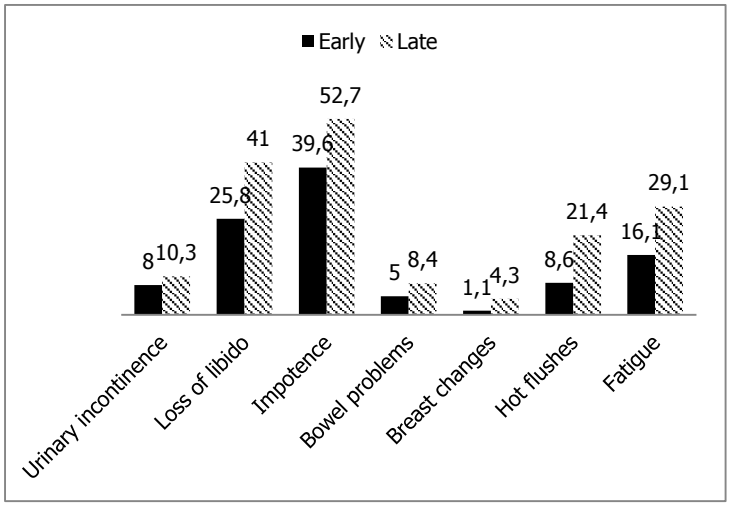

Figure 1b: 'Severe/very severe' side-effects in early and late disease

***Table 1: Characteristics of the survivor group*‖**

Variable	Total population (n=3348)	Early disease (n=1700)	Late disease (n=689)
Jurisdiction			
Republic of Ireland	2567 (76.7)	1431 (84.2)	407 (59.0)
Northern Ireland	781 (23.3)	269 (15.8)	282 (41.0)
Time since diagnosis at start of the study			
2-5 years	1391 (76.7)	743 (43.7)	322 (46.7)
5-10 years	781 (23.3)	745 (43.8)	274 (39.8)
>10 years	522 (15.6)	212 (12.5)	93 (13.5)
Age at diagnosis			
0-59	721 (21.5)	420 (24.7)	147 (21.3)
60-69	1484 (44.3)	796 (46.8)	311 (45.1)
>70	1143 (34.1)	484 (28.5)	232 (33.6)
Living alone			
Living alone	434 (13.0)	210 (12.4)	88 (12.7)
Living with others	2863 (85.5)	1463 (86.0)	593 (86.0)
Education			
Primary	1203 (35.9)	542 (31.9)	276 (40.0)
Secondary	1139 (34)	629 (37.0)	218 (31.6)
Tertiary or higher	860 (25.7)	452 (26.6)	178 (25.8)
Pre-treatment function			
Urinating more frequently	1708 (51.0)	830 (48.8)	348 (50.5)
Pain while urinating	256 (7.7)	101 (5.9)	56 (8.1)
Blood in urine	232 (6.9)	91 (5.4)	55 (8.0)
Impotence/erectile dysfunction	626 (18.7)	302 (17.8)	142 (20.6)
Loss of interest in sex	496 (14.8)	235 (13.8)	118 (17.2)
Back pain	498 (14.9)	227 (13.3)	134 (19.4)
Number of comorbidities			
1-2	1682 (50.2)	863 (50.8)	324 (47.0)
3 or more	208 (6.2)	83 (4.9)	58 (8.5)
Biopsy complications			
No biopsy	367 (11)	139 (8.2)	79 (11.4)
Bleeding into bladder	284 (8.5)	161 (9.5)	49 (7.1)
Bleeding into rectum	203 (6.1)	102 (6.0)	36 (5.5)
Infection	145 (4.3)	85 (5.0)	24 (3.5)
None	539 (16.1)	194 (11.4)	190 (27.5)
TURP	298 (8.9)		
Treatment*			
Radical Prostatectomy	842 (25.1)	503 (29.6)	181 (26.3)
External Beam Radio Therapy	1930 (57.6)	910 (53.5)	484 (70.3)
Hormone Therapy			
No HT	1454 (43.4)	935 (55.0)	182 (26.4)
Previously	888 (26.5)	402 (23.7)	246 (35.6)
Currently	632 (18.9)	159 (9.3)	214 (31.0)
Brachytherapy	184 (5.5)	119 (7.0)	13 (1.9)
Active Surveillance/Watchful Waiting	165 (4.9)	100 (5.9)	6 (0.8)

‖Variables are weighted to assure representativeness for PCa survivors in the population.

*Patients could have had more than one treatment

Factors associated with 'current' side-effects in early disease

Factors, significant associated in multivariate analyses, for 'current' physical side-effects in early disease are presented in table 2. Living with others was associated with a higher risk of 'current' loss of libido (1.56; 1.13-2.11) and impotence (1.39; 1.01-1.91). Higher education was associated with a higher risk of impotence and associated with a lower risk of hot flushes and fatigue. Ten years or more post-diagnosis was associated with a lower risk of fatigue (0.55; 0.35-0.85). Additionally, 5-10 years post-diagnosis was associated with a lower risk of hot flushes (0.60; 0.39-0.92) Living in NI was associated with a higher risk of loss of libido, bowel problems and fatigue.

Treatments were associated with a higher risk of side-effects. RP was associated with a higher risk of urinary incontinence (3.03; 2.28-4.03), loss of libido (1.72; 1.33-2.22) and impotence (3.30; 2.56-4.23). EBRT was associated with a higher risk of bowel problems (3.35; 2.38-4.71) and hot flushes (1.93; 1.15-3.22). Any HT, previously and currently, was associated with a higher risk of loss of libido, breast changes and hot flushes. Currently receiving HT was associated with a higher risk of fatigue (2.16; 1.44-3.26). BT was associated with a lower risk of fatigue (0.46; 0.24-0.89). Also, AS/WW was associated with a lower risk of urinary incontinence (0.40; 0.16-0.99), loss of libido (0.37; 0.21-0.65), impotence (0.21; 0.12-0.34) and fatigue (0.16; 0.05-0.46).

General health at diagnosis was associated with a higher risk of side-effects. Urinating more frequently was associated with urinary incontinence (1.72; 1.25-2.35), bowel problems (1.48; 1.08-2.02) and fatigue (1.45; 1.09-1.92). Loss of interest in sex was associated with a higher risk of loss of libido (1.79; 1.26-2.55). Impotence/erectile dysfunction was associated with a higher risk of loss of libido and impotence. Back pain was associated with a higher risk of fatigue (1.78; 1.24-2.57). Multiple (more than three) comorbidities was associated with a higher risk of urinary incontinence (2.34; 1.34-4.09), loss of libido (1.68; 1.03-2.75), bowel problems (3.29; 1.88-5.76) and fatigue (2.07; 1.21-3.53). Complications after biopsy, more particular, bleeding into bladder was associated with a higher risk of bowel problems (2.32; 1.08-4.96). Bleeding into rectum was associated with a higher risk of breast changes (5.19; 1.76-15.29). No complications after biopsy was associated with a higher risk of impotence (2.35; 1.46-3.78). Experiencing complications after biopsy was associated with a higher risk of impotence (1.72; 1.17-2.54) and loss of libido (1.55; 1.05-2.31).

Factors associated with 'severe/very severe' side-effects in early disease

Table 2 shows the factors, significant in multivariate analyses, associated with 'severe/very severe' side-effects in early disease. Age at diagnosis, especially men aged 70 years and older, was associated with a lower risk of loss of libido (0.48; 0.33-0.68) and impotence (0.71; 0.51-1.00). Higher education was associated with a higher risk of impotence and associated with a lower risk of hot flushes and fatigue. Ten years or more post-diagnosis was associated with a lower risk of fatigue (0.48; 0.28-0.82). Living in NI was associated with a higher risk of loss of libido, hot flushes and fatigue.

RP was associated with a higher risk of urinary incontinence, loss of libido, impotence, hot flushes and fatigue. EBRT was associated with a higher risk of bowel problems, hot flushes and fatigue. Any HT, previously and currently, was associated with a higher risk of loss of libido, breast changes, hot flushes and fatigue. BT was associated with a lower risk of impotence (0.59; 0.38-0.92). Also, AS/WW was associated with a lower risk of loss of libido and impotence.

Loss of interest in sex was associated with a higher risk of loss of libido (2.00; 1.43-2.78). Impotence/erectile dysfunction was associated with a higher risk of impotence (1.62; 1.19-2.20). Back pain was associated with a higher risk of hot flushes (1.72; 1.02-2.89) and fatigue (1.53; 1.13-2.08). Multiple comorbidities was only associated with a higher risk of bowel problems (2.80; 1.22-6.43). Complications after biopsy, more particular, bleeding into bladder was associated with a higher risk of impotence (2.25; 1.33-3.81).

Table 2: Factors associated with side-effects in early disease, resulting from multivariate analyses

Side-effect	**Current**			**Severe/very severe**		
	Predictor		**OR (95% CI)**	**Predictor**		**OR (95% CI)**
Urinary incontinence	Radical prostatectomy	No	1.00	Radical prostatectomy	No	1.00
		Yes	3.03 (2.28-4.03)		Yes	3.62 (2.39-5.49)
	Comorbidities	No	1.00	Age at diagnosis	0-59	1.00
		1-2	1.29 (0.96-1.72)		60-69	0.59 (0.39-0.88)*
		≥3	2.34 (1.34-4.09)*		≥70	0.68 (0.38-1.20)
	Active surveillance/ watchful waiting	No	1.00			
		Yes	0.40 (0.16-0.99)			
	Urinating more frequently	No	1.00			
		Yes	1.72 (1.25-2.35)			
Loss of libido	Hormone therapy	No	1.00	Hormone therapy	No	1.00
		Previously	1.56 (1.19-2.05)		Previously	2.17 (1.58-2.98)
		Currently	2.24 (1.54-3.28)		Currently	2.53 (1.70-3.76)
	Jurisdiction	RoI	1.00	Jurisdiction	RoI	1.00
		NI	1.73 (1.05-2.86)		NI	1.43 (1.05-1.96)
	Impotence/ erectile dysfunction	No	1.00	Age at diagnosis	0-59	1.00
		Yes	1.47 (1.09-1.98)		60-69	0.81 (0.61-1.07)
	Radical prostatectomy	No	1.00		≥70	0.48 (0.33-0.68)*
		Yes	1.72 (1.33-2.22)	Radical prostatectomy	No	1.00
	Active surveillance/ watchful waiting	No	1.00		Yes	1.51 (1.11-2.05)
		Yes	0.37 (0.21-0.65)	Active surveillance/ watchful waiting	No	1.00
	Living alone	Alone	1.00		Yes	0.28 (0.10-0.46)
		With others	1.56 (1.13-2.11)	Loss of interest in sex	No	1.00
	Loss of interest in sex	No	1.00		Yes	2.00 (1.43-2.78)
		Yes	1.79 (1.26-2.55			
	Comorbidities	No	1.00			
		1-2	1.13 (0.91-1.40)			
		≥3	1.68 (1.03-2.75)*			
	No complications after biopsy	No biopsy	1.00			
		Yes	1.18 (0.62-2.26)			
		No	1.55 (1.05-2.31)*			
Impotence	Radical prostatectomy	No	1.00	Radical prostatectomy	No	1.00
		Yes	3.30 (2.56-4.23)		Yes	2.56 (1.99-3.31)
	Active surveillance/ watchful waiting	No	1.00	Age at diagnosis	0-59	1.00
		Yes	0.21 (0.12-0.34)		60-69	1.00 (0.77-1.31)
	Living alone	Alone	1.00		≥70	0.71 (0.51-1.00)*
		With others	1.39 (1.01-1.91)	Education	Primary	1.00
	Education	Primary	1.00		Secondary	1.33 (1.02-1.72)
		Secondary	1.67 (1.29-2.16)		≥Tertiary	1.52 (1.14-2.02)
		≥Tertiary	1.67 (1.25-2.24)	Brachytherapy	No	1.00
	Impotence/ erectile dysfunction	No	1.00		Yes	0.59 (0.38-0.92)
		Yes	1.96 (1.45-2.66)	Active surveillance/ watchful waiting	No	1.00
	No complications after biopsy	No biopsy	1.00		Yes	0.13 (0.06-0.28)
		Yes	2.35 (1.46-3.78)	Urinating more frequently	No	1.00
		No	1.72 (1.17-2.54)		Yes	0.78 (0.62-0.98)

				Impotence/ erectile dysfunction	No	1.00
					Yes	1.62 (1.19-2.20)
				Bleeding into bladder after biopsy	No biopsy	1.00
					Yes	2.25 (1.33-3.81)
					No	1.50 (1.00-2.25)
Bowel problems	External beam radiotherapy	No	1.00	External beam radiotherapy	No	1.00
		Yes	3.35 (2.38-4.71)		Yes	2.25 (1.37-3.72)
	Comorbidities	No	1.00	Comorbidities	No	1.00
		1-2	1.20 (0.87-1.64)		1-2	1.28 (0.80-2.04)
		≥3	3.29 (1.88-5.76)*		≥3	2.80 (1.22-6.43)*
	Jurisdiction	RoI	1.00			
		NI	1.72 (1.21-2.45)			
	Urinating more frequently	No	1.00			
		Yes	1.48 (1.08-2.02)			
	Bleeding into bladder after biopsy	No biopsy	1.00			
		Yes	2.32 (1.08-4.96)*			
		No	1.42 (0.70-2.89)			
Breast changes	Hormone therapy	No	1.00	Hormone therapy	No	1.00
		Previously	3.80 (1.93-7.46)		Previously	4.27 (1.20-15.22)
		Currently	8.79 (4.45-17.36)		Currently	11.69 (3.29-41.53)
	Radical prostatectomy	No	1.00			
		Yes	0.33 (0.13-0.85)			
	Bleeding into rectum after biopsy	No biopsy	1.00			
		Yes	5.19 (1.76-15.29)*			
		No	1.43 (0.52-3.91)			
Hot flushes	Hormone therapy	No	1.00	Hormone therapy	No	1.00
		Previously	3.63 (2.04-6.44)		Previously	12.13 (6.19-23.76)
		Currently	34.61 (19.13-62.63)		Currently	14.23 (7.29-27.78)
	Time since diagnosis at start of study	2-5	1.00	Jurisdiction	RoI	1.00
		5-10	0.60 (0.39-0.92)*		NI	1.81 (1.18-2.76)
		>10	0.77 (0.42-1.39)	Radical prostatectomy	No	1.00
	External beam radiotherapy	No	1.00		Yes	2.45 (1.26-4.75)
		Yes	1.93 (1.15-3.22)	External beam radiotherapy	No	1.00
	Education	Primary	1.00		Yes	3.20 (1.85-5.55)
		Secondary	0.62 (0.40-0.98)	Education	Primary	1.00
		≥Tertiary	0.49 (0.28-0.84)		Secondary	0.90 (0.59-1.38)
					≥Tertiary	0.59 (0.36-0.99)*
				Back pain	No	1.00
					Yes	1.72 (1.02-2.89)
Fatigue	Hormone therapy	No	1.00	Hormone therapy	No	1.00
		Previously	1.13 (0.83-1.54)		Previously	4.60 (3.06-6.91)
		Currently	2.16 (1.44-3.26)*		Currently	4.91 (2.87-8.40)
	Jurisdiction	RoI	1.00	Jurisdiction	RoI	1.00
		NI	2.01 (1.43-2.82)		NI	1.68 (1.18-2.40)
	Time since diagnosis at start of study	2-5	1.00	Radical prostatectomy	No	1.00
		5-10	0.84 (0.64-1.11)		Yes	3.07 (2.00-4.71)
		>10	0.55 (0.35-0.85)*	External beam radiotherapy	No	1.00
	Urinating more frequently	No	1.00		Yes	2.51 (1.71-3.68)
		Yes	1.45 (1.09-1.92)	Time since diagnosis at start study	2-5	1.00
	Back pain	No	1.00		5-10	1.23 (0.92-1.66)
		Yes	1.78 (1.24-2.57)		>10	0.48 (0.28-0.82)*
	Comorbidities	No	1.00	Education	Primary	1.00
		1-2	1.18 (0.89-1.55)		Secondary	0.86 (0.62-1.20)
		≥3	2.07 (1.21-3.53)*		≥Tertiary	0.58 (0.39-0.85)*
	Brachytherapy	No	1.00	Back pain	No	1.00
		Yes	0.46 (0.24-0.89)		Yes	1.53 (1.13-2.08)
	Active surveillance/ watchful waiting	No	1.00			
		Yes	0.16 (0.05-0.46)			
	Education	Primary	1.00			
		Secondary	0.84 (0.62-1.14)			
		≥Tertiary	0.57 (0.40-0.81)*			

‖Weighted to assure representativeness for PCa survivors in the population.

*Significant category, if not all categories are significant.

Factors associated with 'current' side-effects in late disease

Table 3 indicates the factors, significant in multivariate analyses, associated with 'current' side-effects in late disease PCa. Age at diagnosis, older than 59, was associated with a lower risk of impotence, hot flushes and fatigue. Living with others was associated with a higher risk of impotence (1.63; 1.01-2.63). Higher education was associated with a higher risk of impotence. More than five years post-diagnosis was associated with a lower risk of hot flushes (0.57; 0.37-0.86; 0.45; 0.24-0.84) and fatigue (0.65; 0.44-0.95; 0.52; 0.29-0.92). Living in NI was associated with a higher risk of loss of libido, breast changes, hot flushes and fatigue.

Treatment was mainly associated with a higher risk of side-effects. RP was associated with a higher risk of urinary incontinence (4.45; 2.97-6.66) and impotence (1.89; 1.18-3.04). EBRT was associated with a higher risk of bowel problems (2.66; 1.50-4.73) and breast changes (2.06; 1.13-3.78). Any HT was associated with a higher risk of loss of libido, bowel problems, breast changes and hot flushes. Currently receiving HT was associated with a higher risk of fatigue (2.33; 1.36-3.99). AS/WW was associated with a lower risk of impotence (0.03; 0.00-0.62).

General health at diagnosis was associated with a higher risk of side-effects. Urinating more frequently (1.66; 1.14-2.40) and back pain (1.76; 1.16-2.67) were associated with a higher risk of fatigue. Impotence/erectile dysfunction was associated with a higher risk of loss of libido (2.02; 1.36-3.01)) and impotence (1.87; 1.19-2.96). Multiple comorbidities was associated with a higher risk of urinary incontinence (2.27; 1.16-4.44) and one to two comorbidities was associated with a higher risk of fatigue (1.52; 1.04-2.22). More than one comorbidity was associated with a higher risk of bowel problems. Bleeding into rectum after biopsy was associated with loss of libido (2.48; 1.06-5.83). Infection after biopsy was associated with a higher risk of breast changes (3.17; 1.06-9.49). No complications after biopsy was associated with a higher risk of impotence (2.07; 1.17-3.66). Having complications after biopsy was also associated with a higher risk of impotence (1.87; 1.10-3.18).

Factors associated with 'severe/very severe' side-effects in late disease

Factors, significant in multivariate analyses, associated with 'severe/very severe' side-effects are shown in table 3. Age at diagnosis, older than 59, was associated with a lower risk of impotence, breast changes, hot flushes and fatigue. Additionally, aged 70 years or older was associated with a lower risk of loss of libido (0.34; 0.21-0.53). Living with others was associated with a higher risk of impotence (1.66; 1.01-2.71). Higher education was associated with a higher risk of impotence (1.67; 1.12-2.48; 2.31; 1.52-3.49). Living in NI was associated with a higher risk of loss of libido, impotence, hot flushes and fatigue.

In addition treatment was associated with a higher risk of side-effects. RP was associated with a higher risk of urinary incontinence (4.47; 2.60-7.67) and impotence (3.70; 2.15-6.36). EBRT was associated with a higher risk of bowel problems (5.46; 2.09-14.32). Any HT was associated with a

higher risk of loss of libido, hot flushes and fatigue. Previously received HT was associated with a higher risk of impotence (1.81; 1.02-3.20).

General health at diagnosis was associated with a higher risk of side-effects. Impotence/erectile dysfunction was associated with a higher risk of loss of libido (1.97; 1.36-2.84). Multiple comorbidities was associated with a higher risk of fatigue (1.93; 1.02-6.36) and more than one comorbidity was associated with a higher risk of bowel problems (2.37; 1.22-4.63; 7.31; 3.15-16.92). Bleeding into rectum after biopsy was associated with hot flushes (3.02; 1.16-7.88) and fatigue (2.67; 1.12-6.36). No complications after biopsy was associated with a higher risk of urinary incontinence (13.42; 1.26-143.06). Having complications after biopsy was also associated with a higher risk of urinary incontinence (10.98; 1.04-115.53).

Table 3: Factors associated with side-effects in late disease, resulting from multivariate analysis‖

Side-effect	**Current**			**Severe/very severe**		
	Predictor		**OR (95% CI)**	**Predictor**		**OR (95% CI)**
Urinary incontinence	Radical prostatectomy	No	1.00	Radical prostatectomy	No	1.00
		Yes	4.45 (2.97-6.66)		Yes	4.47 (2.60-7.67)
	Comorbidities	No	1.00	No complications after biopsy	No biopsy	1.00
		1-2	1.17 (0.77-1.79)		Yes	13.42 (1.26-143.06)
		≥3	2.27 (1.16-4.44)*		No	10.98 (1.04-115.53)
Loss of libido	Hormone therapy	No	1.00	Hormone therapy	No	1.00
		Previously	1.71 (1.09-2.68)		Previously	1.71 (1.09-2.69)
		Currently	3.06 (2.00-4.70)		Currently	2.33 (1.50-3.63)
	Jurisdiction	RoI	1.00	Jurisdiction	RoI	1.00
		NI	1.53 (1.08-2.17)		NI	2.02 (1.42-2.87)
	Impotence/ erectile dysfunction	No	1.00	Age at diagnosis	0-59	1.00
		Yes	2.02 (1.36-3.01)		60-69	0.83 (0.55-1.26)
	Bleeding into rectum after biopsy	No biopsy	1.00		≥70	0.34 (0.21-0.53)*
		Yes	2.48 (1.06-5.83)	Impotence/ erectile dysfunction	No	1.00
		No	1.63 (1.01-2.65)		Yes	1.97 (1.36-2.84)
Impotence	Radical prostatectomy	No	1.00	Radical prostatectomy	No	1.00
		Yes	1.89 (1.18-3.04)		Yes	3.70 (2.15-6.36)
	Active surveillance/ watchful waiting	No	1.00	Age at diagnosis	0-59	1.00
		Yes	0.03 (0.00-0.62)		60-69	1.11 (0.72-1.72)
	Living alone	Alone	1.00		≥70	0.48 (0.30-0.77)*
		With others	1.63 (1.01-2.63)	Education	Primary	1.00
	Education	Primary	1.00		Secondary	1.67 (1.12-2.48)
		Secondary	1.57 (1.04-2.36)		≥Tertiary	2.31 (1.52-3.49)
		≥Tertiary	1.99 (1.29-3.09)	Hormone therapy	No	1.00
	Impotence/ erectile dysfunction	No	1.00		Previously	1.81 (1.02-3.20)*
		Yes	1.87 (1.19-2.96)		Currently	1.38 (0.80-2.37)
	No complications after biopsy	No biopsy	1.00	Jurisdiction	RoI	1.00
		Yes	2.07 (1.17-3.66)		NI	1.81 (1.26-2.60)
		No	1.87 (1.10-3.18)	Living alone	Alone	1.00
	Age at diagnosis	0-59	1.00		With others	1.66 (1.01-2.71)
		60-69	0.99 (0.61-1.60)			
		≥70	0.50 (0.30-0.83)*			
Bowel problems	External beam radiotherapy	No	1.00	External beam radiotherapy	No	1.00
		Yes	2.66 (1.50-4.73)		Yes	5.46 (2.09-14.32)
	Comorbidities	No	1.00	Comorbidities	No	1.00
		1-2	2.07 (1.31-3.26)		1-2	2.37 (1.22-4.63)
		≥3	3.84 (1.96-7.52)		≥3	7.31 (3.15-16.92)
	Hormone therapy	No	1.00			
		Previously	1.53 (1.11-3.78)			
		Currently	2.05 (1.31-3.26)			
Breast changes	Hormone therapy	No	1.00	Radical prostatectomy	No	1.00
		Previously	2.84 (1.24-6.50)		Yes	0.11 (0.05-0.24)
		Currently	5.14 (2.30-11.52)	Age at diagnosis	0-59	1.00
	External beam radiotherapy	No	1.00		60-69	0.41 (0.27-0.63)
		Yes	2.06 (1.13-3.78)		≥70	0.14 (0.05-0.43)
	Jurisdiction	RoI	1.00			

		NI	2.17 (1.38-3.42)			
	Infection after biopsy	No biopsy	1.00			
		Yes	3.17 (1.06-9.49)*			
		No	1.48 (0.70-3.12)			
Hot flushes	Hormone therapy	No	1.00	Hormone therapy	No	1.00
		Previously	2.49 (1.26-4.93)		Previously	12.90 (4.71-35.30)
		Currently	12.23 (6.30-23.76)		Currently	10.93 (4.06-29.42)
	Time since diagnosis at start of study	2-5	1.00	Jurisdiction	RoI	1.00
		5-10	0.57 (0.37-0.86)		NI	1.99 (1.33-2.99)
		>10	0.45 (0.24-0.84)	Age at diagnosis	0-59	1.00
	Jurisdiction	RoI	1.00		60-69	0.49 (0.27-0.75)
		NI	2.82 (1.88-4.22)		≥70	0.43 (0.25-0.74)
	Age at diagnosis	0-59	1.00	Bleeding into rectum after biopsy	No biopsy	1.00
		60-69	0.45 (0.27-0.76)*		Yes	3.02 (1.16-7.88)*
		≥70	0.60 (0.35-1.03)		No	1.31 (0.64-2.69)
Fatigue	Hormone therapy	No	1.00	Hormone therapy	No	1.00
		Previously	1.07 (0.62-1.84)		Previously	3.28 (1.95-5.52)
		Currently	2.33 (1.36-3.99)*		Currently	3.06 (1.81-5.18)
	Jurisdiction	RoI	1.00	Jurisdiction	RoI	1.00
		NI	1.99 (1.36-2.92)		NI	1.60 (1.11-2.31)
	Time since diagnosis at start of study	2-5	1.00	Age at diagnosis	0-59	1.00
		5-10	0.65 (0.44-0.95)		60-69	0.46 (0.30-0.73)
		>10	0.52 (0.29-0.92)		≥70	0.33 (0.20-0.55)
	Urinating more frequently	No	1.00	Comorbidities	No	1.00
		Yes	1.66 (1.14-2.40)		1-2	1.23 (0.85-1.79)
	Back pain	No	1.00		≥3	1.93 (1.02-6.36)*
		Yes	1.76 (1.16-2.67)	Bleeding into rectum after biopsy	No biopsy	1.00
	Comorbidities	No	1.00		Yes	2.67 (1.12-6.36)*
		1-2	1.52 (1.04-2.22)*		No	1.00 (0.55-1.82)
		≥3	1.68 (0.88-3.23)			
	Age at diagnosis	0-59	1.00			
		60-69	0.44 (0.28-0.69)			
		≥70	0.31 (0.19-0.52)			

‖weighted to assure representativeness for PCa survivors in the population.
*Significant category, if not all categories are significant.

Sensitivity analysis and model diagnostics

Values of factors, significant in multivariate analyses in the pooled dataset, of the original data used for the sensitivity analysis are presented in table 4. The sensitivity analysis showed that there are no changes in significant factors between the original and pooled dataset for urinary incontinence. However, for the side-effect impotence, there were differences present for the variable living alone in early disease and variables; AS/WW, living alone, education, no complications after biopsy and age at diagnosis in late disease. These differences are towards the significance level of these variables, for the odds ratio there was little change.

Model diagnostics are shown in tables 5 and 6. The Hosmer-Lemeshow test showed that models for both 'current' and 'severe/very severe' side-effects were a good fit to the data. For 'current' side-effects, models for breast changes and fatigue in localised disease were significant, and for locally advanced/advanced disease this was the case for hot flushes. For 'severe/very severe' side-effects, only the model for loss of libido did not fit the data according to the Hosmer-Lemeshow test. Additionally, Nagelkerke R^2 was low for all models. There was no correlation present between variables within the different models.

Table 4: Sensitivity analysis values original data*

Side-effects			Early	Late
Urinary incontinence	RP	No	1.00	1.00
		Yes	3.18 (2.37-4.73;p<0.001)	4.55 (3.04-6.81;p<0.001)
	AS/WW	No	1.00	
		Yes	0.33 (0.12-0.93;p=0.036)	
	Comorbidities	No	1.00	1.00
		1-2	1.20 (0.89-1.63;p=0.228)	1.17 (0.77-1.78;p=0.471)
		>3	2.55 (1.44-4.53;p=0.001)	2.24 (1.15-4.39;p=0.018)
	Urinating more frequently	No	1.00	
		Yes	1.83 (1.36-2.47;p<0.001)	
Impotence	RP	No	1.00	1.00
		Yes	3.24 (2.43-4.33;p<0.001)	2.59 (1.47-4.56;p=0.001)
	AS/WW	No	1.00	1.00
		Yes	0.23 (0.12-0.41;p<0.001)	0.05 (0.00-1.05;p=0.053)
	Living alone	Alone	1.00	1.00
		Others	1.13 (0.77-1.64;p=0.541)	1.52 (0.88-2.62;p=0.131)
	Education	Prim	1.00	1.00
		Sec	1.52 (1.14-2.03;p=0.004	1.34 (0.84-2.12;p=0.219)
		≥Tert	1.81 (1.32-2.47;p<0.001)	1.65 (1.02-2.66;p=0.041)
	Impotence/ erectile dysfunction	No	1.00	1.00
		Yes	2.67 (1.96-3.65;p<0.001)	2.59 (1.56-4.29;p<0.001
	No complications	No biopsy	1.00	1.00
		Yes	1.96 (1.15-3.36;p=0.014)	1.43 (0.75-2.73;p=0.281)
		No	1.63 (1.03-2.58;p=0.037)	1.43 (0.76-2.70;p=0.264)
	Age at diagnosis	0-59		1.00
		60-69		1.25 (0.73-2.13;p=0.415)
		>70		0.61 (0.35-1.07;p=0.131)

*Changes in significance level are marked

Table 5: Model diagnostics for early disease

Side-effects		Current	Severe/very severe
Urinary incontinence			
	Nagelkerke R2*	0.089	0.091
	Goodness of fit^{+}	p≥0.834	p≥0.958
	Correlation test	≤0.148	≤0.221
Loss of libido			
	Nagelkerke R2*	0.109	0.087
	Goodness of fit^{+}	p≥0.375	p≥0.006 (1 significant); original=0.144
	Correlation test	≤0.470	≤0.432
Impotence			
	Nagelkerke R2*	0.173	0.169
	Goodness of fit^{+}	p≥0.666	p≥0.355
	Correlation test	≤0.121	≤0.421
Bowel problems			
	Nagelkerke R2*	0.114	0.031
	Goodness of fit^{+}	p≥0.615	p≥0.812
	Correlation test	≤0.042	≤-0.059
Breast changes			

	Nagelkerke R2*	0.166	0.088
	Goodness of fit+	p≥0.004 (1 is significant); original=0.375	1.000
	Correlation test	≤0.341	-
Hot flashes			
	Nagelkerke R2*	0.341	0.266
	Goodness of fit+	p≥0.361	p≥0.166
	Correlation test	≤0.104	≤0.453
Fatigue			
	Nagelkerke R2*	0.126	0.196
	Goodness of fit+	p≥0.015 (3 significant) original=0.015	p≥276
	Correlation test	0.132	0.445

*Pooled pseudo R2

+ Hosmer-Lemeshow test

Table 6: Model diagnostics for late disease

Side-effects		**Current**	**Current**
Urinary incontinence			
	Nagelkerke R2*	0.125	0.143
	Goodness of fit+	p≥0.160	p≥0.095
	Correlation test	≤0.144	≤0.591
Loss of libido			
	Nagelkerke R2*	0.123	0.128
	Goodness of fit+	p≥0.541	p≥0.084
	Correlation test	≤0.198	≤0.238
Impotence			
	Nagelkerke R2*	0.162	0.192
	Goodness of fit+	p≥0.071	p≥0.293
	Correlation test	≤0.259	≤0.612
Bowel problems			
	Nagelkerke R2*	0.095	0.122
	Goodness of fit+	p≥0.223	p≥0.807
	Correlation test	≤0.101	≤0.067
Breast changes			
	Nagelkerke R2*	0.137	0.104
	Goodness of fit+	p≥0.379	p≥0.999
	Correlation test	≤0.138	≤0.145
Hot flashes			
	Nagelkerke R2*	0.311	0.212
	Goodness of fit+	p≥0.022 (2 significant); original=0.085	p≥0.402
	Correlation test	≤0.164	≤0.131
Fatigue			
	Nagelkerke R2*	0.167	0.133
	Goodness of fit+	p≥0.403	p≥0.122
	Correlation test	≤0.204	≤0.134

*Pooled pseudo R2

+ Hosmer-Lemeshow test

Discussion

This study was performed in order to better support treatment decision making of patients and clinicians for both early and late disease separately. Our findings suggest that, in both early and late disease, younger age at diagnosis becomes more important in late disease and for 'severe/very severe' side-effects. Men of 70 years and older were less likely to report side-effects ('current' and 'severe/very severe') compared to younger men (0-59). This could be explained by the fact that older men have a different view of life than younger men and blame some of the side-effects on an aging body instead of their treatment (18). Therefore, older age is not a factor that better supports the decision making, men are just less likely to report side-effects. Living with others was associated with a higher risk of sexual dysfunction (impotence and loss of libido). This could be due to the fact that men living with others, most likely live with their partner, are more likely to be sexually active and face the problem earlier than men living alone. For both 'current' and 'severe/very severe' men with tertiary or higher education were less likely to have hot flushes and fatigue than men with primary education. This could be caused by other socio-economic factors or the fact that these men have more difficulty with understanding what the implications of treatment are and need additional assessment and support (19).

We found that treatment was the strongest factor associated with both 'current' and 'severe/very severe' physical side-effects in early and late disease. Especially, RP was associated with a higher risk for side-effects in early disease for both 'current' and even more for 'severe/very severe' side-effects. For early disease, RP, EBRT and HT were associated with a higher risk of fatigue for 'severe/very severe'. Additionally, our results suggest that AS/WW is a clinical strategy associated with a lower risk of side-effects. This could be an opportunity for eligible men with localised PCa to avoid or delay side-effects, instead of the higher risk of side-effects associated with RP, EBRT and HT. Especially, for those anxious to avoid incontinence and impotence (20). Moreover, BT showed to be associated with a lower risk of 'current' fatigue and 'severe/very severe' impotence. In another study with a small group, BT was found to be the treatment with the highest probability to maintain erectile function (21). However, the men who obtained BT as treatment in our study were a small and highly selected group. Nonetheless, it is an important finding and more research should be done to determine if these results can be replicated in a larger sample size.

Pre-treatment function had an impact on developing side-effects after treatment, in most cases men already experienced the side-effects before treatment. The association of pre-treatment function with a higher risk of side-effects was expected, however was not the strongest factor as was found in another study (7). Probably, caused by the fact that in this study pre-treatment function was reported at 24 months after treatment. Our study involves men from 24 months on to 18 years post-diagnosis, with recall bias playing a bigger role. Number of comorbidities was particularly associated with a higher risk of 'current' side-effects. Furthermore, should be taken into account for early disease, as multiple comorbidities was associated with a higher risk of four out of seven 'current' side-effects.

An interesting finding was the fact that biopsy complications were associated with side-effects after PCa treatment. As, Loeb et al. (22) found, maybe caused by the selection of patient that should have been conducted more carefully. The individualised assessment of the risk-to-benefit ratio is very important to determine if the potential risky procedure of a biopsy should be performed. Thus, should improve determining patient eligibility for biopsy. Our findings suggest that the decision regarding having a biopsy or not, if optional, could have a big impact on a patient's outcomes after treatment, not only emphasizing the treatment but also choices that have been made beforehand i.e. from the decision to have a PSA test.

The following limitations should be considered when interpreting the results. First, the questions used for analyses were not validated. Second, missing data in the outcome variables was included in 'never had the side-effect' and was not included in the multiple imputations method. Third, in some cases it was not possible to include all three variables for 'complications after biopsy' (bleeding into bladder, bleeding into rectum and infection) into multivariate analysis when these were significant in univariate analysis. This was resolved by excluding all three variables from multivariate analysis and including the variable 'no complications after biopsy'. Additionally, unknown stage and grade were excluded from the analysis and were included in the category 'other'. Stage I/II with a high grade (8-10) were also part of this category. Exact numbers can be found in the supplementary table. Last, the Nagelkerke R^2 of the different models showed a low predictive value of the models. Which indicates only a small percentage of the side-effects was explained by the predictors identified in the model. Therefore, the models should be taken into account with caution and other (not identified) factors also play a role. The Hosmer-Lemeshow showed a good fit in most cases and in four models showed to be significant (no fit). However, the Hosmer-Lemeshow test has shown to be sensitive for large sample sizes and more likely to show a significant difference.

In conclusion, treatment is the most important factor associated with side-effects. After treatment, various other factors such as pre-treatment function and comorbidities are strongly associated with a higher risk of side-effects. Therefore, should be taken into account as well. Complications after biopsy and the biopsy itself were more important than expected. Better patient selection for biopsy may lead to less complications and better patient outcomes after treatment. These findings may be used to better support PCa patients and physicians, about the potential side-effects associated with specific treatments. Additionally, use the knowledge of the patient- and disease-related factors associated with a higher risk of side-effects following treatment. Ultimately, leading to a better informed decision-making process regarding treatment and offer better support to patientsp after treatment.

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Appendix I: Supplementary tables

Supplementary table 1: Characteristics of other group

Stage I/II	**High (8 to 10)**	300
Stage I/II	**Unknown**	171
Unknown	**Low (2 to 4)**	40
Unknown	**Intermediate (5 to 7)**	265
Unknown	**High (8 to 10)**	67
Unknown	**Unknown**	116
Total		959

Supplementary table 2: Factors associated with 'current' side-effects, resulting from univariate analyses‖

		Urinary incontinence		**Loss of libido**	
		Early	**Late**	**Early**	**Late**
Predictor		**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
RP	No	1.00	1.00	1.00	1.00
	Yes	2.87 (2.18-3.77)	4.33 (2.84-6.29)	1.31 (1.06-1.61)	0.68 (0.48-0.95)
EBRT	No	1.00	1.00	1.00	
	Yes	0.58 (0.44-0.76)	0.56 (0.38-0.83)	1.26 (1.03-1.53)	
BT	No			1.00	
	Yes			0.63 (0.43-0.95)	
HT	No	1.00	1.00	1.00	1.00
	Previously	0.72 (0.52-1.00)*	0.45 (0.28-0.73)	1.46 (1.16-1.85)	2.03 (1.33-3.11)
	Currently	0.74 (0.44-1.24)	0.50 (0.31-0.80)	1.89 (1.23-2.91)	3.34 (2.23-5.01)
AS/WW	No	1.00		1.00	
	Yes	0.31 (0.13-0.74)		0.33 (0.20-0.54)	
Jurisdiction	RoI		1.00	1.00	1.00
	NI		0.66 (0.45-0.99)	1.31 (1.01-1.70)	1.72 (1.26-2.34)
Age at diagnosis	0-59	1.00	1.00		
	60-69	1.03 (0.75-1.43)	0.62 (0.39-0.98)		
	≥70	0.72 (0.49-1.06)*	0.47 (0.28-0.78)*		
Living alone	Alone			1.00	
	With others			1.44 (1.07-1.95)	
Urinating more frequently	Yes	1.53 (1.13-2.07)			1.67 (1.22-2.30)
Pain while urinating	Yes	1.57 (1.06-2.32)			
Impotence/ erectile dysfunction	Yes	1.44 (1.02-2.04)		1.88 (1.51-2.36)	1.90 (1.27-2.85)
Loss of interest in sex	Yes	1.45 (0.97-2.16)		2.00 (1.54-2.61)	2.01 (1.37-2.94)
Back pain	Yes	1.67 (1.19-2.36)	1.54 (1.01-2.34)	1.28 (1.01-1.62)	1.49 (0.96-2.32)
Comorbidities	No	1.00	1.00	1.00	
	1-2	1.17 (0.88-1.55)	1.00 (0.67-1.49)	1.17 (0.96-1.42)	
	≥3	2.29 (1.34-3.90)*	1.78 (0.95-3.35)*	2.15 (1.36-3.41)*	
Bleeding into bladder after biopsy	No biopsy			1.00	
	Yes			2.02 (1.26-3.25)*	
	No			1.40 (0.93-2.11)	
Bleeding into rectum after biopsy	No biopsy			1.00	1.00
	Yes			1.61 (0.86-2.99)	2.39 (1.05-5.43)*
	No			1.38 (0.86-2.20)	1.43 (0.91-2.24)
Infection after biopsy	No biopsy			1.00	
	Yes			1.76 (1.02-3.02)	
	No			1.44 (1.01-2.06)	
No complications after biopsy	No biopsy			1.00	1.00
	Yes			1.78 (1.13-2.81)	1.85 (1.09-3.15)*
	No			1.58 (1.09-2.29)	1.33 (0.82-2.16)
TURP	Yes		1.47 (0.86-2.51)		

		Impotence		**Bowel problems**	
		Early	**Late**	**Early**	**Late**
RP	No	1.00	1.00	1.00	1.00
	Yes	3.63 (2.58-4.63)	2.56 (1.68-3.89)	0.52 (0.36-0.74)	0.47 (0.28-0.80)

EBRT	No			1.00	1.00
	Yes			3.44 (2.46-4.80)	2.62 (1.54-4.45)
BT	No	1.00			
	Yes	0.62 (0.43-0.92)			
HT	No		1.00	1.00	1.00
	Previously		0.69 (0.43-1.11)	1.70 (1.24-2.33)*	2.30 (1.30-4.09)
	Currently		0.72 (0.48-1.10)	1.15 (0.70-1.89)	2.31 (1.28-4.17)
AS/WW	No	1.00	1.00	1.00	
	Yes	0.18 (0.11-0.30)	0.03 (0.00-0.64)	0.22 (0.07-0.72)	
Jurisdiction	RoI			1.00	1.00
	NI			2.06 (1.48-2.89)	1.67 (1.12-2.48)
Time since diagnosis at start of study	2-5	1.00			
	5-10	1.23 (1.01-1.52)*			
	>10	1.29 (0.95-1.76)			
Age at diagnosis	0-59	1.00	1.00	1.00	
	60-69	0.78 (0.61-1.00)	0.83 (0.52-1.30)	1.01 (0.70-1.46)	
	≥70	0.41 (0.31-0.53)	0.34 (0.22-0.54)*	1.46 (0.99-2.14)*	
Living alone	Alone	1.00	1.00		
	With others	1.50 (1.12-2.00)	1.88 (1.20-2.95)		
Education	Primary	1.00	1.00	1.00	
	Secondary	1.72 (1.36-2.18)	1.80 (1.23-2.63)	0.71 (0.50-1.00)*	
	≥Tertiary	1.72 (1.31-2.26)	2.27 (1.50-3.44)	0.86 (0.60-1.24)	
Urinating more frequently	Yes			1.75 (1.30-2.36)	
Pain while urinating	Yes				
Impotence/ erectile dysfunction	Yes	1.51 (1.19-1.92)	1.52 (1.00-2.33)		
Loss of interest in sex	Yes				
Back pain	Yes			1.65 (1.19-2.29)	1.64 (1.04-2.59)
Comorbidities	No			1.00	1.00
	1-2			1.36 (1.01-1.85)	2.08 (1.33-3.26)
	≥3			1.46 (2.22-6.32)	3.68 (7.90-7.10)
Bleeding into bladder after biopsy	No biopsy	1.00	1.00	1.00	
	Yes	2.30 (1.45-3.64)	2.65 (1.25-5.64)	2.43 (1.11-5.31)*	
	No	2.14 (1.47-3.12)	2.33 (1.45-3.74)	1.46 (0.68-3.11)	
Bleeding into rectum after biopsy	No biopsy	1.00	1.00	1.00	
	Yes	1.71 (0.85-3.43)	2.62 (1.11-6.17)	2.74 (1.13-6.64)*	
	No	2.05 (1.17-3.60)*	2.36 (1.48-3.77)	1.38 (0.60-3.20)	
Infection after biopsy	No biopsy	1.00	1.00	1.00	
	Yes	2.26 (1.32-3.87)	2.58 (1.02-6.54)	2.66 (1.23-5.77)*	
	No	2.26 (1.58-3.21)	2.32 (1.44-3.73)	1.46 (0.81-2.64)	
No complications after biopsy	No biopsy	1.00	1.00	1.00	
	Yes	2.24 (1.44-3.51)	2.11 (1.24-3.61)	2.93 (1.45-5.90)*	
	No	2.40 (1.67-3.45)	2.42 (1.49-3.95)	1.60 (0.85-3.00)	
TURP	Yes		1.06 (0.53-2.11)		

		Breast changes		**Hot flashes**	
		Early	**Late**	**Early**	**Late**
RP	No	1.00	1.00	1.00	1.00
	Yes	0.15 (0.07-0.36)	0.52 (0.30-0.89)	0.23 (0.13-0.39)	0.43 (0.28-0.66)
EBRT	No	1.00	1.00	1.00	1.00
	Yes	1.98 (1.24-3.15)	2.34 (1.36-4.04)	1.97 (1.37-2.82)	1.04 (0.72-1.51)
BT	No			1.00	
	Yes			0.40 (0.16-1.02)	
HT	No	1.00	1.00	1.00	1.00
	Previously	5.49 (2.92-10.34)	4.91 (2.24-10.73)	7.56 (4.48-12.74)	3.54 (1.85-6.76)
	Currently	10.29 (5.32-19.90)	6.39 (2.93-13.94)	0.20 (0.12-0.35)	14.37 (7.71-26.77)
AS/WW	No			1.00	
	Yes			0.21 (0.05-0.80)	
Jurisdiction	RoI	1.00	1.00		1.00
	NI	1.78 (1.07-2.96)	2.91 (1.89-4.48)		3.01 (2.14-4.25)
Time since diagnosis at start of study	2-5			1.00	1.00
	5-10			0.71 (0.49-1.03)	0.53 (0.70-0.77)
	>10			1.60 (1.01-2.52)	0.56 (0.33-0.96)
Age at diagnosis	0-59			1.00	1.00
	60-69			1.20 (0.49-1.03)	0.67 (0.70-1.04)*
	≥70			2.92 (1.80-4.73)*	1.32 (0.84-2.06)
Living alone	Alone	1.00			

	With others	0.59 (0.34-1.02)			
Education	Primary			1.00	
	Secondary			0.47 (0.32-0.70)	
	≥Tertiary			0.37 (0.23-0.59)	
Urinating more frequently	Yes				1.39 (0.99-1.96)
Back pain	Yes				1.05 (0.61-1.80)
Comorbidities	No	1.00			1.00
	1-2	1.16 (0.73-1.82)			1.28 (0.90-1.83)
	≥3	2.06 (0.90-4.71)*			1.68 (0.92-3.04)*
Bleeding into bladder after biopsy	No biopsy				
	Yes				
	No				
Bleeding into rectum after biopsy	No biopsy	1.00			
	Yes	3.39 (1.26-9.12)*			
	No	1.11 (0.46-2.65)			
Infection after biopsy	No biopsy		1.00		
	Yes		2.77 (0.99-7.72)*		
	No		1.39 (0.67-2.89)		
No complications after biopsy	No biopsy		1.00		1.00
	Yes		2.78 (1.28-6.06)*		1.42 (0.81-2.48)
	No		1.02 (0.47-2.20)		0.62 (0.37-1.06)*
TURP	Yes		0.50 (0.21-1.18)		0.58 (0.34-1.01)

		Fatigue	
		Early	**Late**
RP	No		1.00
	Yes		0.69 (0.47-1.01)
EBRT	No	1.00	
	Yes	1.66 (1.29-2.14)	
BT	No	1.00	
	Yes	0.42 (0.22-0.79)	
HT	No	1.00	1.00
	Previously	1.60 (1.21-2.12)	1.33 (0.83-2.12)
	Currently	2.50 (1.68-3.73)	2.63 (1.65-4.21)*
AS/WW	No	1.00	
	Yes	0.20 (0.08-0.51)	
Jurisdiction	RoI	1.00	1.00
	NI	0.51 (0.38-0.68)	1.96 (1.41-2.72)
Time since diagnosis at start of study	2-5	1.00	1.00
	5-10	0.89 (0.68-1.15)	0.69 (0.49-0.98)
	>10	068 (0.45-1.03)*	0.61 (0.36-1.02)
Age at diagnosis	0-59		1.00
	60-69		0.58 (0.38-0.87)
	≥70		0.60 (0.39-0.93)
Education	Primary	1.00	
	Secondary	0.67 (0.51-0.89)	
	≥Tertiary	0.48 (0.34-0.68)	
Urinating more frequently	Yes	1.77 (1.37-2.29)	1.74 (1.24-2.45)
Pain while urinating	Yes	1.54 (1.01-2.34	
Blood in urine	Yes	1.40 (0.83-2.36)	
Impotence/ erectile dysfunction	Yes	1.35 (0.98-1.88)	1.51 (1.03-2.21)
Loss of interest in sex	Yes	1.60 (1.10-2.34)	1.46 (0.98-2.16)
Back pain	Yes	1.92 (1.38-2.67)	2.07 (1.38-3.10)
Comorbidities	No	1.00	1.00
	1-2	1.39 (1.08-1.80)	0.49 (0.27-0.89)*
	≥3	2.84 (1.73-4.66)	0.84 (0.48-1.49)
No complications after biopsy	No biopsy		1.00
	Yes		1.07 (0.62-1.84)
	No		0.59 (0.36-0.99)*
TURP	Yes	0.76 (0.57-1.01)	0.67 (0.46-0.99)

‖weighted to assure representativeness for PCa survivors in the population.

*Significant category, if not all categories are significant.

Supplementary table 3: Factors associated with 'severe/very severe' side-effects, resulting from univariate analyses‖

		Urinary incontinence		Loss of libido	
		Early	Late	Early	Late
Predictor		**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
RP	No	1.00	1.00	1.00	
	Yes	4.14 (2.88-5.96)	4.48 (2.70-7.44)	1.25 (0.99-1.58)	
EBRT	No	1.00	1.00	1.00	
	Yes	0.41 (0.28-0.59)	0.55 (0.34-0.93)	1.25 (1.00-1.56)	
HT	No	1.00	1.00	1.00	1.00
	Previously	0.57 (0.36-0.90)	0.41 (0.22-0.75)	1.79 (1.37-2.35)	1.89 (1.24-2.87)
	Currently	0.42 (0.19-0.89)	0.45 (0.24-0.83)	1.82 (1.21-2.74)	2.20 (1.47-3.30)
AS/WW	No	1.00		1.00	
	Yes	0.22 (0.05-0.97)		0.22 (0.10-0.46)	
Jurisdiction	RoI			1.00	1.00
	NI			1.39 (1.05-1.85)	1.93 (1.42-2.63)
Age at diagnosis	0-59	1.00	1.00	1.00	1.00
	60-69	0.42 (0.29-0.63)	0.56 (0.31-0.98)	0.86 (0.66-1.12)	0.98 (0.66-1.45)
	≥70	0.31 (0.19-0.51)	0.34 (0.17-0.67)	0.58 (0.43-0.79)*	0.52 (0.34-0.79)*
Education	Primary		1.00		1.00
	Secondary		1.65 (0.93-2.91)*		1.11 (0.77-1.59)
	Tertiary		1.05 (0.54-2.05)		1.50 (1.03-2.19)*
Impotence/ erectile dysfunction	Yes			1.55 (1.20-2.00)	1.57 (1.11-2.21)
Loss of interest in sex	Yes			1.74 (1.31-2.30)	
Back pain	Yes	1.47 (0.96-2.24)			
Comorbidities	No			1.00	
	1-2			1.13 (0.90-1.41)	
	≥3			1.63 (1.00-2.65)*	
Bleeding into bladder after biopsy	No biopsy		1.00	1.00	
	Yes		25.54 (2.49-262.5)	1.97 (1.11-3.49)*	
	No		9.60 (0.98-94.03)	1.27 (0.79-2.07)	
Infection after biopsy	No biopsy	1.00	1.00		
	Yes	2.73 (1.11-6.72)*	19.05 (1.73-209.5)		
	No	1.16 (0.57-2.35)	9.06 (1.02-80.78)		
No complications after biopsy	No biopsy		1.00	1.00	1.00
	Yes		10.98 (1.04-115.5)	1.58 (0.94-2.65)*	1.97 (1.14-3.40)
	No		15.21 (1.49-154.9)	1.42 (0.92-2.18)	1.25 (0.75-2.07)

		Impotence		Bowel problems	
		Early	Late	Early	Late
RP	No	1.00	1.00		1.00
	Yes	3.45 (2.77-4.31)	2.94 (2.03-4.26)		0.40 (0.19-0.88)
EBRT	No	1.00		1.00	1.00
	Yes	0.70 (0.57-0.85)		2.26 (1.37-3.72)	5.09 (1.96-13.20)
BT	No	1.00			
	Yes	0.56 (0.37-0.85)			
HT	No		1.00		1.00
	Previously		0.80 (0.54-1.18)		2.12 (0.97-4.65)*
	Currently		0.62 (0.42-0.91)*		1.22 (0.51-2.93)
AS/WW	No	1.00	1.00		
	Yes	0.11 (0.05-0.23)	0.06 (0.00-1.17)		
Jurisdiction	RoI		1.00		1.00
	NI		1.36 (0.99-1.83)		2.12 (1.23-3.65)
Age at diagnosis	0-59	1.00	1.00		
	60-69	0.71 (0.56-0.90)	0.93 (0.62-1.39)		
	≥70	0.37 (0.28-0.49)	0.32 (0.21-0.49)*		
Living alone	Alone		1.00		
	With others		2.15 (1.36-3.40)		
Education	Primary	1.00	1.00	1.00	
	Secondary	1.45 (1.14-1.85)	1.81 (1.26-2.61)	0.59 (0.34-1.01)*	
	≥Tertiary	1.57 (1.21-2.03)	2.72 (1.84-4.02)	0.65 (0.37-1.16)	
Urinating more frequently	Yes	0.76 (0.62-0.93)			
Pain while urinating	Yes		0.63 (0.39-1.02)		
Blood in urine	Yes	0.79 (0.53-1.18)	0.63 (0.40-1.00)		

Impotence/ erectile dysfunction	Yes	1.26 (1.00-1.58)			
Loss of interest in sex	Yes		0.67 (0.47-0.95)		
Back pain	Yes			1.68 (0.94-2.99)	1.77 (0.98-3.17)
Comorbidities	No			1.00	1.00
	1-2			1.35 (0.84-2.16)	2.36 (1.22-4.58)
	≥3			2.76 (1.25-6.11)*	6.63 (2.92-15.07)
Bleeding into bladder after biopsy	No biopsy	1.00	1.00		
	Yes	2.79 (1.70-4.59)	2.74 (1.29-5.85)		
	No	2.06 (1.38-3.08)	1.73 (1.07-2.80)		
Bleeding into rectum after biopsy	No biopsy	1.00	1.00		
	Yes	1.88 (0.59-4.13)	2.00 (0.92-4.35)		
	No	1.84 (0.93-3.65)*	1.80 (1.12-2.88)		
Infection after biopsy	No biopsy	1.00	1.00		
	Yes	2.28 (1.14-4.56)	3.09 (1.24-7.69)		
	No	2.20 (1.47-3.28)	1.78 (1.11-2.86)		
No complications after biopsy	No biopsy	1.00	1.00		
	Yes	1.89 (1.16-3.08)	2.00 (1.17-3.42)		
	No	2.36 (1.57-3.54)	1.82 (1.11-2.97)		
TURP	Yes	0.92 (0.58-1.45)			

		Breast changes		**Hot flashes**	
		Early	**Late**	**Early**	**Late**
RP	No		1.00	1.00	1.00
	Yes		0.18 (0.04-0.79)	0.34 (0.21-0.56)	0.22 (0.12-0.40)
EBRT	No	1.00	1.00	1.00	1.00
	Yes	3.25 (1.04-10.16)	3.70 (1.14-12.07)	5.55 (3.47-8.85)	2.28 (1.44-3.62)
BT	No			1.00	
	Yes			0.26 (0.09-0.82)	
HT	No	1.00	1.00	1.00	1.00
	Previously	4.27 (1.20-5.22)	6.30 (1.48-26.90)	14.67 (8.55-25.15)	14.31 (5.35-38.26)
	Currently	11.69 (3.29-41.5)	4.59 (1.03-20.44)	12.37 (6.78-22.55)	11.18 (4.25-29.41)
Jurisdiction	RoI			1.00	1.00
	NI			2.74 (1.88-3.99)	2.81 (1.94-4.09)
Time since diagnosis at start of study	2-5				1.00
	5-10				0.82 (0.56-1.21)
	>10				0.48 (0.25-0.92)*
Age at diagnosis	0-59		1.00	1.00	1.00
	60-69		0.54 (0.24-1.21)	1.42 (0.90-2.26)	0.64 (0.40-1.02)*
	≥70		0.24 (0.08-0.72)*	1.73 (1.06-2.82)*	0.75 (0.46-1.21)
Education	Primary	1.00		1.00	
	Secondary	0.34 (0.11-1.11)*		0.64 (0.44-0.95)	
	≥Tertiary	0.50 (0.15-1.62)		0.48 (0.30-0.77)	
Blood in urine	Yes		1.69 (0.67-4.30)		
Impotence/erectile dysfunction	Yes				1.31 (0.88-1.95)
Loss of interest in sex	Yes		1.91 (0.88-4.15)		
Back pain	Yes		2.23 (1.03-4.82)	1.54 (1.02-2.35)	
Comorbidities	No			1.00	1.00
	1-2			1.51 (1.05-2.17)	1.33 (0.91-1.97)
	≥3			2.04 (1.01-4.12)	1.80 (0.96-3.41)*
Bleeding into bladder after biopsy	No biopsy			1.00	
	Yes			2.44 (0.97-6.14)*	
	No			1.93 (0.87-4.29)	
Bleeding into rectum after biopsy	No biopsy				1.00
	Yes				3.40 (1.40-8.24)*
	No				1.34 (0.68-2.63)
Infection after biopsy	No biopsy			1.00	
	Yes			2.63 (0.98-7.02)*	
	No			1.85 (0.84-4.10)	
No complications after biopsy	No biopsy			1.00	1.00
	Yes			3.98 (1.65-9.57)*	2.11 (1.06-4.19)*
	No			1.78 (0.79-4.03)	1.33 (0.69-2.56)
TURP	Yes			0.72 (0.79-4.03)	0.45 (0.21-0.96)

		Fatigue	
		Early	**Late**
RP	No	1.00	1.00

	Yes	0.72 (0.53-0.97)	0.50 (0.33-0.75)
EBRT	No	1.00	1.00
	Yes	2.92 (2.18-3.93)	1.88 (1.27-2.78)
BT	No	1.00	
	Yes	0.29 (0.13-0.66)	
HT	No	1.00	1.00
	Previously	4.44 (3.23-6.11)	3.39 (2.09-5.51)
	Currently	3.23 (2.04-5.11)	2.93 (1.80-4.77)
AS/WW	No	1.00	
	Yes	0.05 (0.01-0.34)	
Jurisdiction	RoI	1.00	1.00
	NI	2.06 (1.51-2.81)	2.03 (1.45-2.83)
Time since diagnosis at start of study	2-5	1.00	
	5-10	1.27 (0.97-1.67)	
	>10	0.61 (0.37-0.99)*	
Age at diagnosis	0-59		1.00
	60-69		0.60 (0.30-0.90)
	≥70		0.55 (0.36-0.86)
Education	Primary	1.00	
	Secondary	0.67 (0.50-0.90)	
	≥Tertiary	0.48 (0.34-0.69)	
Urinating more frequently	Yes		1.45 (1.03-2.04)
Impotence/ erectile dysfunction	Yes		1.29 (0.87-1.89)
Loss of interest in sex	Yes		1.32 (0.89-1.97)
Back pain	Yes	2.00 (1.49-2.81)	1.40 (0.95-2.06)
Comorbidities	No	1.00	1.00
	1-2	1.74 (1.32-2.30)	1.27 (0.90-1.80)
	≥3	1.88 (1.05-3.34)	1.82 (1.01-3.27)*
Bleeding into bladder after biopsy	No biopsy	1.00	
	Yes	2.17 (1.18-3.99)*	
	No	1.20 (0.70-2.07)	
Bleeding into rectum after biopsy	No biopsy	1.00	1.00
	Yes	2.23 (1.03-4.83)*	2.99 (1.33-6.72)*
	No	1.18 (0.64-2.16)	1.04 (0.59-1.80)
Infection after biopsy	No biopsy	1.00	1.00
	Yes	2.72 (1.40-5.29)*	2.61 (1.03-6.65)*
	No	1.18 (0.70-1.98)	1.12 (0.65-1.91)
No complications after biopsy	No biopsy	1.00	
	Yes	2.15 (1.17-3.92)*	
	No	1.29 (0.77-2.19)	
TURP	Yes	0.85 (0.62-1.15)	0.63 (0.40-0.98)

‖weighted to assure representativeness for PCa survivors in the population.

*Significant category, if not all categories are significant.