ORIGINAL RESEARCH

Comorbidities, Treatment and Ensuing Survival in Men with Prostate Cancer

Karim Chamie, MD, MSHS^{1,2}, Timothy J. Daskivich, MD^{1,3}, Lorna Kwan, MPH², Jessica Labo, BA¹, Atreya Dash, MD^{4,5}, Sheldon Greenfield, MD^{6,7}, and Mark S. Litwin, MD, MPH^{1,2,8}

¹UCLA Department of Urology, Health Services Research Group, Los Angeles, California, USA; ²Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, CA, USA; ³Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, USA; ⁴Veterans Affairs Long Beach Healthcare System, Long Beach, CA, USA; ⁵Department of Urology, University of California, Irvine, Irvine, CA, USA; ⁶Department of Medicine, University of California, Irvine, Irvine, CA, USA; ⁷Health Policy Research Institute, University of California, Irvine, Irvine, CA, USA; ⁸Department of Health Services, School of Public Health, UCLA, Los Angeles, CA, USA.

BACKGROUND: Comorbidity is poorly integrated into prostate cancer decision making.

OBJECTIVE: We sought to characterize treatment type and subsequent survival for men with no more than a single comorbid condition.

DESIGN AND PARTICIPANTS: We conducted a retrospective study of 1,031 veterans with non-metastatic prostate cancer diagnosed in 1997–2004 at the Greater Los Angeles and Long Beach Veterans Affairs Medical Centers and followed until 2010. We used multivariate analyses to determine probabilities and relative risks of undergoing treatment for each health state and competing-risks regression analyses to model non-prostate cancer mortality.

RESULTS: Compared with subjects without any comorbid conditions, only men with moderate-severe chronic obstructive pulmonary disease were less likely to receive definitive treatment for their prostate cancer (RR 0.74; 95% CI 0.44–0.99). Men with all other individual comorbidities were equally likely as men without comorbidity to receive definitive treatment. Compared with men without any comorbidities, a higher hazard rate for non-prostate cancer mortality was identified among men with diabetes without end-organ damage (HR 2.32; 95% CI 1.32–4.08), peripheral vascular disease (HR 2.77; 95% CI 1.14–6.73), moderate-severe chronic obstructive pulmonary disease (HR 5.46; 95% CI 2.68–11.12), diabetes with end-organ damage (HR 4.27; 95% CI 1.64–11.10), those in need of a mobility device (HR 3.29; 95% CI 1.87–5.80), and men with history of alcoholism (HR 1.77; 95% CI 1.07–2.93).

CONCLUSION: Men with comorbid conditions and health states that portend poor prognoses are nonetheless aggressively treated for their prostate cancer. Advancing age modulates this effect.

KEY WORDS: prostatic neoplasms; comorbidity; outcome assessment; survival; treatment mismatch.

J Gen Intern Med 27(5):492–9

DOI: 10.1007/s11606-011-1869-4

© Society of General Internal Medicine 2011

INTRODUCTION

Despite a 5-year relative survival rate that approaches 100% for localized prostate cancer, men face a daunting task in deciding whether to pursue aggressive treatment.¹ Level I evidence emphasizes that the disease-specific survival benefit is not realized until ten years after treatment.² The impetus behind definitive treatment hinges on whether the patient is expected to live beyond ten years. Therefore, the elderly or those with significant comorbidities who undergo aggressive treatment do not enjoy the survival advantage but instead suffer post-treatment toxicities.^{3–5}

The Charlson Comorbidity Index offers an empirical method to incorporate an individual's comorbidities to estimate the risk of mortality.⁶ The Charlson Comorbidity Index, while a strong predictor of overall survival, was originally designed to predict one-year mortality following in-patient hospitalization. Hence, it is not surprising that the adjustment weights may not correlate with a contemporary cohort managed in the outpatient setting. Moreover, it is primarily used as an adjustment tool for case mix rather than clinical decision making. For these reasons, the impact of specific comorbidities on survival remains poorly integrated in prostate cancer treatment decision making.

Against this backdrop, we sought to determine the probability of prostate cancer treatment and attendant survival among men with a single comorbid condition. We measured the probability and the relative risk of undergoing prostate cancer treatment in the presence of each comorbid condition, while adjusting for patient and tumor characteristics. We then calculated survival rates using competing-risks regression analysis to characterize the impact of comorbidity on non-prostate cancer mortality. Our hypothesis was that men are

Received April 27, 2011

Revised July 29, 2011

Accepted August 25, 2011

Published online September 21, 2011

being aggressively treated for prostate cancer, despite the poor prognosis associated with their comorbid conditions.

METHODS

Data Sources

We used the California Cancer Registry to identify men newly diagnosed with prostate cancer at the Greater Los Angeles and Long Beach Veterans Affairs (VA) Medical Centers in 1997–2004. We reviewed medical records to determine age, race, tumor characteristics, body mass index (BMI), type of primary treatment, comorbidities at diagnosis, need for a mobility device, tobacco use and history of alcoholism. We excluded men with no prostate cancer diagnosis ($N=40$), histology other than adenocarcinoma ($N=46$), incidental diagnosis at radical cystectomy ($N=25$), insufficient data to determine sociodemographic, comorbidities, tumor-risk strata or follow-up information ($N=206$), metastatic disease ($N=115$), more than one listed comorbid condition ($N=265$), and unknown BMI ($N=186$). The final analytic sample was 1,031 subjects. The Institutional Review Boards at UCLA and the two VA sites granted approval.

Study Variables

Comorbidity. We utilized the Charlson Comorbidity Index to generate our list of independent comorbid conditions.⁶ We collected comorbidities at diagnosis by review of the interdisciplinary medical record. Comorbidities had to have been present at the time of the prostate cancer treatment decision. In order to avoid the effects from two or more comorbid conditions on the decision to pursue definitive treatment and attendant survival, we excluded subjects with more than one comorbid condition. Hence, the comorbidities are mutually exclusive and this allowed us to compare a single comorbid condition with no comorbidities in the predictive probability and survival models.

Additional Patient Characteristics. From the medical record, we ascertained additional patient characteristics such as age at diagnosis, race/ethnicity, BMI, utilization of a mobility device, history of alcoholism and tobacco use at the time of diagnosis. A mobility device was defined as a wheelchair, walker, cane or crutch. We also included the VA site of diagnosis.

Tumor Risk. Tumors were risk-stratified using the widely accepted D'Amico criteria, which utilize PSA, Gleason Score, and clinical stage at diagnosis to predict risk of progression, overall mortality, and cancer-specific mortality. Tumors are classified as low- (PSA <10, Gleason score ≤ 6 and clinical stage $\leq cT2a$), intermediate- (PSA 10–19.9, Gleason score 7 or clinical stage $cT2b$), or high-risk (PSA ≥ 20 , Gleason score ≥ 8 or clinical stage $\geq cT2c$).^{7,8}

Treatment Type. The dependent variable for our analysis was receipt of treatment or not, where treatment was defined as radical prostatectomy or radiation therapy (external beam radiotherapy or brachytherapy). Patients who underwent watchful waiting, immediate or delayed androgen

deprivation therapy were classified as not receiving treatment.

We also performed the analysis with treatment being defined as radical prostatectomy only, while patients who underwent radiation therapy, brachytherapy, watchful waiting, immediate or delayed androgen deprivation therapy were classified as not receiving treatment.

Moreover, we performed a sensitivity analysis with treatment defined as surgery, brachytherapy, radiation therapy or immediate hormone therapy to ascertain the treatment rate as it pertains to men with high-risk disease.

Mortality. Survival was measured from date of diagnosis until date of death. We determined date of death using the medical record and the Social Security Death Index. Cause of death was determined using the medical record by the following algorithm. Men were considered to have died from prostate cancer based on: enrollment in hospice or palliative care for prostate cancer; advancing PSA despite secondary hormonal therapy or chemotherapy; or death as a sequela of metastatic disease (bony fracture or organ failure related to metastasis). Non-prostate cancer mortality was defined as death from other causes as noted in the medical record. If cause of death could not be determined from the medical record, subjects were considered to have died from other causes if: PSA was stable five years after local treatment; PSA was stable one year prior to death after local treatment for D'Amico intermediate/high-risk disease or two years prior to death for low-risk disease; PSA was stable six months prior to death while on hormonal therapy for locally advanced or recurrent disease; or if primary hormonal therapy, secondary hormonal therapy, or chemotherapy was not initiated within six months prior to death for locally advanced or recurrent disease.

Statistical Analysis

We first compared clinical and demographic characteristics of our population across treatment type using Chi-square or Fisher's exact tests. For the multivariate model, we restricted our cohort to conditions with at least 20 subjects, yielding: no comorbid condition, cerebrovascular disease (CVD), mild chronic obstructive pulmonary disease (COPD), moderate–severe COPD, diabetes without end-organ damage, mild liver disease, myocardial infarction (MI), peptic ulcer disease (PUD), peripheral vascular disease (PVD), diabetes with end-organ damage and prior malignancy. Since treatment was not a rare event, odds ratios overstate the estimate; hence, we generated multivariate predictive probabilities and relative risks of undergoing treatment while adjusting for patient and tumor characteristics by using the logit command. Confidence intervals (95% CI) were generated by bootstrapping with 1,000 repetitions using a bias-corrected approach. Our independent variables included patient (age, race, BMI, comorbid condition, mobility device, history of alcoholism, tobacco use and VA site) and tumor (D'Amico risk) characteristics. Our dependent variable was defined as undergoing treatment or not.

We then measured the equality of survival functions for each independent variable with differences reported as log-

Table 1. Summary Statistics of Our Cohort Stratified by Receipt of Definitive Treatment

Variables	No Treatment		Treatment		p-Value
	N=327	%	N=704	%	
Comorbidity (Charlson Score)					0.003
None (0)	154	27.9%	397	72.1%	
Diabetes without end-organ damage (1)	39	32.8%	80	67.2%	
Connective tissue disease (1)	5	71.4%	2	28.6%	
PUD (1)	5	23.8%	16	76.2%	
Dementia (1)	9	64.3%	5	35.7%	
Mild liver disease (1)	4	13.3%	27	86.7%	
Mild COPD (1)	27	31.0%	60	69.0%	
Moderate-severe COPD (1)	12	46.2%	14	53.8%	
MI (1)	21	43.8%	26	56.2%	
Congestive Heart Failure (1)	3	27.3%	8	72.7%	
PVD (1)	6	30.0%	14	70.0%	
CVD (1)	15	40.5%	22	59.5%	
Prior malignancy (2)	13	56.5%	10	43.5%	
Lymphoma/Leukemia (2)	1	25.0%	3	75.0%	
Diabetes with end-organ damage (2)	8	40.0%	12	60.0%	
Moderate renal disease (2)	1	100%	0	0%	
Hemiplegia (2)	0	0%	1	100%	
Moderate-severe liver disease (3)	2	66.7%	1	33.3%	
Metastatic cancer (6)	1	50.0%	1	50.0%	
HIV/AIDS (6)	1	16.7%	5	83.3%	
Mobility device					0.001
No	309	30.9%	692	69.1%	
Yes	18	60.0%	12	40.0%	
History of alcoholism					0.01
No	292	33.2%	588	66.8%	
Yes	35	23.2%	116	76.8%	
Current smoker					0.001
No	271	34.5%	515	65.5%	
Yes	56	22.9%	189	77.1%	
Age groups					<0.001
<56	14	11.7%	106	88.3%	
56–65	66	16.3%	339	83.7%	
66–75	126	36.4%	220	63.6%	
>75	121	75.6%	39	24.4%	
Race/Ethnicity					0.25
White	137	30.6%	311	69.4%	
Black	115	29.9%	269	70.1%	
Hispanic	32	37.2%	54	62.8%	
Other	43	38.1%	70	61.9%	
D'Amico tumor risk					<0.001
Low	97	26.5%	269	73.5%	
Intermediate	96	27.6%	252	72.4%	
High	120	41.7%	168	58.3%	
BMI					0.06
<25	84	38.4%	135	61.6%	
25–29.9	137	30.6%	310	69.4%	
30–34.9	81	30.9%	181	69.1%	
≥35	25	24.3%	78	75.7%	
VA Site					0.89
Greater LA	221	31.9%	471	68.1%	
Long Beach	106	31.3%	233	68.7%	
Vital Status					<0.001
Alive	201	25.4%	591	74.6%	
Prostate death	22	71.0%	9	29.0%	
Other death	104	50.0%	104	50.0%	

rank test. While the log-rank test refers to the entire history, we report 5-year and 10-year survival for the sake of brevity. We utilized a maximum likelihood, competing-risks regression model as described by Fine and Gray.⁹ Competing-risks regression analysis was performed to characterize the risks of non-prostate cancer mortality across comorbid conditions. We defined failure as non-prostate cancer mortality and the competing event as prostate cancer-specific mortality. Estimates are reported as sub-hazard ratios (HR) with corresponding 95% confidence intervals. Post-estimation non-prostate cancer mortality curves were generated for statistically significant variables from the competing-risks regression analyses.

Table 2. Life Table and Log-rank Test with Depiction of 5- and 10-year Survival Rates

Variables (sample size)	5-Year Survival Rate	10-Year Survival Rate	Log-Rank
Comorbidity			<0.001
None (551)	0.88 (0.85–0.90)	0.75 (0.70–0.79)	
CVD (37)	0.77 (0.59–0.88)	0.53 (0.31–0.72)	
Mild COPD (87)	0.87 (0.77–0.93)	0.76 (0.60–0.86)	
Moderate-severe COPD (26)	0.50 (0.31–0.67)	0.12 (0.02–0.32)	
Diabetes without end-organ damage (119)	0.79 (0.71–0.86)	0.57 (0.41–0.70)	
Mild liver disease (31)	0.90 (0.73–0.97)	0.63 (0.26–0.85)	
MI (47)	0.83 (0.66–0.92)	0.68 (0.39–0.85)	
PUD (20)	0.68 (0.42–0.84)	0.53 (0.20–0.78)	
PVD (20)	0.65 (0.40–0.81)	0.53 (0.24–0.75)	
Diabetes with end-organ damage (20)	0.57 (0.32–0.75)	0.36 (0.12–0.61)	
Prior malignancy (23)	0.73 (0.49–0.87)	0.60 (0.34–0.78)	
Mobility device			<0.001
No (952)	0.84 (0.81–0.86)	0.69 (0.65–0.73)	
Yes (29)	0.57 (0.37–0.73)	0.17 (0.04–0.38)	
History of alcoholism			0.005
No (836)	0.84 (0.81–0.86)	0.69 (0.64–0.73)	
Yes (145)	0.78 (0.70–0.84)	0.56 (0.44–0.66)	
Current smoker			0.83
No (744)	0.83 (0.80–0.86)	0.69 (0.64–0.73)	
Yes (237)	0.82 (0.77–0.87)	0.63 (0.54–0.71)	
Age groups			<0.001
<56 (114)	0.88 (0.81–0.93)	0.79 (0.66–0.87)	
56–65 (393)	0.89 (0.86–0.92)	0.76 (0.69–0.82)	
66–75 (319)	0.83 (0.78–0.87)	0.64 (0.57–0.70)	
>75 (155)	0.64 (0.55–0.71)	0.43 (0.32–0.54)	
Race/Ethnicity			0.70
White (441)	0.82 (0.78–0.85)	0.65 (0.58–0.71)	
Black (366)	0.84 (0.80–0.88)	0.68 (0.61–0.73)	
Hispanic (65)	0.87 (0.77–0.93)	0.72 (0.57–0.83)	
Other (109)	0.82 (0.73–0.88)	0.78 (0.67–0.85)	
D'Amico tumor risk			<0.001
Low (361)	0.87 (0.83–0.90)	0.76 (0.69–0.81)	
Intermediate (335)	0.87 (0.83–0.90)	0.68 (0.59–0.75)	
High (285)	0.74 (0.69–0.79)	0.57 (0.49–0.64)	
BMI			0.002
<25 (214)	0.80 (0.72–0.85)	0.60 (0.49–0.70)	
25–29.9 (424)	0.85 (0.80–0.89)	0.71 (0.62–0.78)	
30–34.9 (243)	0.87 (0.81–0.92)	0.71 (0.59–0.81)	
>35 (100)	0.81 (0.68–0.89)	0.56 (0.20–0.81)	
VA Site			0.22
Greater LA (655)	0.84 (0.81–0.87)	0.68 (0.63–0.73)	
Long Beach (326)	0.82 (0.78–0.85)	0.66 (0.59–0.71)	

While competing-risks regression analysis does not have a goodness-of-fit statistic, we utilized the Cox model as a proxy. We tested goodness-of-fit using “log-log” plots and Hosmer and Lemeshow analysis.¹⁰ The model fit the data adequately. We used $p < 0.05$ to denote statistical significance, and all tests were two-sided. Statistical analyses were performed in STATA 11.1 (College Station, TX).

RESULTS

A plurality of our cohort was 66–75 years of age White, without comorbidity, overweight, and diagnosed with D’Amico low-risk cancer. On univariate analysis (Table 1), men with connective tissue disease, dementia, moderate-severe COPD and prior malignancy ($p = 0.003$), mobility device ($p = 0.001$), advancing age ($p < 0.001$) and D’Amico

high-risk prostate cancer ($p < 0.001$) were less likely to undergo definitive treatment for their prostate cancer. Men with history of alcoholism ($p = 0.01$) and current smokers ($p = 0.001$) were more likely to undergo definitive treatment. Although not quite statistically significant, there was a trend towards a higher incidence of definitive treatment among morbidly obese men when compared with those of normal weight ($p = 0.06$).

We determined the overall survival difference with corresponding 5-year and 10-year survival rates and log-rank test for each variable (Table 2). The respective 5-year and 10-year survival for those without any comorbid conditions were 88% and 75%; men with moderate-severe COPD were 50% and 12%; diabetes with end-organ damage were 57% and 36%; those in need of a mobility device were 57% and 17%; and those age > 75 had a 64% and 43%.

In Table 3, we measured probability and corresponding relative risks of undergoing definitive treatment (surgery or radiation). When compared with men without comorbidities, only

Table 3. Multivariate Predicted Probability and Relative Risk of Undergoing Treatment

Variables	Surgery or Radiation		Surgery Only	
	Probabilities (95%)	RR (95% CI)	Probabilities (95% CI)	RR (95% CI)
Comorbidity (Charlson score)				
None (0)	0.68 (0.64, 0.70)	Referent	0.39 (0.34, 0.42)	Referent
CVD (1)	0.69 (0.47, 0.81)	1.01 (0.76, 1.20)	0.24 (0.07, 0.39)	0.60 (0.21, 1.00)
Mild COPD (1)	0.64 (0.51, 0.73)	0.94 (0.78, 1.10)	0.34 (0.22, 0.43)	0.87 (0.62, 1.15)
Moderate-severe COPD (1)	0.50 (0.29, 0.66)	0.74 (0.44, 0.99)	0.17 (0.05, 0.32)	0.43 (0.12, 0.83)
Diabetes without end-organ damage (1)	0.69 (0.61, 0.74)	1.01 (0.91, 1.13)	0.38 (0.27, 0.45)	0.96 (0.73, 1.16)
Mild liver disease (1)	0.85 (0.74, 0.92)	1.25 (1.14, 1.38)	0.42 (0.23, 0.59)	1.06 (0.64, 1.55)
MI (1)	0.67 (0.47, 0.77)	0.98 (0.78, 1.15)	0.26 (0.08, 0.56)	0.65 (0.27, 1.06)
PUD (1)	0.68 (0.46, 0.82)	0.99 (0.73, 1.23)	0.43 (0.21, 0.64)	1.10 (0.58, 1.65)
PVD (1)	0.79 (0.58, 0.92)	1.15 (0.89, 1.37)	0.35 (0.14, 0.59)	0.90 (0.38, 1.51)
Diabetes with end-organ damage (2)	0.66 (0.35, 0.83)	0.97 (0.60, 1.22)	0.31 (0.05, 0.56)	0.78 (0.21, 1.44)
Prior malignancy (2)	0.52 (0.26, 0.73)	0.77 (0.42, 1.09)	0.29 (0.12, 0.49)	0.75 (0.33, 1.27)
Mobility device				
No	0.70 (0.66–0.72)	Referent	0.38 (0.35, 0.41)	Referent
Yes	0.57 (0.36, 0.73)	0.82 (0.52, 1.04)	0.40 (0.20, 0.55)	1.05 (0.52, 1.48)
History of alcoholism				
No	0.68 (0.65–0.71)	Referent	0.38 (0.34, 0.41)	Referent
Yes	0.77 (0.69, 0.83)	1.13 (1.01, 1.24)	0.40 (0.32, 0.47)	1.05 (0.84, 1.26)
Current smoker				
No	0.69 (0.65–0.72)	Referent	0.36 (0.32, 0.39)	Referent
Yes	0.72 (0.65, 0.77)	1.04 (0.95, 1.15)	0.45 (0.39, 0.51)	1.25 (1.07, 1.50)
Age group				
<56	0.86 (0.77–0.92)	Referent	0.58 (0.47, 0.67)	Referent
56–65	0.83 (0.78, 0.86)	0.96 (0.88, 1.07)	0.52 (0.48, 0.58)	0.91 (0.75, 1.15)
66–75	0.67 (0.61, 0.72)	0.78 (0.70, 0.88)	0.28 (0.24, 0.34)	0.49 (0.38, 0.65)
>75	0.27 (0.20, 0.36)	0.31 (0.22, 0.43)	0.04 (0.02, 0.09)	0.07 (0.03, 0.17)
Race/Ethnicity				
White	0.71 (0.66–0.74)	Referent	0.38 (0.34, 0.42)	Referent
Black	0.68 (0.63, 0.72)	0.96 (0.88, 1.05)	0.37 (0.32, 0.42)	0.97 (0.82, 1.16)
Hispanic	0.69 (0.58, 0.77)	0.97 (0.82, 1.11)	0.43 (0.33, 0.54)	1.14 (0.87, 1.47)
Other	0.69 (0.60, 0.77)	0.98 (0.85, 1.11)	0.40 (0.31, 0.50)	1.06 (0.81, 1.35)
D’Amico tumor risk				
Low	0.70 (0.65–0.74)	Referent	0.40 (0.35, 0.44)	Referent
Intermediate	0.75 (0.71, 0.79)	1.08 (0.99, 1.17)	0.44 (0.38, 0.49)	1.10 (0.93, 1.29)
High	0.61 (0.55, 0.66)	0.87 (0.78, 0.97)	0.29 (0.24, 0.34)	0.73 (0.57, 0.89)
BMI				
<25	0.68 (0.61–0.74)	Referent	0.38 (0.31, 0.45)	Referent
25–29.9	0.70 (0.65, 0.74)	1.03 (0.92, 1.15)	0.40 (0.36, 0.45)	1.04 (0.83, 1.29)
30–34.9	0.69 (0.62, 0.74)	1.01 (0.89, 1.15)	0.38 (0.31, 0.44)	0.98 (0.75, 1.25)
≥ 35	0.73 (0.65, 0.82)	1.08 (0.93, 1.27)	0.31 (0.23, 0.39)	0.81 (0.57, 1.13)
VA Site				
Greater LA	0.68 (0.64–0.71)	Referent	0.35 (0.31, 0.39)	Referent
Long Beach	0.72 (0.65, 0.76)	1.05 (0.96, 1.14)	0.44 (0.38, 0.50)	1.25 (1.05, 1.47)

men with a diagnosis of moderate-severe COPD (RR 0.74; 95% CI 0.44–0.99) had a lower risk of undergoing definitive treatment. Moreover, this reduced risk was driven by the lower rate of radical prostatectomy (RR 0.43; 95% CI 0.12–0.83). In fact, moderate-severe COPD had a similar rate of undergoing radiotherapy as men without any comorbid condition (33% vs. 29%). Those with advancing age (66–75 and >75) or D'Amico high-risk prostate cancer were less likely to undergo definitive treatment or surgery than younger men or those with low-risk disease. Sensitivity analysis demonstrated that men with high-risk disease were more likely than men with low-risk disease to have been treated if we defined treatment as radiation, surgery, or immediate androgen deprivation (probability of 90% vs. 73%; RR 1.23; 95% CI 1.14–1.33). Additionally, men with mild liver disease and those with prior history of alcoholism had a higher probability of undergoing definitive treatment than men with no comorbid conditions and no prior history of alcoholism, respectively.

Competing-risks regression analysis (Table 4) demonstrated that men with moderate-severe COPD (HR 5.46; 95% CI 2.68–11.12), diabetes without end-organ damage (HR 2.32;

1.32–4.08), PVD (HR 2.77; 95% CI 1.14–6.73) and diabetes with end-organ damage (HR 4.27; 95% CI 1.64–11.10) had a higher hazard for mortality than men without any comorbid conditions. Men with a mobility device (HR 3.29; 95% CI 1.87–5.80), those with a history of alcoholism (HR 1.77; 95% CI 1.07–2.93), and of advancing age (age 66–75: HR 2.43; 95% CI 1.15–2.17 and age >75 HR 5.49; 95% CI 2.32–12.98) had a higher hazard of non-prostate cancer mortality than men without a mobility device, no prior history of alcoholism, and men <56 years of age, respectively.

Competing-risk regression analyses for non-prostate cancer mortality were generated (Fig. 1a–d). As an aid, we have included a marker (black dot) to represent 10-year 50% mortality. For age, the 10-year probability of non-prostate cancer mortality for a 55, 65 and 75 year old were 10%, 21% and 42%, respectively (p-value <0.001) (Fig. 1a). For comorbidity, the 10-year probability of non-prostate cancer mortality were 16% for men without any comorbid conditions; 35% for diabetes without end-organ damage; 49% for PVD; 50% for diabetes with end-organ damage; and 65% for moderate-severe COPD (Fig. 1b). With regard to mobility device, the 10-year mortality rate was 21% for men without a mobility device, and 55% for those in need of the mobility device (Fig. 1c). As to history of alcoholism, the mortality rates were 20% for those without history of alcoholism, and 36% for those with a positive history of alcoholism (Fig. 1d).

In Figure 2, we stratified the four statistically significant comorbidities into three age groups (age 55, 65, and 75). A 10-year mortality rate that exceeds 50% was found among men 65 years of age or older with moderate-severe COPD ($\geq 58\%$) or diabetes with end-organ damage ($\geq 54\%$), and 75-year old men with PVD ($\geq 70\%$) or diabetes without end-organ damage ($\geq 61\%$).

DISCUSSION

In addition to age, diminution in the aggressive treatment rate occurred only with men with moderate-severe COPD. Men with other single comorbidities, in need of mobility device, with history of alcoholism, current smokers or those who are morbidly obese received aggressive treatment for their prostate cancer at similar rates as those without any comorbid conditions or corresponding prognostic factors. We suspect that single comorbid conditions often give patients and their treating physicians a false sense of prolonged life expectancy. Hence, patients and physicians need a physical cue to associate single comorbidity with death, such as dyspnea at rest or oxygen tank (as in the case in moderate-severe COPD) or neurologic deficit, as demonstrated through a sensitivity analysis including multiple comorbidities (hemiplegia: RR 0.63, data not shown). Age 75, while not necessarily a proxy for impending death (10-year mortality of 42%), serves as a very strong cue (RR 0.31). In the competing-risk regression model, men with PVD, diabetes with end-organ damage, moderate-severe COPD, and those in need of a mobility device, had higher 10-year non-prostate mortality rates than an age of 75. If the benchmark for treatment should be a 10-year mortality rate that

Table 4. Competing-risks Regression Analysis with Failure Defined as Non-prostate Cancer-related Mortality and the Competing Risk as Prostate Cancer-specific Mortality

Variables	HR	95% CI	p-value
Comorbidity (Charlson Score)	Referent=None		
CVD (1)	0.96	(0.33, 2.82)	0.94
Mild COPD (1)	1.70	(0.85, 3.41)	0.13
Moderate-severe COPD (1)	5.46	(2.68, 11.12)	<0.001
Diabetes without end-organ damage (1)	2.32	(1.32, 4.08)	0.003
Mild liver disease	1.15	(0.41, 3.24)	0.79
MI (1)	0.63	(0.21, 1.83)	0.39
PUD (1)	2.49	(0.70, 8.89)	0.16
PVD (1)	2.77	(1.14, 6.73)	0.02
Diabetes with end-organ damage (2)	4.27	(1.64, 11.10)	0.003
Prior malignancy (2)	1.61	(0.65, 3.97)	0.30
Mobility device	Referent=No		
Yes	3.29	(1.87, 5.80)	<0.001
History of alcoholism	Referent=No		
Yes	1.77	(1.07, 2.93)	0.03
Current smoker	Referent=No		
Yes	1.42	(0.89, 2.28)	0.15
Age group	Referent <56		
56–65	1.02	(0.46, 2.26)	0.96
66–75	2.43	(1.15, 5.17)	0.02
>75	5.49	(2.32, 12.98)	<0.001
Race/Ethnicity	Referent=White		
Black	0.88	(0.58, 1.36)	0.58
Hispanic	0.76	(0.40, 1.48)	0.43
Other	0.77	(0.37, 1.59)	0.48
BMI	Referent <25		
25–29.9	0.86	(0.53, 1.40)	0.54
30–34.9	0.59	(0.32, 1.09)	0.09
≥ 35	0.94	(0.44, 2.01)	0.87
D'Amico tumor risk	Referent=Low		
Intermediate	1.26	(0.78, 2.03)	0.34
High	1.44	(0.87, 2.37)	0.15
VA Site	Referent=Greater LA		
Long Beach	0.98	(0.66, 1.48)	0.94
Treatment (Surgery or Radiation)	Referent=No		
Yes	0.91	(0.57, 1.44)	0.67

Figure 1. Non-prostate cancer mortality stratified by age (1a), comorbid conditions (1b), need for a mobility device (1c), and history of alcoholism (1d). *Dot represents 10-year 50% mortality.

exceeds 75-years of age, then men 65-years of age or older with either COPD, diabetes with end-organ damage, or PVD may not benefit from treatment. Of the four statistically significant comorbidities, only 65-year-old men with diabetes without end-organ damage have a 10-year mortality rate that was marginally lower than 75-year old men (34% vs. 42%). Hence, the data is open to interpretation—either men with advancing age were under-treated or men with health states that portend a poor prognosis were over-treated.

Mismatches between comorbidity-associated overall survival and aggressive treatment rates may be attributed to either 1) patients and physicians being unable to predict or integrate long-term survival from these comorbid conditions with realized benefit of aggressive treatment, or 2) quality-of-life considerations, treatment availability and patient preferences driving the decision to pursue aggressive treatment. With the former, one would posit a similar treatment rate between any treatment type and surgery only. This was the case for all but two comorbidities—CVD and moderate-severe COPD. With the latter, one would anticipate a difference between any treatment type and surgery. Precisely, men with significant comorbidity would

have been triaged to radiotherapy to avert the perioperative risk of surgery. This was only seen in men with moderate-severe COPD or CVD.

Our findings are unexpected since a plenitude of studies characterizing patterns of care demonstrated a negative association between worsening comorbidity and treatment rate.^{11–15} However, our findings are plausible since a single comorbid condition at the time of treatment may not seem overly concerning for a dismal prognosis. In fact, upon a more thorough review of the extant literature, one discovers that others also failed to find a significant difference in the treatment rate when comparing men with a Charlson Score of 1 or 2 vs. 0.^{16–18} This is attributed to clinicians' 1) overall difficulty in forecasting 10-year survival rates for men with localized prostate cancer;¹⁹ 2) perception that a single comorbid condition is unlikely to impact long-term survival; 3) unease in withholding treatment for men with a single comorbid condition, irrespective of severity; and 4) perception that significant advances made in the management of patients with particular comorbid conditions such as HIV, cardiovascular disease and those with a prior malignancy have changed the landscape for long-term survival. With

Figure 2. Non-prostate cancer mortality stratified by age for moderate-severe COPD (2a), diabetes with end-organ damage, PVD (2c), and diabetes without damage (2 d). *Dot represents 10-year 50% mortality.

regard to the latter, while men with HIV and those with metastatic lung cancer both have a Charlson Score of 6, in the context of anti-retroviral therapy the long-term survival rates are disparate.

Our study is tempered by several limitations. First, the VA cohort may not be representative of US population such as severity of comorbid conditions and omitted variable bias, which may be associated with earlier mortality. However, with chart abstraction and restricting the cohort to a single comorbid condition, we attempted to minimize this effect. Second, our study was retrospective and is subject to response bias. Men with greater access to medical care may have more thorough reporting of comorbidity information and, thus, inflated comorbidity scores compared with healthier men. Third, this study is limited to men with no more than one comorbid condition and hence, some comorbidities (e.g., PVD or diabetes with end-organ damage) may be associated with other comorbidities. One would suspect that the treatment rate for these conditions would be lower than those without any comorbidity. However, in a sensitivity analysis, only men with hemiplegia (RR 0.63; 95% CI 0.22–0.97) or those with prior malignancy (RR 0.73; 95% CI 0.53–0.91) had a lower risk of undergoing definitive treat-

ment than men without any comorbidities. Last, our study is limited by the modest sample size of 1,031. Particular comorbid conditions may have been associated with a lower rate of definitive treatment rate if we had had a larger sample size. Nonetheless, even if it were statistically significant with a larger sample, the mismatch between the effect size of a 3% relative risk reduction among men with diabetes with end-organ damage (RR 0.97) when compared with those without any comorbid conditions is modest when compared with a 69% relative risk reduction with age (RR 0.31 for those >75 vs. <56). Still, our findings should be evaluated with caution until validated in population-level analyses.

Notwithstanding these limitations, our study is strengthened by the selection of men with an equal-access medical care system in the VA, availability of comorbid conditions and other prognostic factors, study design and the reliability of chart abstraction. The purpose of our study was not to invalidate the Charlson Comorbidity Index, but rather characterize the impact of single comorbid conditions on survival. Despite the comparable treatment rates, men with diabetes with or without end-organ damage, PVD, those in need of a mobility device, and men with history of

alcoholism may not benefit from aggressive treatment for their localized prostate cancer.

Author Contributions: Dr. Chamie and Lorna Kwan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis.

Conflicts of Interest: None disclosed.

Funding Source: This work was supported by the American Cancer Society (117496-PF-09-147-01-CPHPS (Principal Investigator: KC)); Ruth L. Kirschstein National Research Service Award Extramural (1 F32 CA144461-01 (Principal Investigator: KC)); Jonsson Comprehensive Cancer Center Seed Grant (Principal Investigator: MSL); and National Institute of Diabetes and Digestive and Kidney Diseases (N01-DK-1-2460 (Principal investigator: M.S.L.))

Financial Disclosures: No financial disclosures to report.

Corresponding Author: Karim Chamie, MD, MSHS; UCLA Department of Urology, Health Services Research Group, 924 Westwood Blvd., Suite 1000, Los Angeles, California 90024, USA (e-mail: kchamie@mednet.ucla.edu).

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics. *CA Cancer J Clin*. 2010;60(5):277-300.
2. Bill-Axelsson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2005;352(19):1977-84.
3. Hu JC, Gold KF, Pashos CL, Mehta SS, Litwin MS. Temporal trends in radical prostatectomy complications from 1991 to 1998. *J Urol*. 2003;169(4):1443-8.
4. Miller DC, Sanda MG, Dunn RL, Montie JE, Pimentel H, Sandler HM, et al. Long-term outcomes among localized prostate cancer survivors: health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. *J Clin Oncol*. 2005;23(12):2772-80.
5. Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst*. 2004;96(18):1358-67.
6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83.
7. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *Jama*. 1998;280(11):969-74.
8. Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML. Mayo Clinic validation of the D'Amico risk group classification for predicting survival following radical prostatectomy. *J Urol*. 2008;179(4):1354-60. discussion 60-1.
9. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
10. May S, Hosmer DW. Hosmer and Lemeshow type goodness-of-fit statistics for the Cox proportional hazards model. In: Balakrishnana N, Rao CR, eds. *Advances in Survival Analysis: Handbook of Statistics Vol 23*. Amsterdam: Elsevier, North-Holland; 2004:383-394.
11. Alibhai SMH, Leach M, Tomlinson GA, Krahn MD, Fleshner NE, Naglie G. Is there an optimal comorbidity index for prostate cancer? *Cancer*. 2008;112(5):1043-50.
12. Harlan LC, Potosky AL, Gilliland FD, Hoffman R, Albertsen PC, Hamilton AS, et al. Factors associated with initial therapy for clinically localized prostate cancer: prostate cancer outcomes study. *J Natl Cancer Inst*. 2001;93(24):1864-71.
13. Klabunde CN, Potosky AL, Harlan LC, Kramer BS. Trends and black/white differences in treatment for nonmetastatic prostate cancer. *Med Care*. 1998;36(9):1337-48.
14. Desch CE, Penberthy L, Newschaffer CJ, Hillner BE, Whittemore M, McClish D, et al. Factors that determine the treatment for local and regional prostate cancer. *Med Care*. 1996;34(2):152-62.
15. Schymura MJ, Kahn AR, German RR, Hsieh M-C, Cress RD, Finch JL, et al. Factors associated with initial treatment and survival for clinically localized prostate cancer: results from the CDC-NPCR Patterns of Care Study (PoC1). *BMC Cancer*. 2010;10(1):152.
16. Parsons JK, Kwan L, Connor SE, Miller DC, Litwin MS. Prostate cancer treatment for economically disadvantaged men. *Cancer*. 2010;116(5):1378-84.
17. Hall HI, Satariano WA, Thompson T, Ragland KE, Van Den Eeden SK, Selvin S. Initial treatment for prostate carcinoma in relation to comorbidity and symptoms. *Cancer*. 2002;95(11):2308-15.
18. Marr PL, Elkin EP, Arredondo SA, Broering JM, DuChane J, Carroll PR. Comorbidity and primary treatment for localized prostate cancer: data from CaPSURE™. *J Urol*. 2006;175(4):1326-31.
19. Walz J, Gallina A, Perrotte P, Jeldres C, Trinh Q-D, Hutterer GC, et al. Clinicians are poor raters of life-expectancy before radical prostatectomy or definitive radiotherapy for localized prostate cancer. *BJU International*. 2007;100(6):1254-8.