Comorbidity and Primary Treatment for Localized Prostate Cancer: Data From CaPSURE™

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Purpose: The optimal approach for treating localized prostate cancer remains controversial, leading to a multifactorial decision making process. We characterized the extent to which the presence and number of comorbidities affects treatment for localized prostate cancer.

Materials and Methods: Data were abstracted from a longitudinal observational database of men with prostate cancer. A total of 5,149 men diagnosed with localized prostate cancer between 1995 and 2001 were included in this analysis if they had been treated with RP, external beam radiation, brachytherapy, hormonal therapy or surveillance. Comorbidity was assessed through a patient reported checklist of conditions. Multinomial logistic regression was used to determine the OR of the likelihood of receiving each type of therapy. The number of comorbidities and specific comorbidities in patients receiving RP were compared with comorbidities in patients receiving other treatment.

Results: The adjusted OR showed a dose response between the number of comorbidities and an increasing probability of any nonRP treatment. In addition, heart disease, stroke or another urinary condition were found to be associated with treatment.

Conclusions: Patient comorbidities affect decision making regarding treatment for localized prostate cancer. Urologists and other physicians treating this disease appear to evaluate patient comorbidities when selecting treatment options.

Key Words: prostate, comorbidity, prostatic neoplasms, practice guidelines

The introduction of PSA testing in 1988 along with increased public awareness led to an increase in the prostate cancer incidence during the 1990s and to diagnosis at earlier stages than 20 years ago.[1] Despite the recent advances made in the diagnosis and staging of prostate cancer treatment for this condition remains controversial.[1,2] It is widely accepted that aggressive therapy such as surgery is most appropriate in men with at least 10 years of life expectancy. Because prostate cancer often presents at an early stage and may have a protracted natural history, men with less than 10 years of life expectancy are more likely to die of causes other than prostate cancer and they are expected to undergo more conservative or palliative treatment, such as hormonal therapy or watchful waiting.

Growing awareness of the importance of concomitant illnesses has led to research on the effects of comorbidities on patients with breast, oral, lung and colon cancer as well as associations with the effectiveness of surgical procedures, such as total hip replacement.[3–5] In a recent article the American Cancer Society requested oncologists to be more aware of the effects of comorbid illnesses in patients with cancer and called for more research in this area. The society specifically called for further understanding of how comorbid conditions influence clinical decisions in elderly patients with cancer.[6]

Many studies in the last decade have shown a clear association between patient comorbidity and all cause mortality in men with prostate cancer.[7–9] These studies showed that comorbid illnesses can decrease survival rates in men treated with radiation, RP or HT. Comorbid illnesses can directly affect survival in men undergoing treatment for prostate cancer and comorbidities might potentially alter therapies, thereby, having an indirect effect on prognosis.[4] Because comorbid conditions can affect life expectancy and patient ability to benefit from treatment, it is reasonable to inquire whether the presence and number of comorbid conditions affect treatment decisions in patients with prostate cancer.

METHODS

CaPSURE™ is a longitudinal, observational disease registry of men with biopsy proven prostate cancer. Established in 1995, CaPSURE™ has enrolled subjects from 40 urology practices nationwide regardless of age, disease severity or treatments received. There is no treatment protocol for CaPSURE™. Rather, patients are treated according to the usual practices of their physicians. Additional details of the project methodology have been reported previously.[10]

Submitted for publication March 4, 2005.

CaPSURE™ is supported by TAP Pharmaceutical Products, Inc., Lake Forest, Illinois and by Specialized Program of Research Excellence (SPORE) Grant p50 c89520 to University of California-San Francisco from the National Institutes of Health/National Cancer Institute.

* Financial interest and/or other relationship with TAP Pharmaceutical Products.

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‡ Financial interest and/or other relationship with TAP Pharmaceutical Products and Imetrikon.

TABLE 1. *Comorbid conditions in 5,149 men with localized prostate cancer*

	No. Pts (%)
Prespecified:	
Hypertension	2245 (44)
Arthritis, rheumatic diseases, musculoskeletal conditions	2018 (39)
Heart disease	1121 (22)
Urinary condition	817 (16)
Stomach intestinal gastrointestinal disease	762 (15)
Ca other than prostate Ca	681 (13)
Diabetes	533 (10)
Lung disease	478 (9)
Stroke, neurological condition	346 (7)
Kidney disease	273 (5)
Blood disease	99 (2)
Patient added:	
Chronic infectious diseases, including HIV/AIDS	67 (1)
Blindness or other eye conditions	68 (1)
Internal organ disease (liver, pancreas, spleen, etc)	63 (1)
Ear, nose & throat conditions	50 (1)
Endocrine disorders	39 (0.8)
Mental health conditions	28 (0.5)

Data collection. The outcome variable, primary treatment, was collected from participating urologists. Study physicians also reported all clinical variables associated with diagnosis and staging (serum PSA, biopsy, Gleason grade and clinical T stage classified using the American Joint Committee on Cancer 2002 convention on tumor classification). We combined PSA, Gleason grade and T stage into a clinical risk variable. High risk was defined as PSA more than 20 ng/ml, Gleason sum greater than 7, primary Gleason 4-5 or clinical stage T3a. Intermediate risk was defined as PSA 10.1 to 20 ng/ml, Gleason sum 7, secondary Gleason 4-5 or clinical stage T2b-T2c. Low risk was defined as PSA 10 ng/ml or less and Gleason sum 2-6 with no 4-5 pattern and cT1c-T2a.

Information about comorbidities was collected from a self-administered questionnaire given to subjects at the time of enrollment. Subjects were asked about the presence of 11 prespecified conditions (table 1). Space was provided for write in text of other conditions and responses were reviewed and recoded as appropriate. Recoding of common write in responses led to the creation of 6 new categories of comorbid conditions (table 1). The number of comorbid conditions was summed over all 17 categories (prespecified plus new). In addition, we examined the 11 prespecified categories individually. Because of the skewed distribution of the number of comorbidities, we categorized this variable as 0, 1 or 2, 3 to 5 and greater than 5. Sociodemographic characteristics, such as patient age, race, education level, marital/relationship status, income, insurance type, and height and weight combined into body mass index in kg/m^2 were also reported on the patient questionnaire.

Analytic population. To be included in the current analysis subjects had to be diagnosed with localized disease between 1995 and 2003 to provide a contemporary cohort of patients. Localized disease was defined as clinical stage T3a or less with no evidence of lymph node involvement or other metastasis. Subjects must have completed a baseline questionnaire with self-reported comorbidity information. Additionally, patients received RP, BT, EBRT, medical or surgical HT, or WW as the primary treatment. Men who received EBRT with BT were classified in a separate category since they appeared different than patients receiving BT alone as primary treatment. Other combination therapy (RP plus hormones or radiation plus hormones) was included with the definitive treatment (RP or radiation). Cryosurgery was initially considered but it was dropped from analysis because it was only offered at 3 of the 40 study sites and fewer than 3% of patients underwent cryosurgery. As of January 2005, 11,583 men were enrolled in CaPSURE™ with 6,693 diagnosed between 1995 and 2003 with localized disease who received 1 defined primary treatment. The comorbidity section of the baseline questionnaire was completed by 5,149 of these men (77%) to form our analysis population.

Statistical analysis. Frequency tables and chi-square analysis were used in univariate analysis to examine associations between the number of comorbidities, primary treatment, and other sociodemographic and clinical study variables. Because the outcome variable of primary treatment is a 6 level categorical variable, we used multinomial logistic regression for statistical modeling with RP as the reference category. We included clinical and sociodemographic variables in a backward stepwise procedure with stay criteria of $p = 0.01$ while forcing in the number of comorbidities, study site and diagnosis year. Study site was included in all models to control for potential confounding due to site based practice patterns. We have previously observed in CaPSURE™ data that the variety of treatments for prostate cancer has changed significantly in the last decade.[11] Therefore, we included diagnosis year in all models. Because of the large number of patients in the analysis, we chose a low p value of 0.01 as our model stay criteria. Covariates that remained after the backward stepwise procedure were used to adjust the findings of all additional models. We also examined interactions between the number of comorbidities and clinical risk as well as the number of comorbidities and age to see if these impacted the primary treatment.

After examining the relationship between the number of comorbidities and primary treatment we examined the effects of the 11 prespecified comorbidities. We again used a backward stepwise model to identify the individual comorbidities associated with primary treatment. All 11 comorbid conditions were included as variables that could be removed in the backward stepwise procedure, while forcing in the group of covariates identified previously. A final model was constructed by including the 3 comorbidity variables that stayed in the model, a variable representing the number of other comorbidities, the clinical and sociodemographic covariates identified previously, study site and diagnosis year. Results are presented as the OR and 95% CI with p values reported. Results were considered statistically significant at $p < 0.05$. All analyses were performed using SAS, version 9 (SAS Institute, Cary, North Carolina).

RESULTS

The most common comorbidities were hypertension, arthritis and musculoskeletal conditions, heart disease, urinary conditions and gastrointestinal disease (table 1). Overall 18% or 913 of 5,149 men reported no comorbidities, while just more than 50% (2,720) reported 1 or 2, 28% (1,432)

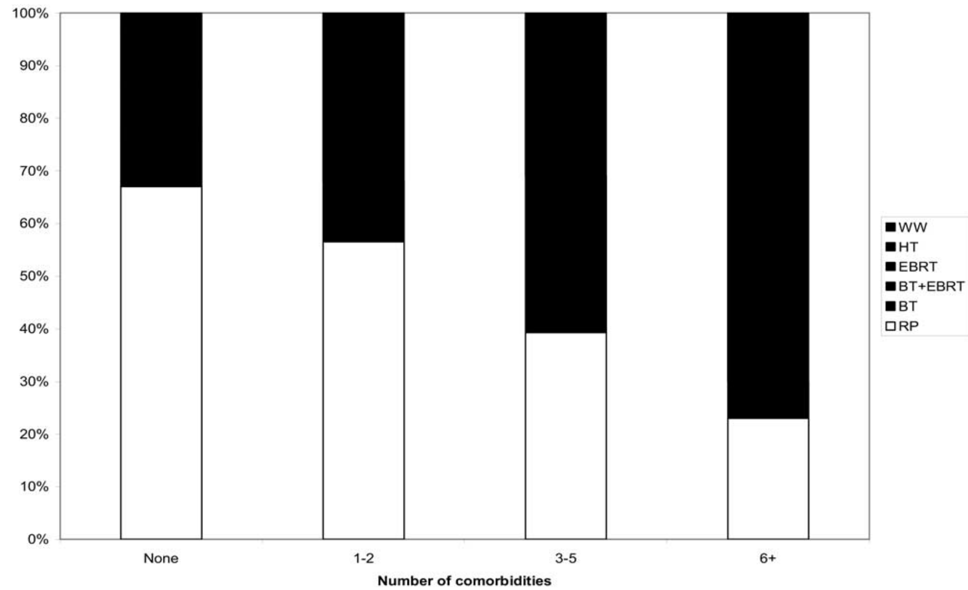


FIG. 1. Treatment type by number of comorbidities

reported 3 to 5 and 2% or 84 reported 6 or more comorbidities.

Men with comorbidities were older, more likely to be single and overweight, have lower incomes and less education, and be on Medicare or other nonprivate insurance than those without comorbid illnesses. There was no association between the number of comorbidities and ethnicity or clinical risk at presentation.

Most of the sample received definitive treatment, including RP in 53% (2,733 of 5,149 men), BT alone in 12% (595), BT and EBRT in 4% (195), and EBRT in 10% (540). In addition, 15% of the men (756) received primary HT and 6% (330) elected surveillance. Figure 1 shows the prevalence of each treatment type by the number of comorbidities. RP was the most common treatment in patients with no and 1 or 2 comorbidities. In patients with 3 or more comorbidities RP was much less common. At 6 or more comorbidities primary HT and surveillance comprised almost half of the treatment plans.

As expected, type of treatment also correlated closely with clinical risk at presentation (table 2). Men receiving RP, BT alone or WW were more likely to present at low clinical risk, while men receiving EBRT, BT and EBRT or primary HT were more likely to present at higher clinical risk. In addition, subjects receiving surgery were generally younger and better educated, had higher incomes, and were more likely to be in a relationship and have private insurance.

The adjusted OR showed a dose response between the number of comorbidities and an increasing probability of nonRP treatment while controlling for age, education, relationship status, body mass index, clinical risk, diagnosis year and study site (fig. 2). Compared to men with no comorbidity men with 1 or 2 comorbidities were 1.3 times more likely (95% CI 0.9 to 2.0) to receive HT over RP with the OR increasing to 2.6 (95% CI 1.7 to 3.8) in those with 3 to 5 comorbidities and increasing to 9.0 (95% CI 3.8 to 21.3) in men with 6 or more comorbidities. The odds of choosing WW over RP increased from 1.2 (95% CI 0.7 to 2.0) in men with 1 or 2 comorbidities to 5.2 (95% CI 1.8 to 15.1) in men with 6 or more morbidities. The OR for EBRT was similar at 1.3 (95% CI 0.9 to 1.9) for 1 or 2 comorbidities to 4.2 (95% CI 1.5 to 11.4) for 6 or more morbidities. The odds of receiving BT alone were not different from those of receiving RP based on the number of comorbidities.

Some men with more than 3 comorbidities underwent RP. However, even in men with 3 or more comorbidities those with a greater number of comorbidities were less likely to undergo RP. For example, men with 6 or greater comorbidities were half as likely to undergo RP as men with 3 to 5 comorbidities ($p < 0.01$). Differences in treatment were also evidenced when comparing men with 1 or 2 comorbidities to those with 3 to 5 ($p < 0.001$). However, we did not find any evidence of an interaction for the number of comorbidities with clinical risk or patient age ($p = 0.99$ and 0.61, respectively).

Three comorbidities were found to be independently associated with treatment choice even when controlling for the effect of the overall number of comorbidities, namely heart disease, stroke or neurological disease and other urinary conditions. Each of these comorbidities was associated with higher odds of receiving a nonsurgical treatment (table 3). Subjects with heart disease were consistently 2 to 3 times more likely to receive any treatment other than RP (all ORs $p < 0.05$). Similarly subjects with a previous stroke or other neurological problem were up to 2 times more likely to receive any other treatment. Subjects with other urinary conditions were most likely to receive HT over surgery (OR 1.5, 95% CI 1.1 to 2.0) or WW over surgery (OR 1.4, 95% CI 1.0 to 2.1). After considering these 3 comorbidities subjects with 3 or more other comorbidities were still almost twice as likely to receive HT as RP (OR 1.9, 95% CI 1.3 to 2.8).

DISCUSSION

In this study clinical decision making for localized prostate cancer treatment appears to be influenced by comorbidities

TABLE 2. *Socioeconomic and clinical patient characteristic by treatment for localized prostate cancer*

	No. RP (%)	No. BT (%)	No. BT + EBRT (%)	No. ERBT (%)	No. HT (%)	No. WW (%)
Comorbidities:						
0	615 (23)	78 (13)	21 (11)	82 (15)	84 (11)	33 (10)
1–2	1,537 (56)	313 (53)	106 (54)	278 (51)	335 (44)	151 (46)
3–5	562 (21)	198 (33)	62 (32)	168 (31)	307 (41)	135 (41)
Greater than 5	19 (1)	6 (1)	6 (3)	12 (2)	30 (4)	11 (3)
Age:						
Older than 60	1,032 (38)	80 (13)	22 (11)	27 (5)	35 (5)	12 (4)
60–64	702 (26)	78 (13)	26 (13)	51 (9)	53 (7)	16 (5)
65–69	685 (25)	168 (28)	42 (22)	113 (21)	106 (14)	41 (12)
70–74	276 (10)	153 (26)	57 (29)	187 (35)	178 (24)	82 (25)
75 or Older	38 (1)	116 (19)	48 (25)	162 (30)	384 (51)	179 (54)
Education:						
Less than high school	305 (11)	97 (17)	47 (24)	104 (20)	208 (28)	67 (21)
High school graduate	661 (25)	163 (28)	57 (30)	149 (29)	187 (25)	90 (28)
Some college	537 (20)	118 (20)	27 (14)	81 (16)	133 (18)	71 (22)
College graduate	1,179 (44)	200 (35)	61 (32)	185 (36)	208 (28)	91 (29)
In relationship:						
Yes	2,447 (94)	518 (90)	169 (89)	432 (87)	609 (84)	271 (85)
No	168 (6)	55 (10)	21 (11)	66 (13)	112 (16)	48 (15)
Income ($):						
Greater than 30,000	533 (22)	201 (39)	80 (45)	201 (45)	337 (53)	126 (48)
30,000–50,000	584 (35)	135 (27)	46 (26)	116 (26)	144 (22)	66 (25)
50,000–75,000	584 (24)	135 (27)	46 (26)	116 (26)	144 (22)	66 (25)
Greater than 75,000	786 (32)	87 (17)	26 (15)	66 (15)	72 (11)	39 (15)
Race:						
White	2,427 (89)	551 (93)	177 (91)	467 (87)	646 (86)	305 (93)
Black	211 (8)	19 (3)	13 (7)	61 (11)	86 (11)	17 (5)
Other	91 (3)	25 (4)	5 (3)	11 (2)	19 (3)	7 (2)
Body mass index:						
Obese	583 (22)	132 (23)	57 (30)	91 (18)	137 (19)	47 (15)
Overwt	1,348 (52)	290 (51)	86 (45)	254 (51)	332 (47)	147 (47)
Not overwt	662 (26)	150 (26)	49 (26)	151 (30)	244 (34)	119 (38)
Insurance:						
Medicare	858 (31)	332 (56)	118 (61)	392 (73)	543 (72)	243 (74)
Private	1,668 (61)	225 (38)	59 (30)	111 (21)	146 (19)	42 (13)
Other	207 (8)	38 (6)	18 (9)	37 (7)	67 (9)	45 (14)
Diagnosis yr:						
1995–1997	803 (29)	72 (12)	14 (7)	219 (41)	253 (33)	112 (34)
1998–2000	603 (22)	219 (37)	74 (38)	116 (21)	172 (23)	68 (21)
2001–2003	1,327 (49)	304 (51)	107 (55)	205 (38)	331 (44)	150 (45)
Clinical risk group:						
Low	1,190 (45)	349 (60)	26 (13)	136 (26)	177 (24)	168 (56)
Medium	1,027 (39)	174 (30)	96 (50)	201 (38)	212 (29)	87 (29)
High	435 (16)	54 (9)	71 (37)	195 (37)	344 (47)	45 (15)

Categories may not total due to missing values and percents may not sum to 100 due to rounding; all treatments p <0.01.

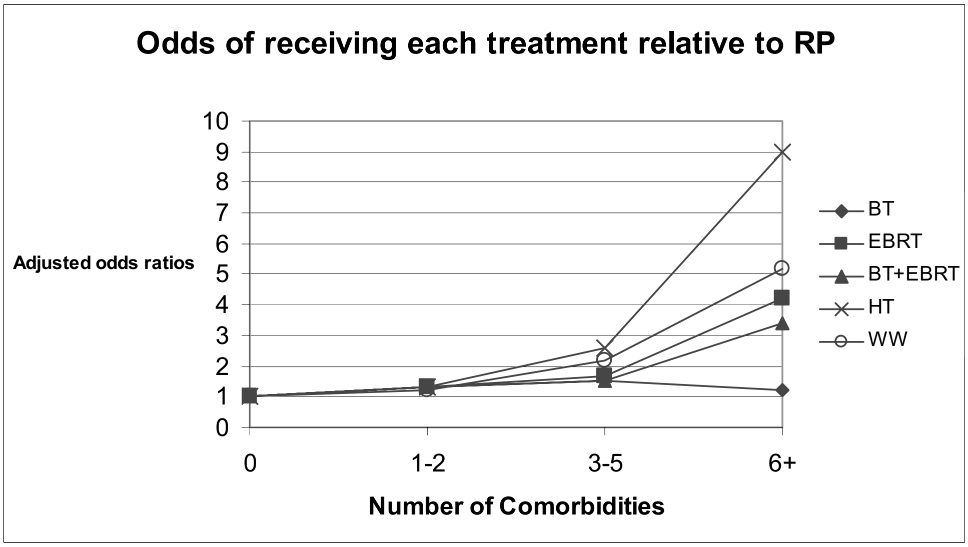
even when controlling for other clinical and demographic factors. These results along with those of 4 other studies[12–15] support the theory that urologists and others are recommending treatments that reflect the current belief that definitive therapy is most appropriate in patients with greater than 10 years of life expectancy and who are good surgical candidates.

However, 3 other studies showed that the number of comorbidities is not associated with treatment for prostate cancer.[16–18] Even when an association was found on bivariate analysis, as in the series of Yan et al,[16] the effect was entirely removed after age and race were controlled for. All studies suggested that other factors, namely age, disease stage and race, are so important in treatment planning that they completely eliminate the effect of comorbid illness. Our findings were also controlled for age and clinical disease characteristics, and yet comorbidity remained a strong predictor of treatment. Other factors, such as education, marital status and body mass, appeared to influence the treatment plan more than ethnicity, which was not retained as a significant covariate in our model. However, the analysis may not have had enough ethnic variation to assess this issue fully.

Similar to our methodology, 3 others groups collected comorbidity information directly from subjects via a self-administered questionnaire or though a telephone interview.[12,15,16] Other studies used inpatient medical records to determine comorbidity.[13,14,17,18] In these studies the number of comorbidities, especially less severe comorbidities, could have been under reported on inpatient discharge diagnoses.

Our study included data from 1995 to 2003, which is a more contemporary period than in previous studies. The 1990s saw an increased use of HT and BT as well as significant stage migration toward nonpalpable tumors.[11] The shift in patient characteristics as well as the increased number of treatment options may account for some discrepancy between prior findings and our findings.

Our analysis of specific comorbid conditions shows that heart disease, stroke or other neurological disease and other urinary conditions are associated with prostate cancer treatment. The biological plausibility of these results lends them legitimacy. A history of stroke or heart disease is associated with significant perioperative risk due to the decreased functionality of major organs. Thus, these 2 groups may be poor candidates for any type of surgery. In addition, the Ameri-



All results adjusted for: Study site, clinical risk, age, ethnicity, and relationship status
Note: RP = radical prostatectomy, BT = brachytherapy, EBRT = External beam radiation therapy, HT = hormonal therapy, WW = watchful waiting.

FIG. 2. OR of likelihood of receiving each treatment relative to RP

can Heart Association estimates that eliminating heart disease related mortality would increase average life expectancy in the United States by more than 7 years.[19] Finding that these patients are indeed more likely to forego RP in favor of any nonsurgical approach is a good confirmation that physicians are selecting appropriate patients for RP.

Only 1 other study was identified that looked at the effect of specific comorbidities on prostate cancer treatment. Hall et al reviewed inpatient medical records 5 years before prostate cancer diagnosis.[17] Their analysis identified cerebrovascular disease, other cancer or metastatic tumor and myocardial infarction as 3 conditions that were predictive of receiving radiation over RP. The results of this study lend weight to our finding that subjects who report having some form of heart disease or stroke are far less likely to undergo surgery.

Our use of patient reported data for comorbidity has strengths and weaknesses. Our instrument was not designed to capture severity and, therefore, a count of comorbidities may not be an estimate of the true comorbidity burden. Another limitation of using patient reported comorbidity information is the potential selection bias introduced by nonresponders, although 77% of our target analysis population completed the comorbidity reporting.

The different geographic locations and treatment settings of participating urologists increase the generalizability of our results. Size was a particular strength in this analysis since it allowed us to make a detailed analysis of specific comorbidities. We were also in a unique position to study 6 distinct treatments individually rather than grouping together aggressive vs nonaggressive therapy or including EBRT and BT under the general category of radiation. We saw different patterns emerge for the effect of comorbidity on these 2 types of radiation.

CONCLUSIONS

Patient comorbidity continues to affect decision making regarding treatment for localized prostate cancer independent of patient age and clinical disease characteristics. Urologists and other physicians treating this disease should continue to evaluate patient comorbidity to determine appropriate treatment options. Specific comorbidities and overall burden of other diseases are important to consider.

TABLE 3. *Adjusted OR of receiving any treatment relative to RP for specific comorbidities*

	OR (95% CI)				
	BT vs RP	EBRT vs RP	BT + EBRT vs RP	HT vs RP	WW vs RP
Heart disease	2.3 (1.7–3.0)	2.4 (1.8–3.1)	2.3 (1.6–3.4)	2.4 (1.9–3.1)	3.0 (2.2–4.2)
Stroke	1.5 (0.9–2.4)	1.8 (1.1–2.9)	1.3 (0.7–2.5)	2.1 (1.4–3.3)	1.2 (0.7–2.2)
Urinary Conditions	0.7 (0.5–1.0)	1.2 (0.9–1.7)	1.2 (0.8–1.9)	1.5 (1.1–2.0)	1.4 (1.0–2.1)
Other comorbidities:					
None	1.0	1.0	1.0	1.0	1.0
1–2	1.0 (0.8–1.4)	1.0 (0.7–1.3)	0.8 (0.5–1.3)	1.2 (0.8–1.6)	1.0 (0.7–1.6)
3	1.1 (0.7–1.6)	1.1 (0.7–1.6)	1.0 (0.6–1.8)	1.9 (1.3–2.8)	1.6 (0.9–2.7)

All results adjusted for study site, diagnosis year, clinical risk, age, education, relationship status and body mass index.

Abbreviations and Acronyms

BT	=	brachytherapy
EBRT	=	external beam radiation therapy
HT	=	hormonal therapy
PSA	=	prostate specific antigen
RP	=	radical prostatectomy
WW	=	watchful waiting

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